PROCEEDINGS
of the
XXXIV National Continuing Medical Education Programme In Surgery

SURGERY UPDATE 2016

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FOREWORD

The National Continuing Medical Education Programme in Surgery organized by the department of Surgery, Maulana Azad Medical College, New Delhi is in its twenty ninth year of existence. During this period has blossomed into a six day academic exercise eagerly looked forward to by the surgeons all over the country and has established itself as the gold standard for Continuing Medical Education Programmes. One of its endearing features is the CME lectures brought out in a bound format simply named the **PROCEEDINGS,** introduced and published in 1998 The PROCEEDINGS have become an integral part of the update since then. It is satisfying to note that the bound lectures are carried by postgraduates all over the country preparing for examinations or for interviews. Those who miss out on attending the CME programme, still manage to procure copies of the PROCEEDINGS in its photocopied form. This year also it gives us great pleasure to present a book on the **PROCEEDINGS OF THE XXXIV NATIONAL CONTINUING MEDICAL EDUCATION PROGRAMME IN SURGERY**, similar to previous years.

Every surgical disorder in the scientific programme has been chosen carefully in the context of its importance to the attending delegates. All the authors are well-recognized authorities with a vast personal clinical experience on the particular subject they were chosen to elaborate. As will be evident from the written texts, they have contributed a very comprehensive account of the respective topics and are also to be commended for submitting the latest references at the end of each chapter for ready referral. The quality of their text reflects their involvement in our programme. A sincere effort has been made to format the book in a uniform manner without any effort to edit the text provided by the contributors.

This year's programme is a full day comprehensive CME on selected topics of particular interest to the postgraduate. Emphasis is on subjects with more bearing on their clinical application. Every year's Proceedings can be considered one part of the trilogy of books which will cover nearly the whole course for the postgraduate student over a three year period.

We sincerely thank the contributors for their effort. We also wish to thank all the colleagues in the department for their encouragement and guidance in making this project possible. Especial thanks are to Prof. Rajdeep Singh, who has been instrumental in collecting the articles and majorly formatting the text to its final form. Our sincere thanks are also due to the resident staff who worked for procuring, proof reading and formatting the text. Finally, we must emphasize the contribution of the authors who have always given an overwhelming response to our endeavor of bringing out the written text of our CME programme over the years. We sincerely hope that the Proceedings will meet the stiff demands of the delegates and serve as a nodal point of learning for the postgraduates.

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सरस्वती वन्दना

PRAYER TO SARASWATI, THE GODDESS OF LEARNING

मन के हजारो द्वार पथ गलीयार सब उजीयार दे
जीवन जगत् को ज्योती का उपहार दे मॉ शारदे।

**MAN KE HAZAARON DVAARA PATHA GALIYAARA SABA UJIYAARA DE,
JEEVAN JAGAT KO JYOTI KAA UPAHAARA DE MAA SHAARADE.**

O! Goddess of learning, Mother Shaaradaa, bestow upon the whole living world
Your blissful light. May our thoughts and minds be illuminated by your knowledge.

जल उठे तेरे भवन मे आज कितने दीप पावन
भाव चिन्तन के महकते फूल अक्षत् धूप चन्दन
कल्पनाओ को सदा आधार दे आकार दे ओ शारदे।

**JALA UTHE TERE BHAVANA MEIN AAJ KITANE DEEPA PAAVANA
BHAVA CHINTANA KE MAHAKATE PHOOLA AKSHAT DHOOPA CHANDANA
KALPANAAON KO SADAA AADHAARA DE, AAKAARA DE, O SHAARADE.**

So many lamps (of writings) have been lighted in your service. Our love towards you is expressed in
Our creative writings which are as if offerings of flowers, unbroken rice, essence and sandal to you.
We pray to you, O Goddess, that you always be kind enough to give our thoughts a direction and
Sense of constructiveness.

वीणाधरा श्वेताम्बर शूभ भाव प्रेरक उज्जवला
मानव कमल विकसित करो ओ पुश्प पावन मॅगला
जन चेतना के पर्त्त सब करूणामयी झॅकार दे ओ शारदे।

**VEENADHARAA SWETAAMBARAA SHUBHA BHAAVA PRERAKA UJJWALAA
MAANSA KAMLA VIKASITA KARO PUNYA PAAWANA MANAGALAA
JANA CHETANAA KE PARTTA SABA KARUNAA MAYEE JHANKAAR DE, O SHAARADE.**

O Goddess! Your ways are soft and musical, so they touch the soul. You are purity within and
without, hence you may drive us to purity and universal welfare. O Goddess! I entreat upon you
again and again that you nourish our mind and in it a deep and pure sense of good for all. You are
blissful, you are pure, you are meritorious, therefore, you will let our conscience and ideas vibrate
with your essence and make them beautiful.

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Disaster Management - An Overview

Ajit Sinha, R. K. Soni

Disaster

It is a sudden, unpredictable, unfamiliar, calamitous event, bringing great damage, uncertainty, and destruction of life and property. WHO defines disaster as an "Any occurrence that cause, ecological disruption, loss of human life, deterioration of health & health services, on a scale, sufficient to warrant an extraordinary response from outside the affected community or area"

From medical perspective, disaster may be defined as events in which needs of patients overwhelm the resources needed to care for them.

Type of Disaster

No.	Category of Hazard	Type of Disasters
1	Geological	Earthquake Tsunami Landslide
2	Hydro-Metrological	Flood Flash Flood Storm Cyclone Drought
3	Biological	Outbreak Epidemic Pandemic Plant & Animal disease
4	Technological	Transportation Industrial
5	Environmental	Bush, Forest Fire
6	Political, Social, Extremism	Conflict Terrorism
7	Weapons of Mass Destruction (WMDs)	Chemical, Biological, Radiological, Nuclear and Explosives

A disaster is followed by:

a) Large number of dead, injured and missing.
b) Large number of unaccompanied children.
c) Loss of normal source of food and potable water.
d) Loss of shelter and household necessities
e) Loss of means of livelihood.
f) Overcrowding and spread of communicable disease.
g) Destruction of environment and communication.
h) Logistics problems.
i) Insecurity and tension.

Disaster Management

Disaster Management can be defined as: the systematic process of using *administrative* decisions, *organization*, *operational* skills and *capacities* to implement *policies* and *strategies* and *enhance coping capacities* of the society and communities to *lessen the impacts* of hazards and related environmental and technological disasters.

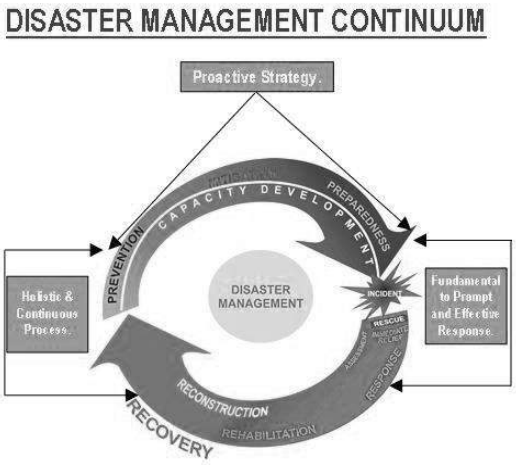
Disasters often differ in quantity of damage caused or in quality of the type of medical consequences. For example earthquake cause a lot of physical injury and fractures, floods cause drowning deaths and infections, chemical leaks cause toxic manifestations, etc. The impact of different disasters demand different type of response or management approach.

Disaster Management follows a multi-disciplinary approach which includes bringing together specialization of different domains into disaster management. Disaster Management Official must have prior coordination and agreements in place with government hospital, police authorities, fire brigade personnel, youth organizations, NGOs. This will ensure immediate response to the disaster with minimum chaos. Disaster managers must ensure that law and order is maintained and people receive adequate information about their missing family members and relatives, regarding their living status and location.

Disaster Managers must get a ***resource mapping*** done of the community so as to have available resources on time when required. Also, mock drill can be conducted with community so that they don't panic in times of disaster and quickly move to safe shelters which are pre-located during the time of resource mapping. Various resources to be indentified are: Water source, safe shelter for community in times of flood, earthquakes, cyclone etc., disaster helpline number, medical assistance number, fire brigade number etc.

Phases of Disaster Management

"The Fundamental Principle of Disaster Management is to do the maximum good to the maximum number of persons."



I. Disaster Phase

During this phase the event of the disaster takes place. This phase is characterized by profound damage to the human society. This damage / loss may be that of human life, loss of property, loss of environment, loss of health or anything else. In this phase, the population and society is in a state of profound shock.

II. Post Disaster Phase

a) **Rescue phase** – This is the period that immediately follows the occurrence of the disaster. All individuals respond to the disaster, but in their own ways. Almost everyone is willing to help. The first important step during first 48 hours after a disaster is to save maximum number of lives as possible. Food, shelter, clothing can be taken care of in later stage. The immediate need is to have **search and rescue** teams in place along-with **emergency medical assistance** which can save lives.

b) **Relief Phase** – Disaster Management must stress on **immediate need assessment** after a disaster. This assessment will be important for government organizations, NGOs as well as international bodies. The accuracy of need assessment will determine the efficiency of management.

Depending on the initial needs assessment, immediate relief like food, clothing and shelter is provided to the survivors. The relief must be adequate and appropriate to the culture of the affected community. The relief is generally provided by external agencies (NGOS, INGOs) and Government resources. Immediate need includes immediate medical assistance, safe drinking water, nutritious food, temporary shelters, clothing, and information on missing relatives, psycho-social assistance to trauma victims, special care to children, elderly and physically challenged and special attention to pregnant and lactating women.

c) **Recovery Phase / Rehabilitation phase** – When the immediate needs of the population are met, when all medical help has arrived and people have settled from the hustle – bustle of the event, they begin to enter the next phase, the recovery phase, which is the most significant, in terms of long term outcome. It is during this time that the victims actually realize the impact of disaster. It is now that they perceive the depth of the loss that they have suffered.

They are often housed in a camp or in some place which is often not there in home, along with other victims. After the victims have recovered from the both physical and mental trauma, they realize the need to return back to normal routine i.e. to pre-disaster life. During this phase, they need resources and facilities so as to enable them to return back to their own homes, pursue their occupation, so that they can sustain their life on their own, as the help from the government and other non-governmental organizations is bound to taper in due course. Thus, they are provided with a whole new environment, adequate enough for them to pursue a normal or at least near normal life. This is called rehabilitation.

During rehabilitation phase, adequate care is taken to follow all safety measure to prevent and minimize future impact of hazard. Also, the sustainable development approach is kept in mind while keeping restructuring the community. During this phase, earthquake resistant houses are built; Tsunami and cyclone resistant houses and flood resistant raised platform houses are built. During rehabilitation, the community is settled in a safe location and as far as possible mixed community settlement is preferred to eliminate social issues of caste and class.

III. Pre-Disaster Phase

a) **Prevention phase** - This is the phase which indicates the start of pre-disaster phase. It engrosses measures to be taken in order to prevent a specific disaster from happening again. There are different measures required for different disasters. Working on this phase is the responsibility primarily of the government. The actions taken in this phase are required to be of high quality and of long term benefit. Only the government has the strength to implement these activities with high funds and necessary resources in place. The measures include increasing the capacity of a dam to prevent floods, activities

promoting communal harmony at all levels to prevent riots, high construction and safety standard in industries, government offices and all other structures to be fire and earthquake resistant. Prevention should be at all levels- community levels, local level and government level.

b) **Mitigation phase** – In this phase, measure are taken in advance of a disaster aimed at reducing its impact on society and environment, if ever a disaster takes place. This phase includes technology and scientific techniques too. For example,
   i) Predicting the path, time to be taken of a cyclone after knowing that it is approaching the country is one mitigation strategy so as to avoid losses of lives and property.
   ii) Having a natural mangroves plantation along the coast is one mitigation measure.
   iii) Construction of earthquake resistant building is another mitigation measure. Working on mitigation phase is also the responsibility of the government because such initiative at the local and community level is very difficult as huge funds and resources are required.

c) **Preparedness phase** – This phase involves the development of awareness among the population on the general aspects of disaster and on how to behave in the face of a future disaster. This includes education on a warning signs of disasters, methods of safe and successful evacuation and first aid measures. Preparedness must be on part of individual organizations as well as community as a whole. Preparedness phase also deals with the predations which are needed on individual, community, authoritative level when a disaster occurrence cannot be avoided and a disaster is sure to happen. Community based disaster management plans must be formed with the help of NGOs.

Community Planning

- Should involve acute care specialists, local hospitals, as well as officials of the local police, fire, security, public health and government agencies.
- Should be frequently tested and reevaluated.
- Must provide for a mean of communication considering all contingencies, such as loss of telephone land line and cellular circuits.
- Must provide for storage of equipment, supplies, and any special resources that may be necessary.
- Must prepare for the transportation of casualties to other facilities by prior agreement.

Hospital Planning – It is vital that each hospital develop a disaster plan. Once a state of disaster has been declared, the hospital disaster plan should be put into effect. Specific procedures should be automatic and include:

- Establishment of an incident command post (ICP).
- Notification of on-duty and off-duty personnel.
- Preparation of decontamination, triage and treatments areas.
- Checking of supplies and other materials, essential to sustain hospital operations.
- Establishment of a public information center and provision of regular briefings to inform family, friends, the media, and the government.

Departmental Planning

Since patient care can best be delivered to individuals patients by care providers working in small teams, every hospital department with responsibility for the care of injured patients must identify its **medical response teams** in advance. They should also be readily accessible in the event of disaster.

The ultimate objective of any specific disaster management process is to reduce the impact of disaster in order to save maximum number of lives and to avoid property damage. We calculate risk in terms of the hazard, vulnerability and the coping capacity.

$$\text{DISASTER RISK} = \frac{\text{HAZARD} \times \text{VULNERABILITY}}{\text{COPING CAPACITY}}$$

There are three ways to reduce the risk of a disaster. This are-

- Avoid the hazard or minimize the probability of a hazard happening.
- Reduce the vulnerability of the community residing.
- Increase the coping capacity of the community residing.

Hazards – Hazards is a potential threat which can create disaster. A hazard poses a significant risk of a disaster. A hazard can be existence of fire, chemical industries, earthquake, flood, etc. For example, earthquake in a desert will just be a hazard and not a disaster. However, earthquake in an urban or rural settlement where population resides can be a huge disaster.

Vulnerability - Vulnerability is defined as the characteristic of a person or group and their situation that influences their capacity to anticipate, cope with, resist and recover from the impact of a natural disaster. Vulnerability can be classified under different heads. These are –

a) *Physical* vulnerability: This type of vulnerability means the direct physical exposure of an individual to the hazard. The vulnerability also depends upon the age, sex, location, physical state of the individual. Physical

vulnerability plays important part at the time of actual disaster. A person who is aged is more vulnerable physically than a person who is young.

b) *Social* vulnerability: This type of vulnerability considers the social patterns existing in the society. This include the class-caste system in the society, status of woman in the society, status of physically and mentally challenged population in the community and such related social practices. Such type of a vulnerability matters mostly at the time of relief and rehabilitation phase of disaster management. In these phases, a family from a lower cast is more vulnerable that an upper class family, a mentally challenged person is more vulnerable that a sound person.
c) *Economical* vulnerability: Economical vulnerability deals with the economic aspect of an individual or a family. It included the income, economic stability, insurance availability of individuals and families. A person who is economically strong is less vulnerable than a person who is economically not healthy.
d) *Geographical* vulnerability: This type of vulnerability deals with respect to the location of the community. This vulnerability is disaster is specific. For floods, people living on height (more above sea level) are less vulnerable than people living on low height. In the same way, in a landslide prone hills, people living on the slops are more vulnerable that the people living on the ridge of the hill.

Coping Capacity – Coping capacity encompasses those strategies and measures that act directly upon damage during the event by alleviating or containing the impact or by bringing about efficient relief. Coping capacity can be summed up as the ability of a group or household to resist a hazard's harmful effects and to recover easily.

Indian Perspective

The recent floods and landslides in Uttarakhand have been a rude reminder for India of its historical disasters, which were overwhelmingly intimidating for the country. Some of the deadliest disasters which happened in India are –

- Bangal famine (1943) - killed at least 40 lakh people.
- Latur earthquake (1993) – killed more than 20 thousand people, damaged more than 2 lakh houses.
- Gujrat (Bhuj) earthquake (2001) - killed 30 thousand people.
- Indian Ocean Tsunami (2004) – affected 1, 50,000 people, killed more than 10,000 people in India alone.

To enhance the preparedness to tackle such catastrophes in a more organized way On 23 December 2005 Government of India enacted Disaster Management Act and formed National Disaster Management Authority (NDMA) -Headed by Prime Minister.

NDMA is an Apex body mandated to lay donor policies, plans, and guidelines for disaster management to ensure timely and effective response to disasters with the aim to build a safer and disaster resilient India by developing a holistic, proactive, multidiscipline and technology driven strategy for disaster management through collective efforts of all governmental and non-governmental organizations.

At the state level State Disaster Management Authority (SDMA) has been formed by various states, headed by Chief Minister.

National Institute of Disaster Management (NIDM) - is a statutory body of government of India formed under the Disaster Management Act-2005 for research, documentation and assisting the government in (under ministry of home affairs) policy planning on all aspect of disaster management.
This body is preparing a detailed report on mega disaster of flash floods and landslides in Uttarakhand on 16th and 17th June 2013.to understand the causes, impact and lesson learnt.
It also publishes a biannual Journal "Disaster and Development".

National Disaster Response Force (NDRF) – It is a specialized force for specialized response to natural and manmade disasters. This force is under direction and control of NDMA, and is supervised by Director General NDRF.

Conclusion

Disaster management involves people from various sectors and from various levels. Coordination among all of them is the key to achieve maximum benefit. Proper planning, preparedness, immediate, and coordinated response helps in reducing impact of disaster and save precious human lives.

Liver Trauma

Deborshi Sharma, Saurab Sekhar

The liver and spleen are the two most commonly injured abdominal organs accounting together for three-quarters of injuries in blunt abdominal trauma. Though the injured spleen is easily removed, the surgical management of liver injuries remains a challenging problem. Paediatric surgeons first introduced the concept of non-operative management of splenic trauma. This approach was subsequently extended to adults with splenic injuries, and later to the management of blunt liver injuries. While a growing number of reports support non-operative management in haemodynamically stable adults, there still exists uncertainty about efficacy, patient selection and details of management. Interventional radiology has further increased the number of patients that can be treated without surgery. The progressive utilization of non-operative management has, therefore, created its own set of complications and controversies.

This chapter will review the assessment and management (operative and non-operative) of liver and splenic trauma, and provide evidence-based practice guidelines.

EVALUATIN OF THE TRAUMA PATIENT

The initial assessment of an injured patient should proceed according to the Advanced Trauma Life Support **(ATLS)** guidelines published by the American college of Surgeons. A detailed Re-iteration of the ATLS algorithm is beyond the scope of this chapter. However, following the initial resuscitation, management may differ based on the mechanism of injury and the haemodynamic status of the patient.
Road traffic accidents and assault account for the vast majority of liver and splenic injuries, though the relative frequency varies according to geography. For example, in the UK and Europe, the majority of injuries are due to road traffic accidents while in South Africa and the US there is a somewhat higher proportion of penetrating trauma. Due to its size and relatively protected anatomical position, splenic injuries are more frequently associated with blunt trauma than penetrating trauma.

Following blunt trauma, a conscious patient who is haemodynamically unstable and has generalized peritonitis should undergo immediate laparotomy. Patients with neurological impairment or with equivocal physical signs traditionally underwent diagnostic peritoneal lavage. However diagnostic peritoneal lavage is invasive and time consuming. Moreover, it is non-specific and oversensitive for the presence of blood, factors that contribute to a high rate of non-therapeutic laparotomies. Diagnostic peritoneal lavage has, therefore, largely been replaced by ultrasonography. The Focused Abdominal Sonography in Trauma (FAST) examination is non-invasive, repeatable, and easily taught to clinicians. The FAST examination can be performed int eh resuscitation area while other assessments are being carried out, and in less time that required for diagnostic peritoneal lavage. The principal drawback of ultrasonography is that it remains operator dependent. While easily adopted in high-volume trauma centre's in North America, the utility of FAST is yet to be proven in lower volume centre's where individual surgeons and emergency physicians may not easily get sufficient experience to master the learning curve. In such centers, examinations performed by radiologists may have a role.

If the patient is haemodynamically stable following blunt injury, time permits more thorough radiological assessment. CT scanning has become the gold standard for the diagnosis of solid organ injuriy. Importantly, CT allows assessment for other visceral injuries that may require operative management. Early reports based on conventional CT suggested that radiological findings following solid organ injury did not correlate exactly with findings at laparotomy. However, with the advent of multidetector CT, scanning times have decreased and resolution has continued to improve. Furthermore, Ct findings in both liver and splenic trauma have been demonstrated to be occasionally helpful in predicting the success of non-operating management and the utility of angiographic embolisation.

Table 1 Liver injury scale (grade and description)

1	Subcapsular heamatoma <10% surface area, laceration < 1 cm deep.
2	Subcapsular haematoma 10-50% surface area, laceration 1-3 cm deep; <10 cm in length.
3	Subcapsular haematoma > 50% surface area or expanding, laceration > 3 cm deep.
4	Parenchymal disruption involving 25-75% of hepatic lobe or 1-3 Couinaud's segments in a single lobe.
5	Parenchymal > 75% of lobe or > 3 couinaud's segments.
6	Hepatic avulsion.

Penetrating trauma to the abdomen more frequently demands operative exploration. However, recent reports have documented successful non-operative management in selected patients with stab wounds and even low velocity gunshot wounds to eh abdomen (see below).

LIVER TRAUMA

GRADING SYSTEM FOR LIVER INJURIES
The grading system proposed by the American Association for the Surgery of Trauma (AAST), initially drafted in 1989 and modified in 1994, has been adopted internationally (Table 1). Grade I or II injuries are considered minor, represent 80-90% of cases, and rarely require operative intervention. Grades III-V are severe and more often require angiographic or surgical intervention. Grade VI injuries are incompatible with life.

NON-OPERATIVE MANAGEMENT OF BLUNT HEPATIC TRAUMA

Paediatric surgeons were the first to realize that the injured liver could be managed without surgery. In 1990, Knudson and colleagues published the first retrospective series of selected adult patients (n = 52) managed successfully without laparotomy. Since that time, there have been a significant number of case series, largely retrospective, confirming the success of non-operative management in selected patients, and this has become the strategy of choice for haemodynamically stable patients following blunt liver trauma. These findings have also been confirmed by several more recent prospective studies. These reports have broadened the selection criteria to include patients with other intra-abdominal injuries not requiring operation, higher grades of hepatic injury, and older patients. The results have shown that non-operative management is associated with fewer liver-related and intra-abdominal complications that operative management, and that non-operative management does not result in a greater need for blood transfusion. In addition, although much of the benefit of non-operative management is attributed to avoidance of an operation the mortality of liver injuries appears to have decreased. Key elements have slowly emerged: neither grade of injury nor degree of haemoperitoneum on CT reliably predicts the outcome of non-operative management. The heamodynamic status of the patient is therefore the most reliable criterion for non-operative management. Between half and two-thirds of patients suffering blunt hepatic injury meet criteria for non-operative treatment in appropriately selected patients exceed 95%.

If a non-operative strategy is selected it should be borne in mind that the risk of hollow organ injury increases in proportion to the number of solid organs injured and that there is a small, but significant, risk of delayed haemorrhage. However, it appears that the natural course of liver injuries is in that any deterioration is usually gradual, with a fall in haemoglobin lever or an increase in fluid requirement, rather that acute haemodynamic decompensation. Therefore, with close supervision, patients who fail with an initial non-operative management of liver injury, the evidence supporting this practice in asymptomatic patients is poor and these scans seldom alter management.

NON-OPERTIVE MANAGEMENT OF PENETRATING HEPATIC INJURIES.

Mandatory surgical exploration for penetrating wounds to the abdomen has been surgical dictum for the greater part of the last century. Initially motivated by the sheer volume of patients and limited resources, several centre's in south America and South Africa began to practice selected non-operative management of abdominal stab wounds. Though not universally accepted, the success of this strategy has subsequently been demonstrated in larger prospective series. Selective non-operative management of stab wounds specifically to the liver has been reported. If haemodynamically stable, a patient with a stab wound that is either directly over the liver or apparently tangential (without likely entrance into the peritoneal cavity) may be evaluated by CT. If the CT suggests an isolated liver injury and a knife tract unlikely to have caused other visceral injury, non-operative management may be pursued. Close serial abdominal examination is essential, and any evidence of generalized peritonitis mandates laparotomy.

Until recently, there has been a broad consensus that a gunshot wound to the abdomen is an indication for laparotomy. However, this strategy has been challenged in selected patients with isolate gunshot wounds of the liver. Demetriades and colleagues reported 52 patients with isolated liver injuries due to abdominal gunshot wounds, of whom 16 were initially managed non-operatively. Five patients subsequently required laparotomy for peritonitis (4) or an abdominal compartment syndrome (1). Eleven patients were, therefore, successfully managed without laparotomy. Given tthat this represented just 7% of all liver gunshot injuries and 21% of isolated liver injuries in the series, the non-operative approach applies in only very selected cases. A more recent prospective seires from South Africa attempted non-operative management in 33 of 124 (27%) patients with liver gunshot injuries, avoiding laparotomy in 31 (94%). These included 14 AAST grade III, 8 grade IV, and 3 grade V injuries, demonstrating success with selective non-operative management in even higher grade injuries. Though experience is mounting with this strategy, at present there is insufficient evidence to justify wide-spread adoption of a non-operative management in gunshot wounds of the liver.

OPERATIVE MANAGEMENT OF LIVER TRAUMA

The trauma laparotomy

Primary operative intervention is indicated for liver injury if the patient is haemodynamically unstable despite adequate initial resuscitation. A long mid-line incision is employed for an emergency laparotomy, although access to the liver can be improved by converting the incision into a 'T' by adding a right transverse component. In situation where surgery is undertaken after initial conservative management, a subcostal incision affords excellent access.

The trauma laparotomy is conducted in a routine fashion – four quadrant packing, control of gross enteric spillage, systematic inspection for injuries, and finally definitive management of injuries. Liver haemorrhage can usually be

initially controlled by direct pressure using packs. Additional techniques include the Pringle manoeuvre (digital compression of the portal triad), bimanual compression of the liver, or manual compressin of the aorta above the coeliac trunk. At this point, further evaluation of the extent of liver injury should be delayed until the anaesthetist has adequately replenished the intravascular volume. A key element of the resuscitation is the availability of adequate blood products: packed red blood cell, platelets, fresh frozen plasma, and cryoprecipitate. Recently, recombinant Factor VIIa has been used as an adjunctive agent in trauma patients with severe coagulopathic bleeding.

After intra-operative resuscitation, the liver must be mobilised adequately to allow a thorough examination of the injury. If necessary, the Pringle manoeuvre may be maintained with a vascular clamp to allow further assessment and operative remedy. A normal liver can tolerate inflow occlusion for up to 1h; however, the ability of a damaged liver to tolerate ischaemia may be impaired. Depending on the injury and the experience of the surgeon, a variety of surgical techniques are then available.

Techniques for haemostasis
Perihepatic packing: In situations where it is thought that definitive control of haemorrhage cannot be obtained, the liver injury should be packed, the incision closed and the patient transferred to a specialist centre for definitive treatment. Packing can also be employed as a damage control strategy in patients who are critically unstable, coagulopathic or acidotic and, therefore, would not tolerate a prolonged operative procedure. In this setting, packing must be employed before the patient has deteriorated to a point ath survival is unlikely under any circumstances. Finally, packing can occasionally also be used in conjunction with interventional techniques.

Packing is remarkably effective at controlling major haemorrhage from liver injuries, even in patients with caval or hepatic venous injuries. The technique of packing involves manual closure or approximation of the parenchyma, followed by sequential placing of dry abdominal packs or a single rolled gauze around the liver and directly over the injury in an attempt to provide tamponade to a bleeding wound. Most surgeons employ skin closure only, leaving the fascia for primary closure at eh subsequent procedure for pack removal.

Hepatorrhaphy: Absorbable sutures on a curved blunt-tipped needle can be used to approximate a fissured parenchymal injury and thus control haemorrhage as an alternative to exploration of the depths of the injury. These sutures are placed as large horizontal mattress stitches, often in conjunction with a bolster of haemostatic material. Though occasionally useful in minor injuries, the disadvantages of this technique are that parenchymal vessels may continue to bleed resulting in a cavitating haematoma, bile duct injuries may not be detected and the suture itself may cause further bleeding, ischaemia or intrahepatic bile duct injury.

Hepatotomy with direct suture ligation: This technique involves extending the liver laceration using the finger fracture technique or the ultrasonic dissector to expose injury vessels. The bleeding vessels can be suture ligated or clipped to achieve haemostasis. Diathermy coagulation can also be used; in this context, the argon beam coagulator (which ‘sprays’ the diathermy current on an argon beam) is invaluable. This strategy has proved particularly effective in penetrating liver trauma.

Omental packing: Stone and Lamb reported in 1975 that the greater omentum could be employed as a pedicled flap to fill a defect in the liver parenchyma. This omental pedicle helps stop oozing form the low-pressure venous system of the liver parenchyma and may fill dead space that might later be predisposed to form an abscess. This technique is used infrequently today.

Mesh wrapping: The use of an absorbable ployglactin mesh to wrap major parenchymal disruptions has also been described. This technique is not indicated where juxtacaval or hepatic vein injury is suspected. Advocates claim that it provides the benefits of packing without the disadvantages (a second laparotomy is not required for removal, abdominal closure is much easier, and respiratory or renal function are less compromised). However, there is some concern about the amount of time needed to apply the mesh wrap in a haemodynamically unstable patient who might be best treated with rapid insertion of perihapatic packs.

Resectional debridement: This technique involves removal of devitalized liver tissue using the lines of the injury, rather than anatomical planes, as the boundaries of the resection. The optimum timing may be to combine debridement with pack removal, as necrotic tissue will be well demarcated 48-h after injury.

Anatomical liver resection: The practical difficulties of undertaking formal anatomical resection in a patient with a significant liver injury (frequently associated with shock, caogulopathy, and concomitant injury) are substantial. Though anatomical resections should be reserved for situations in which no other procedure adequately achieves haemostasis, excellent results have been reported from experienced centers.

Selective ligation of the hepatic artery: This strategy is rarely required. Hepatic arterial ligation to control haemorrhage should only be performed when other manoeuvres have failed, when selective ligation has been unsuccessful and when pedicle clamping has been demonstrated to arrest haemorrhage. Acute gangrenous cholecystitis is a well-recognized complication of hepatic artery ligation, and thus, cholecystectomy must be performed.

Management of hepatic venous and retrohepatic caval injury: suspicion that one of these serious injuries is present should be raised if the Pringle manoeuvre fails to arrest haemorrhage. There is no consensus on an optimal management strategy. Total vascular exclusion (clamping of the inferior vena cava and suprahepatic cava in addition to the Pringle manoeuvre) may be used. However clamping the vena cava seriously compromises venous return in a patient with major trauma. Veno-venous bypass (shunt from common femoral vein to left internal jugular or axillary vien) has th advantage of preserving venous return but as been infrequently used in the trauma setting. Atriocaval shunting via a chest tube though the right atrial appendage into the inferior vena cava, introduced by Schrock in 1968, allows total vascular isolation of the liver whilst preserving venous return, but this technique undoubtedly has produced more manuscripts than survivors. Packing can effectively control bleeding form retroheptic caval injuries, and this is the authors preference, only using vascular exclusion as a last resort.

Liver transplantation: Several reports have been published of severe liver trauma treated by total hepatchtomy followed by liver transplantation. Though experience of this sort of surgery is extremely infrequent, awareness of the therapeutic potential is useful.

ROLE OF INTERVENTIONAL RADIOLOGY

Interventional radiological techniques have become important adjuncts to both non-operative, and occasionally operative, management of liver trauma. Angiography and embolisation have been successfully employed as an extension of resuscitation in the non-operative management of patients with blunt hepatic injuries. Most authors recommend angiography in haemodynamically stable patients with a 'blush' (suggesting active arterial extravastion of constrast) on the initial CT scan. Pooling of contrast may occur within the liver parenchyma or in the peritoneal cavity. While the former is appropriately, and often successfully, manage by embolisation, patients with extravasations of contrast into the peritoneal cavity often quickly become unstable and hence require laparotomy. Transcatheter embolisation is reported to be technically successful in about 80% of cases, and has been described in non-operative management of penetrating injuries. A small percentage of patients may re-bleed despite a technically successful initial embolisation. These patients may require a second angiogram and embolisatiobn, or laparotomym if unstable.

Angiography may also be helpful in conjunction with damage control laparotomy. In the case illustrated in the patient sustained a Grade IV injury due to a road traffic accident. At the initial laparotomy, profound haemorrhage was controlled by packing. A subsequent CT demonstrated a pseudo-aneurysm of the right hepatic artery. This was successfully coiled, with complete resolution of the pseudo-aneurysm on a follow-up CT. Complications of embolisation include hepatic necrosis and gallbladder infarction.

COMPLICATIONS OF NON-OPERATIVE AND OPERATIVE MANAGEMENT

Non- operative management of liver trauma can result in two important categories of complications. First, co-existing intra-abdominal injuries may not be recognized at the time of initial presentation or may only become apparent after initial delay. A small portion of patients that 'fail' non-operative management do so only because they require laparotomy for other intra-abdominal injuries. The second type of complication is that related to th live injury itself. Septic complications such as intra-abdominal abscess and bile leak are recognized late complications and may require radiological, endoscopic or surgical intervention.

The complications after liver surgery for trauma are largely similar to those encountrered after any form of hepatic surgery. Haemorrhage due to encountered after any form of hepatic surgery. Haemorrhage due to coagulopathy requires correction with fresh frozen plasma and platelets. If haemorrhage occurs despite normal coagulation, angiography may provide diagnostic information and may permit therapeutic embolisation. Other complications include haemobilia, arterioportal fistulas, and sepsis due to infected collections of bile, blood or related to devitalized liver parenchyma.

OUTCOME/VOLUME RELATIONSHIP

Mounting evidence suggests that victims of significant trauma are best served at specialized, high-volume trauma centers. However, patients with liver trauma often present initially to surgeons without specialist hepatobiliary experience. The surgeon operating on a patient in this situation should, therefore, attempt to control bleeding by pacing, and then transfer the patient to the care fo a specialist hepatobiliary surgeon.

SPLENIC TRAUMA

The spleen is the second most frequanly injured organ in abdominal trauma, and a missed splenic injury is the most common cause of preventable death in trauma patiensts. Published series of splenectomies following trauma from the first half of the 20th century cited mortality rates 50% or more. In the absence o diagnostic imaging, these patients presented in this fashion were, not surprisingly, significant, and the standard treatment was, therefore, splenectomy. This practice was further supported by scattered reports of delayed splenic rupture as a complication of blunt trauma. The published results following trauma splenectomy improved significantly as a result of the experience of the Second World War. However, enthusiasm was soon blunted as case reports and small studies began appearing in the 1950s describing a fulminant, rapidly progressive and frequently lethal systemic infection following splenectomy. The development of diagnostic peritoneal lavage in the 1960s and later CT scanning resulted in many laparotomies for more minor splenic injuries. Spolenorrhaphy became the management of choice.

Key Points for Clinical Practice

- Selection of patients for non-operative management of liver injuries should be dictated primarily by haemodynamic stability.
- The principles of operative management of hepatic injuries are: (i) Arrest haemorrhage and enteric contamination, Before (ii) Careful systematic inspection for injuries, and (iii) Deffinitive management by an appropriately trained surgeon.
- Angiography and embolisation are important adjuncts to both non-operatve, and occasionally operative, management of liver trauma.
- Centres without specialist hapatobiliary experience should transfer patients with complex liver injuries as soon as stability permits.
- Selection of patients for non-operative management of splenic injuries depends primarily on haemodynamic stability.
- Angiography and embolisation are important adjunctsd to management of splenic injuries.
- Following successful non-operative management of blunt splenic trauma, repeat imaging should be considered in those patients with subscpsular haematomas and more devere injuries (Grade III or higher).

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Renal Trauma

Sanjay Gupta

Introduction

Kidney is the commonest genitourinary organ involved in trauma. The traditional teaching has been to manage blunt trauma conservatively and penetrating renal injuries surgically. While this is still correct in the majority of patients of renal trauma, there is a select group of patients who would do better otherwise. Rapid advancements in the imaging technology and minimally invasive surgery have permitted more accurate grading of renal injuries, thus reducing both unnecessary explorations for renal injuries as well as missed significant renal injuries.

Mode of injury

Kidney is most commonly injured by blunt trauma due to vehicular accidents, assault, falls and contact sports. Penetrating trauma due to gunshot and stabs is the next common mode of renal injury. Renal trauma due to penetrating injury is more severe and less predictable than that occurring due to blunt injury. Iatrogenic renal injury occurring during percutaneous nephrolithotomy (PCNL) and renal angiography is now an increasingly common mode of renal trauma.

Classification of renal injuries

The most widely accepted grading of renal injuries is that proposed by American Association for the Surgery of Trauma (AAST). It is based on abdominal CT or direct renal exploration. It correlates well with preservation or removal of the injured kidney as well as post-injury mortality and morbidity.

Table: AAST renal injury grading scale [1]

Grade	Description of injury
1	• Contusion or non-expanding subcapsular hematoma • No laceration
2	• Non-expanding peri-renal hematoma • Cortical laceration <1 cm deep without extravasation
3	• Cortical laceration > 1 cm deep without extravasation
4	• Laceration through cortico-medullary into collecting system • Vascular: segmental renal artery or vein injury with contained hematoma, or partial vessel laceration, or vessel thrombosis.
5	• Laceration: shattered kidney • Vascular: renal pedicle or avulsion

Note: Advance one grade for bilateral injuries up to grade 3

Diagnosis

History and physical examination

After the initial resuscitation, a quick history should be taken and physical examination done. The mode of injury may suggest the possibility of renal trauma which is commonly associated with major deceleration event (fall from height and high speed vehicular accident) or a direct blow to the flank. In penetrating injuries, the size and caliber of the weapon should be enquired about.

A history of pre-existing hydronephrosis, renal cyst, calculus, and tumor or horseshoe kidney should be sought since this makes renal injury more likely, even with minor trauma [2]. Similarly, presence of a solitary functioning kidney will influence the subsequent management of renal trauma.

Hemodynamic stability of the patient should be decided upon at the earliest. Findings on physical examination such as hematuria, flank pain, flank abrasions and ecchymoses, fractured ribs, abdominal tenderness, distension, or mass could indicate possible renal involvement. A thorough examination should be made of the thorax, abdomen, flanks, and back for penetrating wounds.

Laboratory evaluation

Urinalysis is the basic test in the evaluation of suspected renal trauma patients. Presence of microscopic (>5 RBCs/ hpf) or gross hematuria is an indicator of urogenital tract injury. However, hematuria does not correlate well with the degree of renal injury. Major renal injury, such as disruption of the uretero-pelvic junction, renal pedicle injuries or segmental arterial thrombosis may occur without hematuria. Hematuria that is out of proportion to the history of trauma may suggest pre-existing renal disease.

The decrease in hematocrit and the requirement for blood transfusions is an indirect sign of the rate of blood loss and, along with the patient's response to resuscitation, is valuable in the decision-making process. Serum creatinine level within 1 hour of trauma reflects the pre-existing renal function.

Imaging

The need for imaging is based on the mechanism of injury and hemodynamic stability. Blunt trauma patients with macroscopic or microscopic hematuria with hypotension (systolic blood pressure < 90 mmHg) should undergo radiographic evaluation. Radiographic evaluation is also recommended for all patients with a history of rapid deceleration injury and/or significant associated injuries [3]. All patients with any degree of hematuria after penetrating abdominal or thoracic injury also require urgent renal imaging [4].

- **Ultrasonography:** Though this is usually the first imaging modality used, its usefulness has been questioned. There may be difficulty in obtaining a proper acoustic window in a trauma patient. The extent and depth of renal lacerations are not adequately assessed by ultrasound. Additionally, it does not provide information about renal function or urine leak. Some of these limitations are overcome if contrast enhanced ultrasonography is used. Ultrasonography is useful in following up stable renal injury patients [5]. When used in the initial assessment of injured patients, it helps in identifying those patients of renal injury who need further radiological evaluation.
- **Computed tomography:** CECT is the gold standard for evaluation of stable patients with renal trauma. It provides superior anatomical details including depth and location of renal lacerations, contusions, devitalized segments and presence of associated abdominal and pelvic injuries. It also establishes the presence and function of contralateral kidney and demonstrates any existing renal anomaly. Absence of enhancement on contrast administration or presence of parahilar hematoma suggests renal pedicle injury. However, it is difficult to directly visualize renal vein injury. Standard CECT scans may miss collecting system injury which is best detected by repeating the scan 10-15 minutes after contrast injection [6].
- **Standard IVP:** Standard IVP should be used only if other imaging modalities are not available. Non-functioning kidney suggests extensive trauma or renal pedicle injury. Extravasation of contrast indicates severe injury with disruption of collecting system. Delayed excretion, incomplete filling or distortions of pelvicalyceal system are other findings of renal injury. In order to grade renal injury, the IVP should include nephrotomogram phase.

- **One shot IVP:** Unstable patients with blunt trauma selected for immediate operative intervention (and thus unable to have a CT scan) should undergo one-shot IVP in the operating theatre. The technique consists of a bolus intravenous injection of 2mL/kg of radiographic contrast followed by a single plain film taken after 10 minutes. It provides important information concerning the injured kidney, as well as the presence of a normal functioning kidney on the contralateral side. One shot IVP is of no significant value in assessing penetrating abdominal trauma patients who undergo exploratory laparotomy for associated intra-abdominal injuries, and should be reserved only for patients with a flank wound or gross hematuria following penetrating trauma [7].
- **Magnetic resonance imaging:** It is accurate in detecting peri-renal hematomas, renal lacerations and pre-existing anomalies but does not detect urine extravasation. MRI is not the first choice in managing patients with trauma because it requires a longer imaging time and limits access to patients when they are in the magnet during the examination. MRI is therefore useful in renal trauma only if CT is not available.
- **Angiography:** The most common indication for arteriography is non-visualization of a kidney on IVP after major blunt renal trauma when a CT is not available. It is the test of choice for evaluating renal venous injury. Angiography is also indicated in stable patients to assess pedicle injury if the findings on CT are unclear, and for those patients who are candidates for radiological control of hemorrhage [8].

Treatment

Indications for exploration

The aim in management of renal trauma is to minimize mortality and morbidity and preserve renal function. Irrespective of the mode of injury, hemodynamic instability due to renal hemorrhage is an absolute indication for renal exploration [9]. Grade 5 renal injury in a stable patient and expanding or pulsatile peri-renal hematoma seen at laparotomy for associated injuries are other indications for exploration. Following grade 1-4 blunt renal trauma, stable patients should be managed conservatively with bed rest, prophylactic antibiotics, and continuous monitoring of vital signs until hematuria resolves. Following grade 1-3 stab and low-velocity gunshot wounds, stable patients, after complete staging, should be selected for expectant management.

Operative management

The goal of renal exploration following renal trauma is control of hemorrhage and renal salvage. The approach is trans-peritoneal with early control of renal pedicle by placing the incision over aorta, just medial to inferior mesenteric vein. Temporary occlusion of the pedicle during the exploration of kidney reduces blood loss without increasing post-operative morbidity [10]. Renorraphy or partial nephrectomy is used to manage parenchymal laceration. Attempt should be made for a watertight closure of collecting system. Raw areas should be minimized by using renal capsule, omentum or fibrin glue. Repair of Grade 5 renal injury is rarely successful and nephrectomy is usually the best option, except in case of a solitary kidney. Retroperitoneum should be drained following renal exploration.

Non-operative management

All grade 1-3 blunt and penetrating injuries in stable patients can be managed conservatively with bed rest, hydration and antibiotics. The majority of patients with grade 4 and 5 renal injuries presents with major associated injuries, and consequently experience high exploration and nephrectomy rates. Persistent bleeding represents the main indication for renal exploration and reconstruction. Of late, the trend is to adopt a conservative approach in higher grade of injury, provided the patient is stable, the injury is well defined and there is no other indication for exploration.

Post-trauma care and follow up

Repeat imaging is recommended for all hospitalized patients within 2-4 days of significant renal trauma, especially in cases of fever, flank pain, or falling hematocrit [11]. Nuclear scintigraphy before discharge from the hospital is useful for documenting functional recovery. Within 3 months of major renal injury, patients' follow-up should involve physical examination, urinalysis, individualized radiological investigation, serial blood pressure measurement and serum determination of renal function. Long-term follow-up should be decided on a case-by-case basis but should at the very least involve monitoring for renovascular hypertension.

Complications

Early complications occur within the first month after injury and can be bleeding, infection, peri-nephric abscess, sepsis, urinary fistula, hypertension, urinary extravasation, and urinoma. Delayed complications include bleeding, calculus formation, chronic pyelonephritis, hypertension, arteriovenous fistula, hydronephrosis, and pseudoaneurysms. Peri-nephric abscesses are best managed by percutaneous drainage. Delayed bleed and arterio-venous fistula are managed by angiographic embolization. Treatment of hypertension is required if it persists, and could include medical management, excision of the ischemic parenchymal segment, vascular reconstruction, or total nephrectomy. Urinary extravasation after renal reconstruction often subsides without intervention as long as ureteral obstruction and infection are not present. Persistent urinary extravasation from an otherwise viable kidney after blunt trauma often responds to stent placement or percutaneous drainage.

Special cases

- **Pediatric renal trauma:** Children are more prone to renal trauma as the kidneys are lower in the abdomen, less well-protected by the lower ribs and muscles of the flank and abdomen, more mobile, have

less protective peri-renal fat and are proportionately larger in the abdomen than in adults. Hypotension is a less reliable sign and significant injury can be present despite stable blood pressure. Indications for radiographic evaluation of children suspected of renal trauma include

- blunt and penetrating trauma patients with any level of hematuria;
- patients with associated abdominal injury regardless of the findings of urinalysis;
- patients with normal urinalysis who sustained a rapid deceleration event, direct flank trauma or a fall from a height.

- **Iatrogenic vascular injury:** These are reported after renal angioplasty and stenting and include arterio-venous fistulae, pseudoaneurysms, dissection or contrast extravasation. Treatment includes balloon tamponade followed by bypass grafting or nephrectomy, if required. Renal vein injuries during elective abdominal operations represent serious complication with significant morbidity. Most patients with operative venous injuries have partial lacerations that can be managed with relatively simple techniques, such as venorrhaphy. Patch angioplasty with autologous vein or PTFE graft may be required if venorrhaphy is not possible.
- **Renal injury in polytrauma patient:** Polytrauma patients with associated renal injuries should be evaluated on the basis of the most threatening injury. In cases where surgical intervention is chosen, all associated injuries should be evaluated simultaneously. The decision for conservative management should consider all injuries independently.
- **Percutaneous renal procedures:** Procedures like percutaneous nephrostomy, percutaneous nephrolithotomy and renal biopsy are occasionally associated with significant complications such as hematuria, arteriovenous fistula and urinary leak can most often be managed by arterial embolization and stenting.

In conclusion it can be said that an increasing number of published reports supports the conservative management of grade 1-4 blunt renal parenchymal injuries in the absence of hemodynamic instability of renal origin. Even some select patients with grade 5 parenchymal injuries can undergo an attempted trial of conservative management. Penetrating renal injuries can be managed non-operatively in selected patients who are hemodynamically stable. Renal imaging should be used to rule out associated injuries and ureteral and renal pelvis injuries that might require operative intervention. Low-velocity gunshot wounds might allow expectant management better than high-velocity wounds. Damage control can be used in the poly-trauma patient to aid in renal salvage. The ultimate goal of conservative management is to minimize the incidence of negative explorations and unnecessary repairs and decrease iatrogenic nephrectomy rates, without increasing morbidity or mortality.

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Gastric Outlet Obstruction

Jainendra K. Arora

Introduction

Gastric outlet obstruction (GOO, also known as pyloric obstruction), it is a consequence of any disease process that produces a mechanical obstruction to gastric emptying. The causes of GOO are divided into benign and malignant causes. Earlier when peptic ulcer disease (PUD) was more prevalent, benign causes were the most common, now more commonly obstruction is secondary to malignancy, an increase in the number of cases of GOO seems to be noted secondary to malignancy, this is possibly due to improvements in cancer therapy, which allow patients to live long enough to develop this complication.

Etiology

The bengin causes of gastric outlet obstruction (GOO) includes PUD, gastric polyps, ingestion of caustic, pyloric stenosis, congenital duodenal webs, gallstone obstruction (Bouveret syndrome), pancreatic pseudocysts, and bezoars.

Bezoars are collections of indigestible material that accumulate in the GI tract and are most often located in the stomach. Bezoars may result from gastroparesis, altered physiology, including delayed gastric emptying or decreased acid production because of previous gastric surgery, or even ingestion of large amounts of indigestible material.

PUD manifests in approximately 5% of all patients with GOO ulcers within the pyloric channel and first portion of the duodenum usually are responsible for outlet obstruction. Obstruction can occur in an acute setting secondary to acute inflammation and edema or, more commonly, in a chronic setting secondary to scarring and fibrosis.
Within the pediatric population, congenital hypertrophic pyloric stenosis constitutes the most important cause of GOO.

Malignant causes includes
Pancreatic cancer is the most common malignancy causing GOO. Other tumors that may obstruct the gastric outlet include ampullary cancer, duodenal cancer, cholangiocarcinomas, and gastric cancer.

Gastroparesis is delayed gastric emptying in the absence of organic causes such as stricture, ulcer, tumor, superior mesenteric artery syndrome, or mechanical obstruction, and in the absence of nonorganic causes such as functional dyspepsia, rumination syndrome, cyclic vomiting syndrome, or bulimia/anorexia nervosa.

The most common causes of gastroparesis are diabetes, which accounts for about a third of cases, and idiopathic. Diabetic gastroparesis typically develops after diabetes has been present for more than 10years and patients have evidence for autonomic dysfunction.3 Other less common causes of gastroparesis include post- viral infection, postsurgical (especially with intended or inadvertent vagotomy), Parkinson disease, scleroderma, and pseudo-obstruction.

The diagnosis of gastroparesis is usually made after extensive testing to rule out other organic causes. The nuclear medicine solid-phase gastric emptying test is the current gold standard for the diagnosis of gastroparesis, in the absence of gastric outlet obstruction.

Clinical presentation

Nausea and vomiting that is non billous are the cardinal symptoms of gastric outlet obstruction. This vomiting usually occurs within 1 hour of taking meals.

Patients can also have symptoms of gastric retention, including early satiety, bloating or epigastric fullness, indigestion, anorexia, nauses, vomiting, epigastric pain, and weight loss. These patients are frequently malnourished and dehydrated and have a metabolic insufficiency. Weight loss is frequent when the condition approaches chronicity and is most significant in patients with malignant disease.

Physical examination often demonstrates the presence of chronic dehydration and malnutrition. A dilated stomach may be appreciated as a tympanic mass in the epigastric area and/or left upper quadrant.

These patients commonly have metabolic disturbance in the form of hypochloremic- hypokalemic metabolic alkalosis due to recurrent vomiting

They may also have succussion splash, may be audible on shaking the patient's abdomen.

If the obstruction is long standing they may have paradoxical aciduria because in initial stages bicarbonate is excreted along with sodium. So patients over a period becomes hyponatremic and gets further dehydrated. Now to save sodium kidney excrete potassium and hydrogen in preference leads to paradoxical aciduria and hypokalemia.

Because of alkalosis there is lowering in ionized calcium leading to tetany.

Investigations

- The various investigations include:
- Plain abdominal radiographs
- Upper GI contrast studies (Gastrografin or barium),
- CT scans with oral contrast
- Upper GI endoscopy can help visualize the gastric outlet and may provide a tissue diagnosis when the obstruction is intraluminal.
- In the presence of PUD, perform endsocopic biopsy to rule out the presence of malignancy.
- In the case of peripancreatic malignancy, CT scan-guided biopsy may be helpful in establishing a preoperative diagnosis.
- Needle-guided biopsy also may be helpful in establishing the presence of metastatic disease. This knowledge may impact the magnitude of the procedure planned to alleviate the GOO.

Treatment:

First line of management whatever is the cause, correction of acid base disturbance by starting intravenous isotonic saline with potassium supplementation and antisecretory agents alongwith nasogastric aspiration and lavage.

Perform standard preoperative evaluation in these patients. Correct fluid and electrolyte abnormalities prior to surgery.

Perform gastric decompression by NGT and suction and alert the anesthesiologist to the potential risk for aspiration upon induction.
Perform a preoperative nutritional evaluation and initiate appropriate nutritional therapy (i.e., TPN or enternal feedings via a percutaneous jejunostomy placed distal to the obstruction) as soon as possible. Maximizing preoperative nutrition can greatly reduce or eliminate postoperative complications related to delayed healing.

Acute ulcers associated with obstruction due to edema and/or motor dysfunction may respond to intensive antisecretory therapy and nasogastric suction. But most patients with significant obstruction from chronic ulceration will require some sort of more substantial measures.

In such cases H pylori eradication treatment or acid suppression treatment with endoscopic dilatation is the main stay of treatment now once malignancy is ruled out. Several attempts of dilatation, usually five are required for good long term results. However dilataion can have perforation as a complication.

The various surgical procedures performed for GOO due to PUD are vagotomy and antrectomy, vagotomy and pyloroplasty, truncal vagotomy and gastrojejunostomy, pyloroplasty..

While truncal vagotomy with antrectomy is the ideal treatment option reserved for refractory obstruction.

If the duodenum is inflamed or scarred which in most of the cases is scarred, in such cases truncal vagotomy and drainage is a preferred procedure.

The role of the laparoscopic approach in the treatment of GOO represent a valid form of treatment with low morbidity.

Management of malignant disease
The management of GOO secondary to malignancy is controversial of patients with periampullary cancer, 30-50% present with nausea and vomiting at the time of diagnosis. Most of these tumors are unrespectable (approximately 40% of gastric cancers and 80-90% of periampullary cancers). when tumors are found to be unresectable, 13-20% of patients eventually develop GOO before they succumb to their disease.

Gastrojejunostomy remains the surgical treatment of choice for GOO secondary to malignancy

Laparoscopic gastrojejunostomy is gaining popularity, comparison of laparoscopic GI anastomosis versus the open procedure have revealed less morbidity and mortality, shorter hospital stays, fewer blood transfusions, and faster GI transit recovery time.
There are reports of endoscopic transgastric approaches to create a gastrojejunostomy in a porcine model. As natural orifice transluminal surgery gains more widespread interest, these novel approaches may become more popular.

Self-expandable metallic stents also have been used for the treatment of GOO in a malignant setting.With the development of newer stents and delivery systerus, metallic stents may have a role in the nonsurgical treatment of gastroduodenal obstruction. Stents may allow the physician to avoid complicated surgical procedures. Currently, only the Wallstent has FDA approval for palliation in malignant gastroduodenal obstruction. Significant complications include the following malposition, misdeployment, tumor ingrowth or overgrowth, migration, bleeding, and perforation
There is clinical success rate of 80-90% with stents and restenting is reported to be required in only few patients. The covered metallic stents that have a lower incidence of tumor in uncovered stents versus a 10% rate of tumor in growth in covered stents has been reported. Further more, with the double stent technique, that is, simultaneous placement of both covered stents and uncovered stents, lower early restenosis rates have been achieved.

Several studies have been performed to compare the results of stenting versus surgical intervention. Survival rates are equivalent; however, costs, length of stay, and number of subsequent procedures are all decreased following stenting. In addition, a delay of gastric emptying and morbidity decrease with the use of metallic stents. These promising results suggest that stents may eventually replace surgery as palliative intervention for unresectable periampullary malignancies.

The role of prophylactic gastrojejunostomy in cases of malignant gastric outlet obstruction (GOO) is a question that has not been answered. Some surgeons argue that prophylactic gastrojejunostomy increase postoperative morbidity, primarily due to delayed gastric emptying

For patients with advanced gastric cancer, resection and bypass are the two most commonly used surgical techniques for palliation. Although resection may offer a greater chance at disease-free survival, the specific circumstances of each patient may dictate the need for bypass. Overall, if resec- tion can be performed safely, the functional outcome is better and it may help to slow the continued spread of disease through removal of the primary tumor. However, some patients may be unable to tolerate, both anatomi cally and physically, a resection and the need for a gas- trojejunal bypass procedure could be required.

Endoscopic techniques, as mentioned earlier, are options for resection for certain patients. The same holds true for their use in the palliative setting. Lasers for recan- nulization and stenting can be used in select cases to improve symptoms, but none offer any benefit in terms of survival. Their use is mostly limited to patients with obstructive symptoms and in need of less invasive tech- niques at palliation

Once a diagnosis of Bezoar has been made, treatment may consist of medical management, endoscopic removal, or surgery. Dissolution therapy with papain, cellulase, or even cola has been described, albeit with variable results. Most bezoars require endoscopic therapy to fragment the bezoar and remove the pieces, with high success rates. Surgery is required if endoscopic removal is unsuccessful or if complications, such as bleeding, obstruction, or perforation, occur. Once a bezoar has been cleared, therapy aimed at prevention of recurrence should be instituted, and should include consideration for psychiatric assessment, if appropriate.

Pancreatic pseudocysts may become symptomatic as a result of the mass effect that they exert on other struc tures. Although duodenal obstruction is the most common manifestation of mechanical obstruction secondary to pseudocyst formation, obstruction of the stomach, esophagus, jejunum, and colon may be identified.

The preferred operative approach for most uncomplicated pseudocysts requiring surgical intervention is inter- nal drainage. The three standard options include cystojejunostomy to a Roux-en-Y jejunal limb, cystogas- trostomy, and cystoduodenostomy. Cystojejunostomy is the most versatile technique of operative drainage and is particularly appropriate when a pseudocyst is located at the base of the transverse mesocolon and is not adherent to the posterior gastric wall. Cystogastrostomy is a faster and less technically demanding procedure that is used when the pseudocyst is adherent to the posterior wall of stomach.

In addition to the conventional open techniques of internal drainage of pancreatic pseudocysts, several centers have performed laparoscopic drainage procedures. Large retrogastric pseudocysts can be drained internally by endogastric approaches, as well as by laparoscopic transgastric and laparoscopic extragastric approaches.
Laparoscopic cystojejunos- tomy can be performed in select patients for better dependent drainage.
Natural Orifice Transluminal Endoscopic Surgery (NOTES) cystogastrostomy has recently been described as an endoscopic method to achieve the technical results similar to open and laparoscopic cystogastrostomy surgery.

Gastroparesis is treated by correcting fluid and elec- trolyte abnormalities, nutritional deficiencies, identifying and treating underlying causes, and suppressing the symptoms of nausea and vomiting. Diets are changed, using softer solid foods, more liquid supplements, and smaller, more frequent meals. If the patient cannot maintain satisfactory body weight, total parenteral nutrition may be necessary. In a diabetic patient, tight glucose control should be achieved, as hyperglycemia has been shown to worsen gastroparetic symptoms. Hyperglycemia may impair both antral contractions and antropyloric coordination. The mainstay of medical treatment for gastroparesis is the use of both antiemetic and prokinetic.

Complications
Operative complications in patients undergoing surgery for gastric outlet obstruction (GOO) often are related to the nutritional status of the patients. Commencing nutritional support upon recognition of the presence of GOO is important. If surgery is anticipated, delaying the surgery or any intervention until TPN has been instituted for at least 1 week is often prudent.

Acute intervention may be technically difficult because of significant gastric dilatation and gastric wall edema. This circumstance may increase the rate of anastomotic leak. On occasion, delaying surgical intervention for several days while the stomach is decompressed by nasogastric suction may be prudent. Alert patients undergoing gastric resection for benign or malignant disease to the possibility of well-known postgastrectomy syndromes, such as dumping, alkaline gastritis, and afferent loop syndrome. Severe symptoms may be present in 1-2% of patients.

Follow-up
Closely monitor patients after surgery and upon discharge. After relief of gastric outlet obstruction, patients may continue to experience gastric dysmotility and may require medication to stimulate gastric emptying and motility. In patients with malignancy, the potential for progressive and recurrent disease always remains. These patients should be monitored by a surgeon or an oncologist.

Closely monitor patients whose treatment consisted of balloon dilatation because most of these patients require subsequent dilatations to achieve satisfactory results.

Neonatal intestinal obstruction

Anup Mohta

Intestinal obstruction is one of the most common surgical emergencies in newborns and is a major cause of morbidity and mortality. . The diagnosis can be made in the prenatal period using fetal ultrasonography or within the first 30 days of life based on clinical signs and symptoms. It is due to either an anatomical lesion (e.g. atresia) or functional disorders such as Hirschsprung's disease. If one considers gastrointestional tract from oesophagus to anal opening, common sites of intestinal obstruction include the following:

a) Oesophagus: Oesophageal atresia with or without tracheo-esophageal fistula
b) Stomach: Antral web/pyloric stenosis
c) Duodenum: Duodenal atresia; malrotation with volvulus
d) Jejunum: Jejunal atresia
e) Ileum: Ileal atresia
f) Colon: Colonic atresia ; Hirschsprung’s disease
g) Rectum and anus: Anorectal malformations

Esophageal atresia and anorectal malformations are beyond the scope of this presentation.

Etiology

Some of the above conditions are associated with the following factors while many conditions do not have a definitive etiology.

a) Genetic factors: Duodenal atresia and its association with trisomy 21
b) Environmental exposure in utero may lead to VACTERL syndrome (vertebral anomalies, anal atresia, and cardiac, tracheoesophageal, renal/radial, and limb anomalies)
c) Thromboembolic event(s) may cause mesenteric vascular accident leading to atresia.

Causes of intestinal obstruction could be classified as

a) Intrinsic: The obstructed bowel may be in continuity along with a web as in duodenal atresia; or it may be discontinuous bowel along with a gap in the mesentery
b) Intraluminal: Obstruction may occur by thick meconium ie. meconium ileus
c) Extraluminal: There may be compression by a band (malrotation, Meckel's diverticulum) or by a duplication cyst, twisting by a volvulus, or kinking in an incarcerated internal or external hernia

Diagnosis:

Prenatal diagnosis can be made by ultrasonography which may show polyhydramnios; family history ie cystic fibrosis, and conditions and syndromes which have higher incidence of associated intestinal obstruction. If a prenatal diagnosis of any anomaly leading to intestinal obstruction is diagnosed, the mother should be transferred to a centre where facilities of surgery for neonate are available.

Cardinal signs of neonatal intestinal obstruction include:

a) History of maternal polyhydramnios
b) Feeding intolerance
c) Bilious vomiting
d) Abdominal distention
e) Delayed passage of meconium

Imaging is a mainstay of the diagnosis of intra-abdominal pathology and should be readily performed in a neonate with suspected intestinal obstruction. Noninvasive techniques, such as plain radiography and ultrasonography are usually adequate to diagnose intestinal obstruction but occasionally a Gastrografin (diatrizoate) enema may be required and is both diagnostic and therapeutic. The clinicians must ensure the infant is well hydrated prior to the contrast examination.

Double bubble appearance in duodenal atresia is pathogomic. Intestinal atresias present with multiple air-fluid levels, and the number of levels may suggest the site of obstruction. Intra-abdominal calcification is suggestive of meconium ileus/peritonitis.

Computed tomography (CT) scans may be useful in the diagnosis of malrotation/volvulus. Normally, the superior mesenteric artery lies to the left of the superior mesenteric vein and reversal of this spatial relationship suggests malrotation with midgut volvulus.

General management:

Intestinal obstruction leads to fluid loss and an electrolyte imbalance due to vomiting, in cases of proximal obstruction, or third-space sequestration of fluid within the intestine's lumen, in more distal obstructions. It is necessary to treat these life-threatening consequences of the obstruction, while simultaneously identifying and treating the underlying pathology to minimize mortality and morbidity. this would include

a) Gastric intubation and decompression.
b) Respiratory and cardiovascular support to maintain hemodynamic stability.
c) Administration of intravenous antibiotics. As the bowel distends in response to increased intraluminal pressure, perfusion to the intestine diminishes leading to bacterial invasion. In addition, bacterial overgrowth occurs in association with intestinal obstruction.

Duodenal atresia

Duodenal atresia results from defective canalization of the solid duodenal anlage, wherein vacuoles form and coalesce, creating a lumen. This process occurs during the eighth week of gestation. It could lead to

a) There may be a membranous obstruction, which is usually located near the ampulla of Vater; the dilated proximal duodenum and diminutive distal duodenum are in continuity. Mucosal webs may be fenestrated, creating a partial obstruction.
b) Sometimes, the obstructing web protrudes into the distal lumen like a "wind sock"; the etiology of the obstruction may not be immediately apparent to the surgeon when the duodenum is opened through the transition point.
c) There may be discontinuity, with a gap of varying lengths, between the dilated proximal duodenum and the hypoplastic distal duodenum.
d) An annular pancreas may denote the site of the obstruction without being the actual cause of the obstruction.

Malrotation

In malrotation, the proximal and distal ends of the midgut, the duodenum and the cecum, are bound to one another around the superior mesenteric vessels by peritoneum, termed "Ladd bands" .These peritoneal bands normally form the ligament of Treitz, securing the duodenojejunal junction to the retroperitoneum in the left upper quadrant and the ascending colon to the retroperitoneum along the right lateral aspect of the peritoneal cavity. In malrotation, their ectopic course partially obstructs the duodenum and creates a mesentery with a narrow base, which may lead to volvulus of the midgut.

Jejunoileal atresia
Jejunoileal atresia is an accident of fetal development and not a preprogrammed embryonic anomaly. The extent of intestinal loss and the appearance of the atretic intestinal segment varied according to the timing and degree of the disruption of the mesenteric blood supply.
Atresias may be single or multiple. Interruption of the proximal tributaries of the superior mesenteric vasculature results in a proximal atresia; the distal intestine survives because of retrograde blood flow from the ileocolic vessels. It may be associated with gastroschisis or intrauterine intussusception.

Meconium ileus
Meconium ileus is associated with cystic fibrosis, an autosomal recessive condition characterized by abnormalities in cellular membrane physiology and chloride ion transport that contribute to progressive respiratory failure, derangements in cellular secretory patterns, and diminished mucosal motility. 10-20% of the newborns with cystic fibrosis present with meconium ileus.

Meconium plug syndrome refers to inspissated meconium that obstructs the colon.Conditions that predispose to dysmotility of the neonatal bowel (maternal preeclampsia, maternal diabetes mellitus, maternal ingestion of magnesium sulfate, prematurity, sepsis, and hypothyroidism) may be responsible for the formation of the meconium plug. A contrast enema can be both diagnostic of and therapeutic for this condition.

Hirschsprung disease
Propagation of peristaltic waves through the intestine requires sequential contraction and relaxation, which is mediated by neuroenteric ganglion cells located in the submucosa. Neural crest cells migrate caudally along the mesentery and reach the rectum around the tenth gestational week. The embryonic migration of ganglion cells is arrested proximal to the rectum in Hirschsprung's disease—usually the sigmoid colon. Barium enema is helpful and the "transition point" is determined by biopsy and ultimately becomes the "pull-through" segment, the neorectum, when the definitive operation is performed. anorectal manometry, if available, contributes to diagnosis.

Surgical Management

a) **Duodenal atresia:** Correction of duodenal atresia requires identifying the cause of the obstruction (ie, atresia, annular pancreas, or web), locating the duodenum above and below the obstruction, and bring the two lumens into continuity. This generally requires duodenostomy

b) **Malrotation with volvulus:** Malrotation with midgut volvulus is a true surgical emergency. Delay in diagnosis may result in catastrophic loss of the bowel and death. In patients with irreversible ischemia, the entire midgut becomes non-viable, and the child cannot survive without an intestinal transplant.

Ladd's procedure is done for malrotation/volvulus. Bowel is exteriorized; derotated antclockwise; any bands are divided, and base of the mesentery is widened. involves evisceration of the small intestine. The bowel is returned to the abdomen- duodenum to the right, colon to the left, midgut in the center—so as to spread out the small bowel mesentery. The appendix is removed, because its new location is the left upper quadrant, where a future diagnosis of appendicitis would be problematic.

c) Jejunoileal atresia: Surgical treatment of jejunoileal atresia involves resection and primary anastomosis of the proximal and distal segments of the intestine. A diverting enterostomy may be rarely required.Resection or tapering of the proximal dilated segment is occasionally necessary to limit the dysmotility that occurs in grossly dilated bowel.

d) Meconium ileus: Calcification on scout radiography indicates that an intestinal perforation occurred in utero and spontaneously sealed; if not, the extruded meconium is walled off by adjacent intestine to form a pseudocyst. Laparotomy is undertaken with drainage of the meconium pseudocyst and identification of the site of the perforation, which is converted to an enterostomy. In uncomplicated meconium ileus, an enterotomy with irrigation and evacuation of the obstructing meconium may successfully relieve the intraluminal obstruction. In other patients, an ostomy for diversion and access for proximal and distal irrigation with N-acetylcysteine may be necessary.

e) Meconium plug syndrome: Operative intervention is indicated in infants with meconium plug syndrome only if diatrizoate enemas are unsuccessful in loosening the whitish meconium plug, thereby permitting the baby to evacuate the black and tarry meconium.

f) **Hirschsprung disease:** Treatment of Hirschsprung enterocolitis includes bowel irrigations and decompression, administration of antibiotics, and fluid resuscitation. Colostomies expeditiously decompress the bowel and allow affected babies to resume feedings with minimal delay. Pull-through procedures are usually performed at age 3-6 months.

If there is no history of enterocolitis, pull-through procedures are performed during the newborn period. commonly performed procedures include Modified duhamel's, endorectal pull through ie soave's and Swenson's procedure. Traditionally, these procedures were performed as staged procedure ie intial colostomy and levelling biopsies, pull through and then colostomy closure. Present trend is to perform single stage procedures with the assistance of frozen section biopisy. Laparoscopy assisted procedures are being done increasingly.
Innovations in the treatment of Hirschsprung disease include minimally invasive techniques, such as the transanal laparoscopic pull-through procedures.

Post operative management:
In the postoperative period, derangements in fluid balance, glucose metabolism, and respiratory status may occur. Many infants following laparotomy have third-space fluid sequestration, and their intravenous fluid requirements may be increased.

The adequacy of fluid resuscitation can be monitored by by checking the patient's heart rate and blood pressure, peripheral perfusion (capillary refill), and urine output. Serum electrolyte levels should be closely monitored, because fluid shifts between the intravascular and extravascular spaces are common and require prompt management by appropriate fluids.

Continuous post-operative gastric decompression to give rest to bowel and protect anastomotic site is necessary. Analgesic management is of paramount importance.

The duration of antibiotic therapy depends on whether there was contamination of the peritoneal cavity and are not generally required beyond the immediate preoperative period.. Total parental nutrition (TPN) is indicated until return of bowel function permits delivery of adequate enteral nutrition. A period of trophic feeding may stimulate mucosal regeneration, and a predigested or elemental formula may be better tolerated. Cardiovascular and coagulation complications, such as shock and disseminated intravascular coagulation, may occur with intestinal ischemia or necrosis. Management of these issues may also challenge the clinician during the postoperative period.

Benign Biliary Stricture

Nilesh Patil, Neeraj Goel, Sundeep Singh Saluja, P K Mishra

Introduction

Benign biliary stricture is a feared complication of many surgical and endoscopic procedures. If improperly treated, it may lead to cholangitis, portal hypertension (PHTN) & cirrhosis, which can increase the morbidity and mortality. Treatment of this disease is challenging as well as rewarding, as most of the patients are in younger age group. The key determinants for favorable long term outcomes are early detection, appropriate evaluation and management at the experienced centers.

Causes of Benign Biliary Stricture[1]

A list of causes of benign biliary stricture is as underneath. By far, the most important cause of biliary stricture is an injury to bile duct during cholecystectomy. Bile duct injury may lead to loss of reputation & may also lead to litigation.

Incidence: Bile duct injuries are reported in 0.2 to 0.3 % of open cholecystectomy and 0.4 to 1.3% of laparoscopic cholecystectomy in larger studies[2,3]. Actual incidence may be higher. As compared to open surgery, bile duct injuries sustained during laparoscopic cholecystectomy are usually closer to the porta hepatis, more commonly associated with persistent bile leak and more likely to present earlier. It is important to note that not all injuries lead to benign biliary stricture. Stricture requiring intervention will develop in 30-60% of patients.

Mechanism of injuries:

Laparoscopic cholecystectomy is one of the commonest surgical procedures in the world. Higher injuries in laparoscopic cholecystectomies may be due to the learning curve and inherent problems of laparoscopic approach as even experienced laparoscopic surgeons may inflict some of these. Mostly, it is due to wrong interpretation of the biliaryanatomy[4]e.g. mis-identification of the common bile duct or aberrant right sectoral duct as the cystic duct. An important aspect in the prevention is to remember that there is no normal biliary anatomy. If the clip does not fit across the entire width of the cystic duct, the surgeon must consider the possibility that the structure about to be divided is not the cystic duct but the common duct. Upward traction on the gallbladder, with insufficient lateral traction on the infundibulum, fails to open Calot's triangle adequately. This causes the cystic duct and common hepatic duct to become aligned within the same plane. Classical laparoscopic injury consists of removal of a portion of CBD with or without clipping of the proximal hepatic duct[5]. Excessive dissection of CBD may disrupt its blood supply and lead to late stricture. Operating in patients with inflammation or choledocho-duodenal fistula orMirizzi's syndrome is also potentially hazardous. Plane of dissection away from gallbladder wall into the liver bed may injure Right hepatic duct. Injudicious use of electrocautery for dissection or bleeding control is hazardous.

I. Congenital strictures **A.** Biliary atresia
II. Bile duct injuries **A.** Postoperative strictures **1. Cholecystectomy or common bile duct exploration** ***2.*** *Biliary-enteric anastomosis* **3.** Hepatic resection **4.** Portocaval shunt **5.** Pancreatic surgery **6.** Gastrectomy ***7.*** *Liver transplantation* **B.** Strictures after blunt or penetrating trauma **C.** Strictures after endoscopic or percutaneous biliary intubation
III. Inflammatory strictures **A.** Cholelithiasis or choledocholithiasis ***B.*** *Chronic pancreatitis* **C.** Chronic duodenal ulceration **D.** Granulomatous : tuberculosis **E.** Parasitic infections, abscess **F.** Recurrent pyogenic cholangitis **G.** Autoimmune cholangiopathy
IV. Primary sclerosing cholangitis
V. Radiation-induced stricture
VI. Papillary stenosis
VII. Ischemic : Portal biliopathy, Hepatic artery thrombosis/stenosis, vasculitis

Role of intra operative cholangiography in prevention of bile duct injury is still controversial. But, there is evidence that it can identify the biliary injury more often when it occurs. It is not practiced by most and should be performed carefully to avoid additional injury to the biliary tree.

Classification:

Bismuth's classification[6] (Fig no. 1)is the most accepted classification of biliary injuries, as it is excellent in terms of outcome of bile duct injury and for planning the operative repair. Based on the level of injury, it stratifies the patients of established biliary stricture.

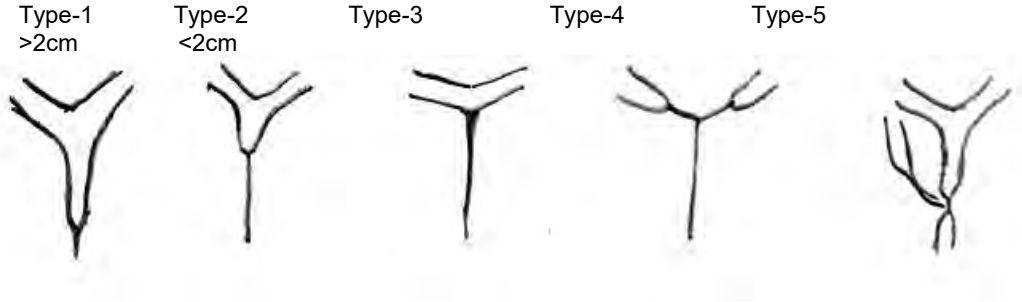

Figure 1 Bismuth's classification

Strasberg classified bile duct injuries from A to E[7] (Fig no. 2) It takes into consideration the entire spectrum of injuries (especially bile leaks), which is the major lacuna of Bismuth's classification. Type A is minor leak still in continuity with CBD, such as from cystic duct stump or injury to duct of Luschka. Type B is ligation of right aberrant sectoral duct. Type C is transection of right aberrant sectoral duct without occlusion reflecting the leak of bile. Type D is a lateral injury to bileduct. Type E is bile duct stricture classified as per Bismuth from E1 to E5. Although widely used, both these classification do not factor in the associated vascular injury, presence of sepsis or cholangitis, pattern of presentation, time since injury, presence of portal hypertension, atrophy/hypertrophy complex or any previous repairs. Several other classifications have been proposed like Hannover, Amsterdam, Neuhaus, Stewart – Way and ATOM (anatomic, time of detection, mechanism). Each has its drawbacks and is not used extensively like Strasberg – Bismuth system.

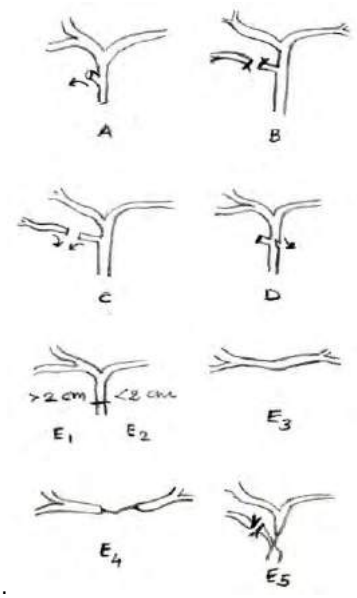

Figure 2 Strasberg classification

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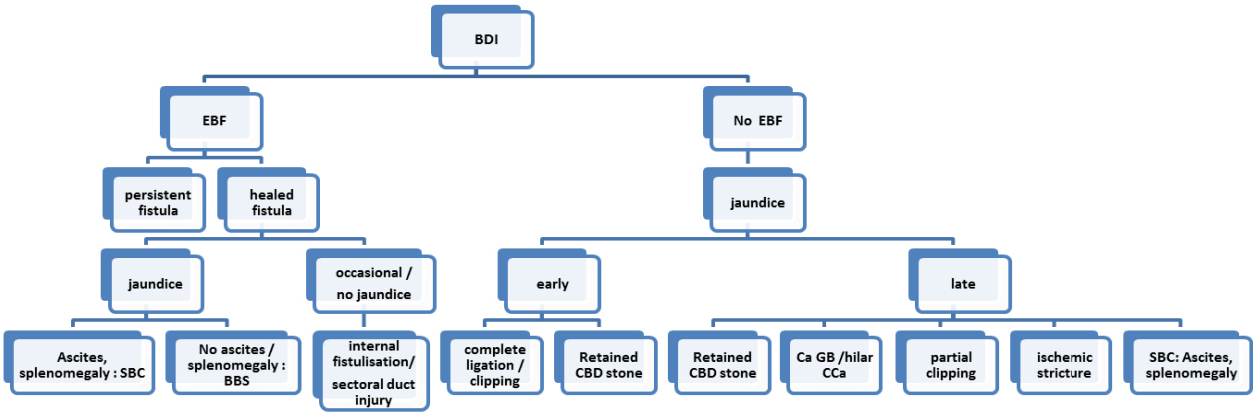
Presentation

Some of these injuries may be obvious intra-operatively (First Category). Experienced help should be sought in dealing with these. Others may present later with biliary strictures with or without external biliary fistula. Any patient, who does not recover normally after cholecystectomy or develops mild jaundice, should be suspected for bile duct injury. Initial signs may be subtle, such as malaise, mild fever, uneasiness or tachycardia. Patients with bile duct leaks usually present early with signs of sepsis or general illness (2nd category). If the drain is in place, bile leak is obvious (3rd category). Patients with complete cut off also present early with progressive jaundice (4th Category). Fifth category of patients is of those, who have partial injuries which gradually present over next few months. These also include patients with leak which have stopped with constriction of the bile duct. Neglected cases present with secondary biliary cirrhosis. About 70% of injuries have presented by 6 months. Some of these may have recurrent cholangitis, fever, pruritus or unexplained malaise and weakness. During examination, tender hepatomegaly may be seen in those having long standing obstruction, cholangitis or abscess. Presence of splenomegaly should alert the surgeon for portal hypertension. This may arise due to concomitant vascular injury, secondary biliary cirrhosis, recurrent cholangitis or coexistent liver disease. Icterus and signs of pruritus are usually present.

It can be summarized as below



Pathological consequences

Portal hypertension: Approximately 15-20% patients with biliary stricture can develop portal hypertension secondary to portal fibrosis, portal vein injury and/or underlying liver parenchymal disease. As these patients with portal hypertension have a hospital mortality of 25- 40%, documentation with liver biopsy is must for both

management and medico legal purpose. It has been found that patients of biliary stricture usually have latent portal hypertension without clinical, radiological or endoscopic evidence of portal hypertension. Presence of portal hypertension increases the complexity of surgery and post-operative morbidity. Shunt surgery may be required in these patients before considering definitive repair for biliary stricture. Portal pressures normalizes after Biliary decompression[9].

Fibrosis: The high concentration of bile salts in the biliary canaliculi incite a inflammatory process resulting in fibrogenesis which is the deposition of collagen and other extracellular matrix proteins[8]. Untreated biliary stricture can cause secondary biliary cirrhosis, it rarely results in typical features of cirrhosis. In advanced cases, there is marked fibrosis with well-preserved lobular structure. Though it takes several years to manifest these pathological features, it can occur within two years of development of
stricture. After biliary decompression, these pathological changes are potentially reversible and the liver function gradually normalizes. If patient develops clinical features of liver failure- like spider angiomata or encephalopathy, preexisting liver parenchymal disease should be ruled out.

Atrophy: In view of prolonged asymmetric involvement of biliary ducts and associated vascular injury, there usually develops a lobar atrophy with compensatory hypertrophy of the remaining liver. Atrophy-hypertrophy complex may also develop due to secondary biliary cirrhosis. It results in rotational deformity and anatomical changes in the hilar area which influence the operative approach for these patients. In addition, it increases the chances of recurrent strictures. Usually in long standing benign biliary strictures, there is atrophy of right lobe with gross hypertrophy of left lobe.

Investigations
Biochemical parameters: Liver function tests usually show evidence of cholestasis with fluctuating serum bilirubin level. When elevated, serum bilirubin is usually below 10 mg/dL, unless secondary biliary cirrhosis has developed, or there is complete cut off. Serum alkaline phosphatase is usually elevated. Serum aminotransferase levels can be normal or minimally elevated except during episodes of cholangitis. If advanced liver disease exists, hepatic synthetic function can be impaired, with lowered serum albumin and a prolongation of prothrombin time.

Radiologic Examination: Detailed pre operative evaluation of the type and extent of bile duct injury along with control of sepsis, cholangitis & bilioma optimizes the chances for favorable outcome. Abdominal ultrasound and computed tomography (CT) play an important initial role in the evaluation of patients with benign postoperative biliary strictures.

Ultrasonography abdomen as an initial, non-invasive study can assess for dilated intrahepatic radicals, biliomas and approximate level of biliary obstruction.. Along with Duplex imaging it can be used to assess the vascular injury, which occurs in about 12-32% of the patients[10]. This evaluation is very important in terms of successful outcome of the surgical biliary reconstruction, as biliary injury along with vascular injury has less favorable outcome. It also has medico-legal implications. Though it guides us initially, it is limited in assessing the extent and type of Biliary stricture. It is also operator dependent.

Contrast enhanced CT abdomen is probably best initial study to evaluate a case of Bile duct injury. Properly done CT helps in assessing any intra-abdominal collections, dilated intrahepatic radicals and associated cholangitic abscesses and also vascular injury with liver atrophy-hypertrophy complex. But CT is limited in evaluation of the type and extent of biliary stricture.

Both USG and CT help in guided drainage of biliomas.
The gold standard for evaluation of patients with established bile duct strictures is cholangiography. In the present era of MRCP, invasive procedures such as ERCP and PTC are less commonly used as they are associated with definite morbidity and mortality. PTC defines the anatomy of the proximal biliary tree that is to be used in the surgical reconstruction. Furthermore, PTC can be followed by placement of percutaneous transhepatic catheters, which can be useful in decompressing the biliary system either to treat or prevent cholangitis or to control an ongoing bile leak. These catheters can also be of assistance in surgical reconstruction and provide access to the biliary tree for non-operative dilation. Although some groups have advocated routine use of these stents, we have not felt the need for these for identification of ducts at GB Pant and Max Superspeciality Hospital. PTC plays an important role during dilatation of strictured hepaticojejunostomy.

ERC: For patients with lateral injury with bile leak, ERCP is both diagnostic and therapeutic in identifying the leak and biliary stenting at the same time, which may avoid surgical intervention. However, it has limited role in bile duct injuries where the biliary –enteric continuity is lost and also in patients with isolated duct injuries.

The development of **magnetic resonance cholangiopancreatography (Fig no.3)** has provided non-invasive technique that provides excellent delineation of the biliary anatomy without any IV contrast[11]. The quality of these images have led this technique to be advocated as the initial step in the evaluation of patients with suspected bile duct injuries. But, it doesn't have therapeutic potential. In addition, it can miss minor bile leakage and biliomas or metal clips may obscure the anatomical details of biliary radicles.

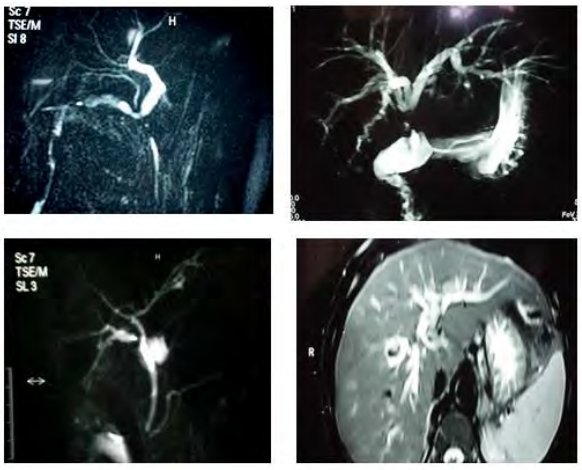


Figure no .3

In patients suspected of having early postoperative bile duct injury (especially when the drain is not put intra operatively), a radio-nucleotide biliary scan **(HIDA)** can confirm bile leakage. In addition, the biliary enteric continuity and the adequacy of external drainage of biliary fistula can be assessed. It can be useful in assessing patients with underlying liver disease to document liver dysfunction or obstruction to clearance and their relative contribution.

In patients with postoperative external biliary fistula, injection of water-soluble contrast media through surgically or percutaneously placed drain (**Fistulogram**) can often define the site of leakage and the anatomy of the biliary tree. This is a simple and easily available tool, which may give valuable information. But, at present, it has limited role and it may not show all the ducts or fail to delineate the biliary tree in the presence of biliomas. In addition, it may lead to cholangitis and should be sparingly used under antibiotic cover.

Distinction between benign and malignant stricture
Though it is very difficult to clearly distinguish the nature of stricture pre operatively, certain featurescan guide us in their differentiation.

	Benign	Malignant
Age	Usually young	Elderly
Duration of symptoms	Variable	Short duration
Cholangitis	Usual	Unusual, if no intervention
Depth of Jaundice	Variable usually <15mg%	>15mg% not unusual
Weight loss/Anorexia	Rare	Common
Imaging of stricture	Long stricture with regular margins & sectoral involvement	Short stricture, irregular margins, thick walled, more dilated proximal ducts with bile duct hyper enhancement in portal venous phase
Other features	History suggestive of difficult cholecystectomy, bile leak with normal histology of GB	May have other signs as gastric outlet obstruction, ascites etc.

Management
Theoretically, these patients can be managed by endoscopic, radiological percutaneous and surgical therapy. However, endoscopic and radiological methods, although very useful as adjuncts, are suitable for definitive management in very few cases. By and large these patients are young and surgery is the treatment of choice.

Preoperative management
Aim of the preoperative management is to precisely define the injury, determine any complications like atrophy-hypertrophy, portal hypertension, or secondary biliary cirrhosis. Associated renal complications, fluid and electrolyte imbalance, nutritional derangement, cholangitis, coagulopathy and sepsis(secondary to intra abdominal collections or biliary peritonitis) should be taken care of. Patients with severe cholangitis and sepsis are unlikely to respond to antibiotics alone and should be submitted to percutaneous or endoscopic drainage before surgery. Essentially the surgery should be done in optimum condition without any hurry about 8-12 weeks after the injury, especially in patients with concomitant external biliary fistula[12]. Early surgery is done in our cases in case it presents within 48hrs and in cases of complete cut off without bile leak or sepsis. Timing of surgical repair may not have any impact on the success rate if the repair is performed in an experience center in a patient with an optimal general condition. Adequate blood and fresh frozen plasma should be arranged. Type IV injuries may require hepatotomy and are generally more difficult. Similarly, patient with portal hypertension and secondary biliary cirrhosis may have difficult

operative course. At the time of consent these information should be discussed with relatives.

Operative Procedure

The first surgical reconstruction ("end-to-side" Choledochoduodenostomy) of iatrogenic bile duct injury was performed by Mayoin 1905. The first Roux-en-Y hepaticojejunostomy (HJ) was described by Monprofit in 1908. Dahl noted Roux-en-Y HJ for surgical treatment of bile duct injury in 1909. In 1954, Hepp and Couinaud described the hilar plate and long extrahepatic course of the left hepatic duct.

Restoration of bile flow is achieved by a bilio-enteric anastomosis. Rarely, when the stricture is in pancreatic or immediate supra-duodenal CBD, a choledocho-duodenostomy can also be constructed. Most often the reconstruction is by a Roux loop with hepaticojejunostomy. Requirements of a good bilioenteric anastomosis are:

1. Wide Anastomosis
2. Good vascular supply
3. Tension free anastomosis
4. Should drain all segments of the liver
5. Mucosa to mucosa anastomosis.

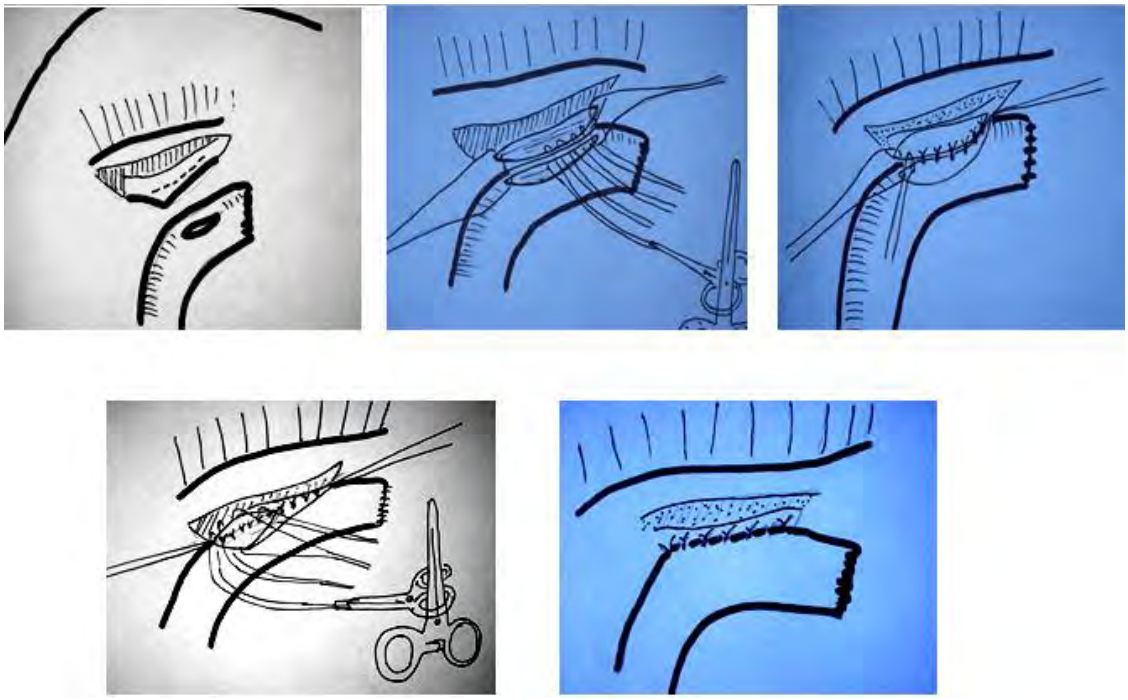


Figure no. 4

Access to proximal ducts is relatively easy in Bismuth type I and II strictures. In Type III and IVstrictures the hilar plate lowering technique is used. In this Hepp-Couinaud technique (Fig no. 4) the left duct is approached by incising the Glisson's capsule at the base of Quadrate lobe. This lowers the left bile duct and by further dissection, gradually the area of confluence and the extra hepatic right duct. This allows space for mucosa-to-mucosa side-to-side anastomosis between the jejunal Roux loop and the healthy bile duct above the stricture. If extra length of left duct is required the dissection can be taken into the ligamentum Teres. Type IV strictures may rarely require hepatotomy or part excision of quadrate lobe to approach the right duct.

Isolated Sectoral duct Injury (Fig no. 5): These are difficult to manage especially if accompanied by bile leak, as the ducts are small and difficult to approach. If recognized intraoperatively and the size of duct is adequate (>3mm), immediate repair should be performed by specialist hepatobiliary surgeon. Asymptomatic remote injuries should be left alone. Symptomatic injuries with recurrent cholangitis should be treated with repair or resection of the segment depending on the atrophy.[13] The management of type C injuries depends upon the trend of fistula. Conservative approach may be considered in patients with low output fistula or decreasing trend of fistula.

Use of stent for bilioenteric anastomosis is controversial. Some use it routinely in all cases[14]. Advantages are post-operative decompression, access for imaging and intervention. We use it only in cases of difficult/unsatisfactory anastomosis, friable ducts or small ducts (<5mm). How long should these stents be kept is also variable and can be from couple of weeks to a year.

Previously, an access loop was made, when it was anticipated that patient might again have stricture or in cases of second or more interventions after Hepaticojejunostomy [15]. The distal limb of the roux loop, beyond the HJ, was left long and brought out subcutaneously or subperitoneally. This allowed for easy access for radiologic interventions.

With the present radiological expertise of percutaneous transhepatic access, the access loop is now rarely used.

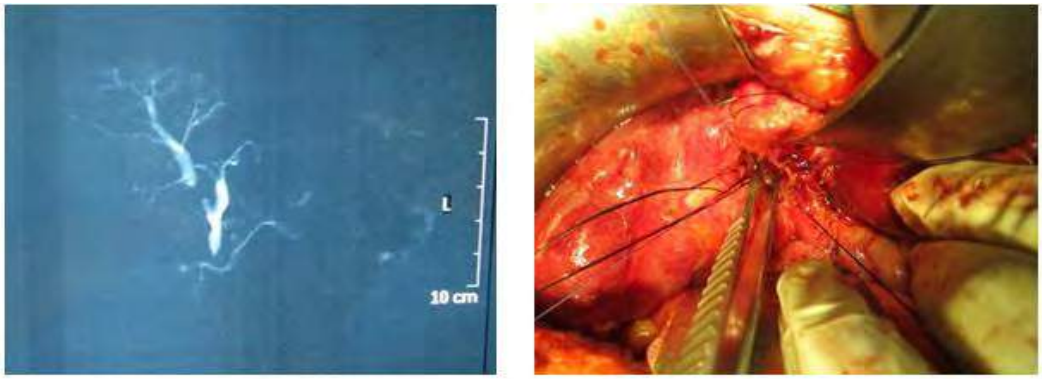


Figure no. 5: RPSD injury (Strasberg type B)

Results: Previous series reported 5-8% mortality. This has been reduced substantially with wider experience in specialized centers and many large series have reported no mortality. Still, patients may succumb while awaiting definitive management with sepsis, pseudoaneurysmal bleed and other complications.. Overall 80-90% good results are reported[1, 16].

Poor prognostic factors reported in the literature:

Proximal stricture (Bismuth types 3 and 4)
Multiple prior attempts at repair
Portal hypertension
Hepatic parenchymal disease (cirrhosis or hepatic fibrosis)
End-to-end biliary anastomosis
Surgeon inexperience
Intrahepatic or multiple strictures
Concurrent cholangitis or hepatic abscess
Intrahepatic stones
External or internal biliary fistula
Intra-abdominal abscess or bile collection
Hepatic lobar atrophy
Advanced age or poor general health

However, our study could not find any such factor affecting outcome following surgical repair as poor outcome was noted in only 4% of our patients[16]. As per our opinion, the important key determinants of favorable long term outcome are early referral, complete delineation of the injury, definitive repair in the absence of sepsis and performance of a wide mucosa-mucosa biliary enteric anastomosis. In addition, the combination of percutaneous dilatation and revision surgery can give good outcome in most of the patients with restricture.

Non-operative Approaches: These include endoscopic and the radiologic percutaneous balloon dilatation and stenting. These can only be used for partial injuries (Strassberg type A & D) and the results are not better than the surgical management[17]. However in post-operative strictures, in patients in whom surgery is contraindicated and as part of multimodality approach these are extremely useful. This approach should be offered to the patients who are motivated enough to adhere to the treatment protocol.

Biliary stricture with Portal Hypertension: This is a difficult group of patient with high rate of complication and mortality[16, 18]. If serious bleed is encountered then a splenorenal shunt should be done before definitive repair.

Liver Transplantation: Very rarely, transplant may be required for long standing biliary stricture with secondary biliary cirrhosis with portal hypertension although even there it should not be the first line approach[19].

Biliary Stricture after Other Operations

These may arise after Gastric and hepatic resection, portocaval shunts and CBD explorations. Strictures after liver transplantation are another category of patients, which should be dealt with at specialized centers only.

Post-Inflammatory Bile Duct Stricture

Recurrent cholecystitis in some cases may lead to ongoing inflammation and stricture of the bile ducts. Gallstones may erode into the CBD in Mirizzi's syndrome. Recurrent pyogenic cholangitis may lead to intra-hepatic stones and strictures. Chronic pancreatitis causes a smooth, long stricture at the lower end. The management depends upon the underlying cause of stricture. .

Post Traumatic Biliary Stricture[20]

Both blunt and penetrating injuries may lead to biliary stricture. During damage control surgery, hemorrhage and associated injuries take precedence in management. Bile flow is diverted and a later definitive repair is done. Biliary fistulas after hepatic injury, which do not close after prolonged conservative treatment, may require either endoscopic intervention or fistulo/hepatico –jejunostomy.. Bilio-enteric anastomosis is done for ductal injuries. Endoscopic or percutaneous approaches can also be used, especially in patients with intra hepatic and partial extrahepatic biliary injuries. Hepatic resection is mainly required in patients with unreconstructable biliary injuries.

Our Experience

We analysed biliary injuries and biliary strictures from 2003 to 2013 and published our experience in Indian J of Surgery in 2015.[16] Out of 205 bile duct injuries that we encountered, 133 were open and 72 were laparoscopic. The presentations included acute bile duct injury (n=9), bile collection (n=64), external biliary fistula (n=74) and stricture (n=58). After initial management 4 patients died (sepsis n=2, pseudo aneurysmal bleed n=2). Of 164 patients who underwent definitive repair, 3 died (portal hypertension n=2, sepsis n=1). At 30 months median follow-up 154 (93.9%) patients had good outcome (grade A, B) and seven had bad outcome (grade C, D) as per McDonald grading.

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Further Reading:

- **Sundeep Singh Saluja, Nilesh Patil, Neeraj Goel. Bile Duct Injury, Biliary Fistula and Benign Biliary Stricture. Text Book of Surgical Gastroenterology (by Dr. PK Mishra). Jaypee Publishers, 2016.**

Choledochal cysts

Aamir Parray, Vivek Mangla

Introduction and demographics

Choledochal cysts (CCs) manifest as dilatation of the intra- and extrahepatic biliary tree. The incidence is 1:100,000 - 150,000 live births. Although most (85%) are diagnosed in the first decade or in children under 15 years of age, 20% of cysts may be diagnosed in older patients.

Classification

Alonso-Lej *et al*. described 3 types of CCs, types I–III. Later Todani *et al*. modified it by adding types IV and V. Type I make up about 50%–80% of all CCs, type II 2%, type III 1.4%–4.5%, type IV 15%–35%, and type V 1%.

- Type IA is cystic dilatation of entire extrahepatic biliary tree with sparing of intrahepatic ducts. Type IB is focal segmental dilatation of extrahepatic biliary tree. Type IC is fusiform dilatation of entire extrahepatic biliary tree.
- Type II is saccular diverticulum of the CBD.
- Type III (also termed choledochoceles) represents cystic dilatation of intramural portion of distal CBD with bulge into the duodenum.
- Type IV are further subclassified into type IVA and type IVB. Type IVA is characterized by both intrahepatic and extrahepatic dilatation of biliary ducts. Type IVB represents multifocal dilatation of extrahepatic biliary tree only.
- Type V (Caroli's disease) represents multiple dilatation of intrahepatic biliary ducts. It is termed Caroli's syndrome when associated with congenital hepatic fibrosis.

Etiology

1. Babbitt's theory: According to this theory, CCs are supposed to be caused by an APBDJ (anomalous pancreaticobiliary duct junction, although APBDJ is observed in only 50–80% cases of CCs.
2. Obstruction of distal CBD which is supported by studies on animal models.
3. Sphincter of oddi dysfunction may predispose to CCs.
4. Kusunoki *et al*. proposed a pure congenital theory suggesting that abnormally few ganglion cells are seen in distal CBD in patients with CCs resulting in proximal dilatation in the same manner as achalasia of esophagus or Hirschsprung's disease.

APBDJ

APBDJ is defined as a junction between the pancreatic and bile ducts located outside of the duodenal wall. The length of common channel varies from 10–45 mm. This long common channel allows pancreatic juice to reflux into biliary system and cause inflammation and ectasia. Kimura et al. classified APBDJ by analyzing the fusion pattern between the pancreatic and bile ducts. In the P-C type, the main pancreatic duct appears to join the common bile duct, while the common bile duct appears to join the main pancreatic duct in the C-P type (Fig 1). Komi's classified APBDJ according to the angle of this ductal union. In type I, the common bile duct joins the pancreatic duct at a right angle. In type II, the common bile duct joins the pancreatic duct at an acute angle. In Type III, the common bile duct and the pancreatic ducts form a complicated network.

Lilly *et al*. have described "*forme fruste*" CCs, when patients present with symptoms typical of CCs and anomalous pancreaticobiliary duct junction (APBDJ) in the absence of dilatation of bile ducts.

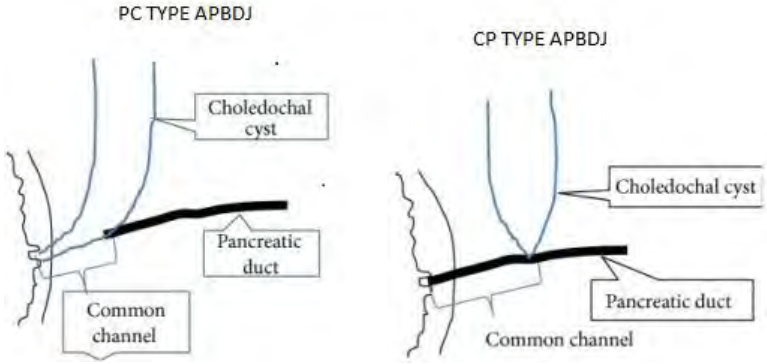

Figure 1: Kimura classification of APBDJ

Clinical features

CCs most commonly present in childhood and about 20% patients present in adulthood. The classic triad of symptoms, which includes pain abdomen, palpable abdominal mass, and jaundice, is seen in less than 20% of cases. Adults are more likely to present with biliary or pancreatic symptoms and abdominal pain, while children are

more likely to present with an abdominal mass. Cyst rupture is seen only in neonates and infants. Adults with CCs are more likely to have symptomatic gallstones (45% to 70% of patients) or acute cholecystitis. As a result, adult patients are more likely to have undergone previous biliary procedures including surgery and biliary stenting.

Complications

1. Cystolithiasis (70% of adults, rare in children, hepatolithiasis common in type IVA due to associated septal stenosis)
2. Pancreatitis (30%, acute, relapsing and mild)
3. Pseudopancreatitis (70%)
4. Cholangitis and intrahepatic abscess
5. Portal hypertension and cirrhosis (15%)
6. Malignancy (2.5% to 17.5%, extrahepatic bile duct in 50–62% patients, gall bladder in 38–46%, intrahepatic duct in 2.5%, and in liver and pancreas in about 0.7%)

Evaluation

Ultrasound

The sensitivity for diagnosing choledochal cysts is 71- 97%. Presence of a distended gall bladder helps differentiate from cystic biliary atresia.

Magnetic Resonance Cholangiopancreaticogram (MRCP)

It is the investigation of choice and represents the "gold standard" today. MRCP helps to clearly outline the proximal extent of resection and distally pancreaticobiliary malunion. The imaging of common channel and distal pancreatic duct, peripheral ducts and filling defects less than 3 mm may however be suboptimal. MRCP is able to diagnose choledochal cysts with an accuracy of 82% - 100%.

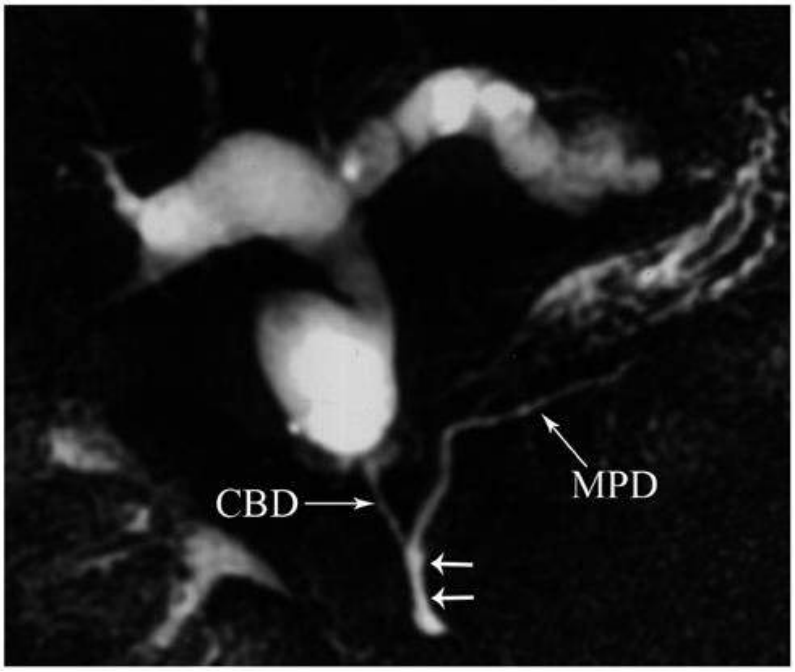

Figure 2: Type IV A CC with APBDJ (double arrow shows common channel)

CT

It is a useful for detecting choledochal cysts, but it is difficult to delineate pancreatic and bile duct union. Multidetector computed tomography (MDCT) allows very thin collimation with a high-quality multiplanar reformation (MPR), which provides detailed information on the pancreatic and bile ducts. CT cholangiography (CTC) is used to evaluate the anatomy and abnormalities of bile ducts.

Heptobiliary scintigraphy

It is rarely used as an initial investigation to diagnose or plan the extent of resection. The characteristic finding is delayed filling of the bile duct cysts followed by persistent radioisotope retention. This modality is more useful for assessing the patency of a high biliary-enteric anastomosis postoperatively.

Endoscopic retrograde cholangiopancreatography (ERCP)

It is reported to be the most sensitive diagnostic modality for CCs. However it should not be used for diagnosis of CCs as it is an invasive procedure, and may cause cholangitis and pancreatitis. These complications are reported to be higher in CCs patients. ERCP in CCs also need large amount of dye to fill cyst, which increases the risk of

cholangitis and pancreatitis. ERCP in adult patients can be used in patients with cholangitis and for extraction of calculi in the distal bile duct when associated.

Endoultrasound (EUS)
EUS is particularly useful in adults with newly diagnosed CCs as it helps to rule out dilatation of the bile duct secondary to small pancreatic or distal bile duct tumors which maybe missed on CT or MRCP. It may also help to rule out malignancy in the background of CC in adult patients.

Management

1. ***Timing of definitive surgery-*** (a) Antenatally diagnosed patients who are symptomatic should be offered definitive surgery in the first two months of life for best results and if they are asymptomatic, definitive surgery should be carried out by the sixth month. (b) Older children and adults should be offered definitive resection when diagnosed. (c) in patients with cholangitis, definitive surgery should be delayed for 6-12 weeks. (d) Following internal drainage procedures, 70% patients require re-operation for cholangitis and hepatolithiasis. Even asymptomatic patients should be offered early definitive cyst resection and reconstruction as prophylaxis against malignancy.
2. ***Cyst excision with Roux en Y hepaticojejunostomy:*** The aim of definitive surgery for choledochal cyst includes: (a) Excision of the cyst wall and the gall bladder thereby reducing the risk of malignancy. (b) Interruption of reflux of pancreatic juice into the biliary tree (c) Reconstruction of the biliary-enteric channel. The cyst is divided proximally till there is change in the nature and caliber of the hepatic ducts. Distally the dissection enters the intrapancreatic tapering part of the bile duct. A sufficiently wide end-to-side anastomosis is made between the hepatic duct and a 70 cm retrocolic Roux-en-Y loop of jejunum. Type IV choledochal cysts with localized intrahepatic involvement can be offered relevant partial hepatectomy along with excision of extrahepatic biliary tree with hepaticojejunostomy. Patients with involvement of both right and left ductal systems with evidence of biliary cirrhosis are best managed with liver transplantation.

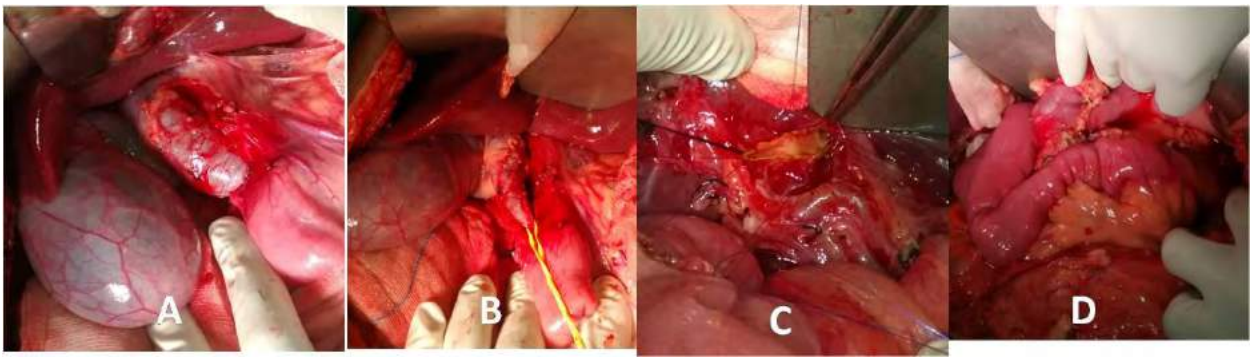

Figure 3: Intra-operative photographs of excision of a Type I Choledochal cyst. Choledochal cyst (A), after circumferential dissection of the cyst (B), after excision of the cyst (C) and at completion of hepaticojejunostomy (D)

3. Options for difficult cyst following recurrent cholangitis, pancreatitis or spontaneous cyst perforation-peritonitis, where the planes of surgical dissection will be obscured, are: (a) Lillys technique- where the medial and posterior walls are dissected in the submucosal plane from the hepatic artery and portal vein respectively. (b) Internal drainage of the cyst to the duodenum or jejunum with plan to resect the cyst after 6-12 weeks. (c) Hepp procedure- Partial cyst excision and choledochocysto-jejunostomy.
4. Type II CCs are managed by simple excision. Usually these cysts are excised without the need for bile duct reconstruction. Type III CCs are managed by endoscopic sphincterotomy or transduodenal excision and sphincteroplasty.
5. Type V (Caroli's disease) management consists of liver resection or orthotopic liver transplantation (OLT). Localized or unilobar cystic disease is best managed with hepatic resection. Incomplete resection of cystic disease leads to poor long term outcomes; therefore, an aggressive surgical approach is recommended.

Minimally Invasive Surgery
Laparoscopic CC excision with RYHJ reconstruction is safe with outcomes comparable to open resection in retrospective analyses, with improved intraoperative visualization of deeper structures, decreased postoperative pain, shorter hospital stay, improved cosmetic result, and decreased postoperative ileus. Palanivelu *et al*. reported the largest series on laparoscopic treatment of CCs in adults. In their review of 35 patients, including 16 adults, they found that laparoscopic surgery for CCs is safe, feasible, and advantageous. But this is a technically demanding procedure and usually leaves behind a cuff of dilated duct above the anastomosis, as it is difficult to perform hepaticojejunostomy on a collapsed, undilated duct and the long-term implications of laparoscopic surgery are yet to be reported.

Outcome
Postoperative morbidity and mortality is typically very low in children and young adults. Late complications include anastomotic stricture, cancer, cholangitis, and cirrhosis. Overall, CCs resection has an excellent prognosis, with an 89% event-free rate and 5-year overall survival rates over 90%. The risk of biliary malignancy remains elevated even 15 years after CC excision, so long-term surveillance is warranted, particularly in patients with persistent intrahepatic biliary dilatation due to presence of intrahepatic CC.

Summary
Choledochal cysts is a rare disease entity, most commonly presents in childhood and uncommonly in adults. It is associated with increased risk of cancer involving the gall bladder or the bile ducts. MRI is the imaging technique of choice. Management includes total cyst excision and bilioenteric reconstruction. Regardless of CC subclass, appropriate therapy results in good outcomes and low complication rates.

Approach to a patient with colonic mass

Trilok Chand

Introduction:
The diagnosis of a colonic mass is built on three pillars: History, Physical examination and investigation. Taking a good accurate and targeted history, performing a careful and revealing physical examination and choosing the right investigation require skill and acumen.

HISTORY:
We need to ask the right questions to our patients to know what to look for an examination and what to look for it. the astute clinician should inquire about the patient bowel habits typical diet, smoking, alcohol intake and use of medications and also document comorbid condition such as diabetes and previous history of inflammatory bowel disease. A relevant family history should have documented. In case of tuberculosis history of contact or previous infection should be asked.

A patient with colonic mass may present other associated symptoms. Patient must be asked about the age of patient, gender such as carcinoma of colon generally a disease, of old age but diverticulitis occurs in young Tuberculosis can present in both groups.

Clinical presentation of colonic lesions

1. **Change in Bowel Habits:**
   Chang in bowel habit is most frequent complaint of the patient with colorectal cancer. It is also more common in cecal tuberculosis. A change in bowel habits, including diarrhoea or constipation or a change in the consistency of stool, that lasts longer than four weeks. Right-sided lesions are more likely to bleed and cause diarrhoea, while Left side of colon carcinoma presents with constipation because left side colonic lumen is narrow in size and the cancer presents as a concentric growth. Due to concentric growth patent may give history of passing of thin stool (ribbon like). The range of normal stool frequency is three times per day to three times per week. Patient may give the history of feeling that bowel doesn't empty completely.
   Spurious Diarrhoea: this is characteristic of papilliferous growth in sigmoid colon which give rise a feeling of need to evacuate which results in tenesmus accompanied by passage of mucus and blood., especially in early morning.

1. **Abdominal Pain**: abdominal pain is common symptom that has a vast differential diagnosis focus by analyzing pain according to its timing, nature, pattern, site and context**.**
   Sharp and steady pain occurs in infectious process and tumor.
   Colicky pain (intermittently crampy) pain that builds to a crescendo, then eases and then build again.it is caused by obstruction may be caused by carcinoma colon ileocolic tuberculosis**.**
   Constant pain which is made worse by breathing or moving due to infection, which is causing peritoneal irritation suggestive of perforation peritonitis it may occurs in diverticulitis, tuberculosis, later stage of colonic malignancy.
   Pain associated with diarrhea is caused by colitis, irritable bowel syndrome, diverticulitis or tumor. Pain associated with abdominal distention and reduction in bowel movements may be caused by large bowel obstruction.
   Onset of pain: sudden onset of pain indicates acute event e.g. perforation, volvulus. Gradually increasing pain is more likely caused by contained sepsis or tumor.
   Site of pain: Colonic pain may be felt anywhere in the abdomen, chest, back, pelvis. Patients age, gender and past history guide the differential diagnosis of abdominal pain. colon cancer is more common in elderly patients and colitis is more typical in young. Lymphoma is also present in older age group.

2. Per rectal bleeding:

a. **Outlet bleeding** (bright red) Seen only on toilet paper or in the water, and generally due to benign conditions such as hemorrhoids.
b. **Suspicious bleeding**: dark blood, blood associated with mucous, blood on or in the stool. If bleeding is associated with mucus discharge, then the possibility of colorectal cancer should have kept in mind. It occurs when there is a ulcerative lesion and hard stool damage the friable mucosa. It can also occur by necrotic process of malignancy.

2. **Abdominal Distention:** it may be a due to of colonic distention. It may be painful or pain less, pain full distention is due to mechanical obstruction and painless due to colonic ileus. It may be associated with vomiting. Vomiting is a late feature in colonic obstruction. In case of metastatic malignancy abdomen may be distended due to ascetic fluid.
3. **Abdominal lump:** If patient presents with abdominal lump it may be asymptomatic or with nonspecific symptoms such as anorexia weight loss. Lump may be painless and slow growing as in case of lymphoma or it may be rapidly growing as in case of colorectal carcinoma it may be associated with pain as in diverticulitis. In amebomas lump may appear after an episode of colitis is over.
4. **Fever:** High grade fever with night sweats and significant weight loss (>10% in the last 6 month) constitute the B symptoms of lymphoma. If a colonic mass present with these symptoms the diagnosis of lymphoma should considered. If a right ileac fossa lump present with low grade evening rise of temperature and altered bowel habit, then the diagnosis of ileocecal tuberculosis should have considered.
   Painful lump present in left lower abdomen with high grade fever the possibility of diverticulosis should kept in mind.
5. The other symptoms may be constitutional symptoms such as anorexia, weight loss, malaise may be presented.

EXAMINATION:

General Physical Examination:

1. The patient may have **Cachexia or malnutrition** due to debilitating illness like tuberculosis or malignancy.
2. Patient may present with **significant pallor** with or without overt blood loss. It is dictum if an elderly male is presenting with significant pallor the diagnosis of colorectal carcinoma should kept in mind if proven otherwise.
3. **Lymphadenopathy**
   Generalized Lymphadenopathy: if patient presents with generalized lymphadenopathy or left iliac fossa lymph nodal mass with any other lymph node group involvement. Then the diagnosis of lymphoma should be considered. Presence of left supraclavicular lymph node mass in case of colonic mass, a malignant pathology large bowel malignancy should be considered.
4. **Pedal edema:** Pedal edema may be present as unilateral or bilateral. unilateral pedal edema can be due to local compression effect by mass. Bilateral pedal edema could be a manifestation of hypoproteinemia associated with tuberculosis or underlying malignancy.

LOCAL EXAMINATION:

Inspection: Shape and extent of swelling
Visible pulsation
Visible peristalsis
Cough impulse.

Visible peristalsis some time seen over the swelling or in the swelling.
Palpation: First confirm swelling is parietal or intraperitoneal by leg raising test or Valsalva maneuver.
Temperature and tenderness, if swelling is inflammatory it will tender.
Then the consistency of lump.
If lump is intra abdomen, then it should be differentiated into intraperitoneal or retroperitoneal lump by Examination in knee elbow position.
Then check the fixity and mobility of lump.
What is the consistency
Either lump pulsatile or not.

In case of right sided colonic malignancy a hard non tender lump palpable, it may have fixed to posterior abdominal wall or mobile. If lump is slightly higher up in right iliac fossa, fixed, irregular surface and having some tenderness. it occurs in tuberculosis. Left sided colonic mass may be due to carcinoma colon or diverticulitis. There may be hard mobile lump suggestive of sigmoid malignancy. Sometime a firm mobile lump which indents on pressing may be palpable due to impacted feces

Digital Rectal Examination(DRE) A large sigmoid malignancy may be palpable in pouch of Douglas or metastasis deposits in the POD may be palpable. DRE can detect 10% of the colorectal malignancy
Bimanual palpation: Sigmoid or descending colon malignancy can be palpated bimanually (Abdominorectal).
Percussion: percussion over the lump and rest of the abdomen should be done. liver dullness should be access. To elicit the presences of ascites.
Auscultation: it should be done over lump and rest of abdomen to find out any evidence of intestinal obstruction.

Most Common differential diagnosis of colonic mass;

Carcinoma Colon
Tuberculosis
Lymphoma
Amebomas
Diverticulitis
Gastrointestinal tumors[GIST]

Carcinoma of colon

INCIDENCE: carcinoma of colon is the second most common cancer in women and third most common cancer in men worldwide, resulting in more than 1 million cases each year.[(1)] It is second most common cause of cancer death with in the western world[1]. North America, Europe, Australia, and New Zealand had the highest rates of colonic carcinoma[(2)]. Whereas lowest rate is found in Africa and Asia. The risk for developing invasive colon cancer increasing with age. The incidence of colon cancer in men from 1998 to 2005 decreased at a rate of 2.8%/ year and for women at a rate of 2.2%/year. This reflects the identification and removal of
(a) precancerous polyps at screening;
(b) colon cancer at earlier stage during screening
;(c) improved risk factor profile; improvement in treatment of colon cancer. There has been significant increase in five-year survival rate over the last 30 years.

Recognized Risk Factors for Colon Cancer

FAMILY HISTORY
Colorectal cancer
Inherited syndrome; e.g., familial adenomatous polyposis(FAP)
Racial and ethnic background; e.g., African, American.

PERSONAL HISTORY
Age
Male gender
Previous colonic polyps or colorectal carcinoma
History of inflammatory bowel disease
Diabetes mellitus.

LIFESTYLE
Obesity
High consumption of alcohol, smoking
Diet high in red meat and fat, low in fibers.

Colon cancer occurs in hereditary, sporadic or familial form hereditary forms are characterized by family history, young age at onset, and presence of other specific tumors and defects. Familial adenomatous polyposis(FAP) and hereditary non polyposis colorectal cancer(HNPCC) have provided significant insights into pathogenesis of colorectal cancer.
About 80% of colon cancer are sporadic and occurs in absence of family history, generally affects an older population (60-80 year) and usually present as an isolated colon or rectal lesion.

Clinical presentation
Colorectal adenocarcinoma grows slowly. symptoms depend on lesion location, type extent and complications.

Change in bowel habit:
The right colon has a larger caliber, a thin wall, and its contents are liquid; thus obstruction is a late. right side of lesion generally present with occult **bleeding. Fatigue and weakness** caused by severe anemia. Anemia will not respond to hematinic Right-sided lesions are more likely to bleed and cause diarrhea, while left-sided tumors are usually detected later and may present as bowel obstruction.

Bleeding: This is second most common symptom common symptom in colorectal cancer. It may be overt or occult. The blood may be bright red, purple black, or in apparent. Bleeding can represent relative an early sign of cancer of bowel, it is often neglected symptoms. It dictum to ask all adults about visible rectal bleeding

Mucus : The presences of mucus either as a discharge or mixed with the stool, is another symptom it often accompanies bleeding . the presences of mucus and bleeding should be considered a highly suggestive combination that warrant urgent bowel examination.

Pain: Abdominal pain resulting from a tumor imply an obstructing or partially obstructing lesion. This pain is usually colicky in nature and may associated with abdominal distention, nausea vomiting. Intestinal obstruction is a presenting complaint in 5%to 15% individual with colorectal cancer. Back pain from retroperitoneum extension of a tumor of the ascending descending colon is an unusual and late sign.

Mass; A palpable or visible abdominal mass in absence of other sign and symptoms implies a slow growing tumor.

Intussusception: Patients usually present with the sign and symptoms of intestinal obstruction, two third of colonic intussusceptions are associated with primary carcinoma of colon.

Duration of symptoms: Short history of symptoms do not have a better prognosis.
Other presenting symptom are Appendicitis, peritonitis, septicemia, inguinal hernia and cutaneous manifestations

EVALUATION:

Stool occult blood: fecal occult blood testing the only colorectal screening test with supportive evidence from prospective randomized trials with demonstrative reduction in colorectal cancer mortality of 15% to 30%. The blood released is not usually visible in the stool, but it can be detected with a fecal occult blood test (FOBT) or fecal immunochemical test (FIT). This small amount of blood may be the first and sometimes the only sign of early colon cancer, making the FOBT and FIT valuable screening tools for colorectal (colon and rectal) cancer. Methods for testing include a guaiac-based test (gFOBT), an over-the-counter (OTC) flushable reagent pad, and an immunochemical method (iFOBT or FIT). It is recommended that testing be performed on at least three stool samples collected on different days.

Guaiac-based test (gFOBT) is commonly practiced in this test the health practitioner or laboratory will typically provide three test cards. Separate stool samples are collected from different bowel movements, usually on three consecutive days. For each test, a stool sample should be collected into a clean container and should not be contaminated with urine or water. A test card is labeled with the person's name and the date; then, with an applicator stick, a thin smear of stool is put onto a designated area on the card and allowed to dry. Once it is dry, it is stable for several weeks at room temperature.

For guaiac-based FOBT methods, there are special dental, dietary, and drug restrictions. These tests detect any blood that enters the digestive tract. Therefore, steps that are taken to avoid introducing blood into the digestive tract will increase the quality of the test sample.

Digital rectal Examination

William J. Mayo remarked "The Physician often hesitates to make the necessary examination because it involves soiling the finger "If u do not put your finger in you will put your foot in. The index finger has also been termed "God's bio probe". However, the efficacy of digital examination today for identifying colorectal cancer is about 10%.

Colonic Tuberculosis:

Gastrointestinal tuberculosis constitutes 70-78% cases of abdominal tuberculosis. Abdominal tuberculosis is a most common type of extra-pulmonary tuberculosis Ileocecal area is the most commonly involved site due to the abundance of lymphoid tissue (Peyer's patches) followed by the colon and jejunum.

Isolated colonic tuberculosis refers to involvement of the colon without ileocecal region, and constitutes 9.2 per cent of all cases of abdominal tuberculosis. It commonly involves the sigmoid, ascending and transverse colon. Multifocal involvement is seen in one third (28 to 44%) of patients with colonic tuberculosis. The median duration of symptoms at presentation is less than 1 yr.

Pathophysiology:

Colonic tuberculosis can occur primarily or it can be secondary to a tubercular focus elsewhere in the body. Colonic tuberculosis occurring due to ingestion of milk or food infected with Mycobacterium can result in **primary intestinal** tuberculosis. Infection by Mycobacterium tuberculosis causing abdominal tuberculosis is acquired in following ways:

- •Dissemination of primary pulmonary tuberculosis in childhood
- Swallowing of infected sputum in active pulmonary tuberculosis
- Hematogenous dissemination from a focus of active pulmonary tuberculosis or military tuberculosis
- Mycobacteria can spread from infected adjacent organs like fallopian tubes
- Intestinal infection can occur by lymphatic spread from infected mesenteric lymph nodes
- Mycobacteria can also get disseminated through bile from tubercular granulomas of the liver.

The characteristic intestinal lesions produced in tuberculosis

(i) Ulcerative- It is most common form of intestinal tuberculosis (60%). Ulcers are circumferential transvers often multiple, girdle ulcer with skip lesions. Long standing ulcer cause fibrosis and later stricture formation. Intestinal nodes are involved with caseation.

(ii) Hyperplastic: fibroblastic reaction in submucosa and sub serosa causing thickening of bowel wall and lymph node enlargement leading to nodular mass formation (tumor- like). It is 10% and due to loss of virulence and adequate host resistance. It is common in cecal part. It causes extensive chronic inflammation, fibrosis, bowel adhesion and nodal enlargement. it often present mass in right ileac fossa and can cause subacute intestinal obstruction

(iii) Ulcerohyperplastic (30%)

Pain is the predominant symptom in 78-90 per cent of patients and **hematochezia** occurs in less than one third. The bleeding is frequently minor and massive bleeding is less common. Singh et al reported rectal bleeding in 31 per cent of patients with colonic tuberculosis, and it was massive in 13 per cent. Bhargava et al reported bleeding in 70 per cent cases. Overall, tuberculosis accounts for about 4 per cent of patients with lower gastrointestinal bleeding. Other manifestations of colonic tuberculosis include **fever, anorexia, weight loss** and **change in bowel habits**. Patients complain of **colicky abdominal pain**, borborygmi and vomiting. Abdominal examination may reveal no abnormality or a doughy feel. **About 35% patients present mass in right ileac fossa**. It is hard, nodular, non-mobile, non-tender with impaired resonance which may mimic carcinoma of caecum or large bowel lymphoma The diagnosis is suggested **Ileocecal tuberculosis.** The most common complication of small bowel or ileocecal tuberculosis is obstruction due to narrowing of the lumen by **hyperplastic cecal tuberculosis**.

Tuberculosis accounts for 5-9 per cent of all small intestinal perforations in India, and is the second commonest cause after typhoid fever. Evidence of tuberculosis on chest X-ray and a history of subacute intestinal obstruction are important clues. Pneumoperitoneum may be detected on radiographs in only half of the cases. Tubercular perforations are usually single and proximal to a stricture.

COLONIC LYMPHOMA
Primary lymphoma of the colon is a rare tumor of the gastrointestinal (GI) tract and comprises only 0.2-1.2% of all colonic malignancies. The most common variety of colonic lymphoma is non-Hodgkin's lymphoma (NHL)[3,5]. The GI tract is the most frequently involved site, accounting for 30-40% of all extra nodal lymphomas, approximately 4-20% of which are NHL [4]. The stomach (50-60%) is the most common location of GI lymphomas, followed by the small intestine (20-30%). Colorectal lymphoma is third most common malignancy of the large intestine after adenocarcinoma and carcinoid [6]

DEMOGRAPHY; The Incidence of primary colorectal lymphoma has been shown to increase with age with the peak incidence noted in patients between 50 and 70 years of age. Slightly male predominance (1.5:1.0) M/F ratio.
RISK FACTOR; Inflammatory bowel disease, chronic immunocompromised (HIV), chronic infection with Epstein Barr virus.

Diagnostic criteria: In order to make the diagnosis of primary gastrointestinal lymphoma standard criteria introduce by Dawson et al.
Dawson's criteria for primary intestinal lymphoma

1.Absence of clinically enlarged lymph node on clinical examination.
2. Absence of enlarged mediastinal lymph nodes on chest x-ray.
3.Normal hematologic lab value on bone marrow biopsy.
4. Normal appearing liver and spleen.
5.Only regional lymph node present at the time of laparotomy.

CLINICAL PRESENTATION: The most common presenting symptom is abdominal pain (66%) and weight loss (43%). Less commonly present with a change in bowel habit (27%)and lower GI bleeding (20%) . Ileocolic lymphomas can present as an intussusception. The most common physical finding is palpable abdominal mass. In contrast to adenocarcinoma of the colon, patients rarely present with colonic obstruction or perforation. This is suggestive of a relatively indolent disease progression accounting in part for the absence of pathognomic symptomatology.

Most common site of involvement **cecum (57%).** Followed by ascending colon Less commonly these lesions located in the transverse colon (10%), descending colon (5%), and sigmoid colon (10%).
IMAGING: Computed tomography and double-contrast barium enema are the main imaging modality used in the diagnosis of colorectal lymphoma.

DIVERTICULITIS:
Diverticulitis is the result of a perforation of a colonic diverticulum. A diverticulum is an abnormal sac or pouch protruding from the wall of hollow organ. Most colonic diverticula are pseudodiverticula that occur, when mucosa and submucosa herniate through muscularis propria. The saccular herniation develops in areas of relatively structural weakness of colonic wall, where small nutrient arteries (vasa reacta) penetrate the circular muscle layer. In the western world sigmoid and descending colon are most commonly affected. In Asia colonic diverticulum are predominantly right sided.

EPIDEMIOLOGY:
Diverticulosis is prominent in western society with 30-40% prevalence.in rural Asia it occurs only 1%, now a day's incident is increasing in cities due to change in dietary patterns.
Risk Factors:

1. Low dietary fiber intake
2. Use of steroids(corticosteroids)
3. Lac of physical activity(obesity).

Pathogenesis:
two main factors are associated in the formation of diverticula are Increase intraluminal pressure and weakening of bowel wall. Diverticula most commonly affects sigmoid colon and confined to sigmoid colon in 50% of patients with diverticulosis. Sigmoid colon has smallest luminal diameter. There is muscular thickening of colonic wall due to hypertrophy is characteristic of diverticulosis and it is usually confined to sigmoid colon. If the food is having low amount of fibers there is decreased colonic luminal content, requiring the generation of increased colonic pressure to propel the feces forward. This high intraluminal pressures are thought to be responsible for herniation of colonic mucosa through the anatomically weak points in the colonic wall.
Diverticulitis is the result of a perforation of colonic diverticulum. It is an extra luminal peri colic infection caused by the extravasation of feces through perforated diverticulum. The patients with diverticulitis usually present with **left lower quadrant abdominal pain that may radiate to suprapubic area, left groin or back.** alterations in bowel

habit, fever, chills and urinary urgency are common symptoms. Rectal bleeding is not usually associated with an acute attack.

Physical findings are dependent on the site of perforation amount of contamination. **Tenderness in left lower quadrant**, **voluntary guarding of the left abdominal** musculature and a **tender mass in left lower abdomen** is suggestive of a phlegmon or abscess. Abdominal wall distention may be present if small bowel obstruction secondary to inflammatory process. Complicated diverticulitis can be present as **a fistula** between colon and vagina, urinary bladder, or small bowel. **diverticulitis is a more common cause of a fistula between the colon and bladder than crohns disease or cancer**. Sigmoid-vesicular fistula may present **pneumaturia, fecaluria, recerent UTI and significant urosepsis in men with prostatic hypertrophy. Cystoscopy** reveals cystitis and bullous edema at the site of fistula.

AMEBOMAS:
Localized infection of the colon by Entamoeba histolytica may form a segmental mass called amebomas. Generally, it occurs Years after the last attack of dysentery Amebiasis caused by Entamoeba histolytica is the most significant gastrointestinal parasitic infection in developing countries like India. Presentation ranges from diarrhea to dysentery and liver abscess. However, colonic ameboma has become rare even in endemic areas because of the availability of effective therapy**. When it is found in association with amebic liver abscess, it can mimic metastatic colon cancer**[(7)]**.**

Amebiasis constitutes an important global problem, especially in the tropical and subtropical regions. It primarily affects the colon but the liver is the most common extra intestinal organ involved. The presentation of intestinal amebiasis ranges from asymptomatic carrier state, **colitis**, through abscess formation to **perforation**. The parasite has been shown to be carried to the liver from the large bowel via the portal venous system. Trophozoites of E. histolytica are responsible for the invasive disease. Intestinal invasion results in flask-shaped ulcers. Rarely, patients **with long-standing or partially treated infection develop tumorous, exophytic, cicatricial and inflammatory masses known as "amebomas**" or **amebic granulomas**. It has been estimated that of all the cases with amebiasis, ameboma formation occurs in only about 1.5% of the patients. The tissue necrosis in amebic colitis is replaced by extensive inflammatory reaction and psuedotumor formation, possibly because of secondary bacterial infection. Amebomas are usually solitary but can be multiple. Men between the ages of 20 and 60 years are usually affected. In decreasing order of frequency, lesions develop in **the cecum**, the appendix and the rectosigmoid region. Other sites include the hepatic flexure, the transverse colon and the splenic flexure.

Amebomas may cause **obstructive symptoms**. **Alternating diarrhea and constipation, weight loss and low-grade fever** may be seen. In endemic areas, **cramping lower abdominal pain and a palpable mass suggest diagnosis**. The **differential diagnosis** includes **Crohn's disease** and appendiceal abscesses in younger individuals and **colon cancer** and diverticulitis in the elderly [(8)]. **Colonic ameboma accompanied by amebic liver abscess may be misdiagnosed as metastatic carcinoma of the colon.**

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Management of patient with colonic lesion

Sushanto Neogi

It is recommended for further investigations whenever there is suspicious history or examination, namely.[1]

- Aged 40 years and older, reporting rectal bleeding with a change of bowel habit towards looser stools and/or increased stool frequency persisting for six weeks or more.
- Aged 60 years and older, with rectal bleeding persisting for six weeks or more without a change in bowel habit and without anal symptoms.

- Aged 60 years and older, with a change in bowel habit to looser stools and/or more frequent stools persisting for six weeks or more without rectal bleeding.
- Of any age with a right lower abdominal mass consistent with involvement of the large bowel.
- Of any age with a palpable rectal mass (intraluminal and not pelvic; a pelvic mass outside the bowel would warrant an urgent referral to a urologist or gynaecologist).
- Who are men of any age with unexplained iron-deficiency anaemia and a haemoglobin of 11 g/100 ml or below. In third world countries scenario, the level of anemia may be taken less depending on the level of Hb taken as normal for that set up.
- Who are non-menstruating women with unexplained iron-deficiency anaemia and a haemoglobin of 10 g/100 ml or below. Similarly the level of Hb may be changed for the country and set up.[1]

Investigations of suspected colonic lesions:

Colonoscopy — Colonoscopy is the most accurate and versatile diagnostic test for Colo- rectal cancers (CRC) and suspected neoplasms, since it can localize and biopsy lesions throughout the large bowel, detect synchronous neoplasms (Synchronous CRCs, defined as two or more distinct primary tumors diagnosed within six months of an initial CRC, separated by normal bowel, and not due to direct extension or metastasis, occur in 3 to 5 percent of patients) and remove polyps.[2]

The vast majority of colon and rectal cancers are endoluminal masses that arise from the mucosa and protrude into the lumen .The masses may be exophytic or polypoid. Bleeding (oozing or frank bleeding) may be seen with lesions that are friable, necrotic, or ulcerated. Circumferential or near-circumferential involvement of the bowel wall correlates with the so-called "apple-core" description seen on radiologic imaging. Cancers that arise from nonpolypoid (sessile) adenomas may be more difficult to visualize colonoscopically, but colonoscopy is thought to have superior sensitivity in this situation than does Barium enema or computed tomography (CT) colonography.[3]

For endoscopically visible lesions, methods for tissue sampling include biopsies, brushings, and polypectomy. For lesions that are completely removed endoscopically (with polypectomy, endoscopic mucosal resection, or endoscopic submucosal dissection), tattooing is important for subsequent localization if an invasive neoplasm is found, and additional local therapy is needed. Tattoos are typically placed adjacent to or a few centimeters distal to the lesion, with the location being documented in the colonoscopy report.[3]

Among asymptomatic patients, colonoscopic miss rates for CRCs in the hands of experienced operators range from 2 to 6 percent, and are highest on the right side of the colon.[3]

Incomplete colonoscopy — Non-completion rates for diagnostic colonoscopy in symptomatic patients are approximately 11 to 12 percent. Reasons for incompleteness include the inability of the colonoscope to reach the tumor or to visualize the mucosa proximal to the tumor for technical reasons (eg, partially or completely obstructing cancer, tortuous colon and poor preparation) and patient intolerance of the examination.[3]

The available data concerning miss rates for CRC among symptomatic patients undergoing colonoscopy are as follows:

- In a randomized trial comparing colonoscopy versus CT colonography for individuals with symptoms suggestive of CRC conducted by SIGGAR (Special Interest Group in Gastrointestinal and Abdominal Radiology) investigators, none of the 55 cancers that were diagnosed in the cohort of 1072 patients who were randomly assigned to colonoscopy were missed. [4]
- In a systematic review and meta-analysis of 25 diagnostic studies providing data on 9223 patients with a cumulative CRC prevalence of 3.6 percent (414 cancers), the sensitivity of optical colonoscopy for detection of CRC was 94.7 percent (178 of 188, 95% CI 90-97.2). Thus, the miss rate was 5.3 percent.[5] If a malignant obstruction precludes a full colonoscopy preoperatively, the entire residual colon should be examined soon after resection.

In the absence of an obstruction, where colonoscopy is incomplete, another option is Pill Cam colon 2, a wireless colon video endoscopy capsule approved for CRC screening, although its use in patients with symptoms suggestive of CRC (eg, anemia, rectal bleeding, weight loss) is controversial.

Flexible sigmoidoscopy — Over the last 50 years, a gradual shift toward right-sided or proximal colon cancers has been observed both in the United States and internationally, with the greatest increase in incidence is in caecal primaries. Because of this, and because of the high frequency of synchronous CRCs, flexible sigmoidoscopy is generally not considered to be an adequate diagnostic study for a patient suspected of having a CRC, unless a palpable mass is felt in the rectum. In such cases, a full colonoscopy will still be needed to evaluate the remainder of the colon for synchronous polyps and cancers.[6]

Barium enema — Barium enema is widely available and may be used to investigate patients with symptoms suggesting of CRC However, the diagnostic yield of both double-contrast barium enema (DCBE) alone and the

combination of DCBE plus flexible sigmoidoscopy is less than that of colonoscopy or CT colonography for the evaluation of lower tract symptoms.[7]

The yield of DCBE alone was addressed in a randomized trial comparing DCBE versus CT colonography in 3838 patients with symptoms suggestive of CRC. Of the 2527 patients assigned to DCBE, the detection rate for CRC or large polyps was significantly lower (5.6 versus 7.3 percent with CT colonography). Rates of additional studies after the initial procedure were significantly lower after DCBE than CT colonography (18 versus 24 percent) with three years of follow-up. The need for additional studies following CT colonography was due mostly to the higher polyp detection rate; CRC was subsequently diagnosed in more patients who had initially undergone DCBE (miss rate 14 versus 7 percent).[7]

If a polyp or mass is detected by barium enema, colonoscopy is recommended to establish the histology, remove the polyp, and search for synchronous lesions.[7]

CT colonography — CT colonography (also called virtual colonoscopy or CT colography) provides a computer-simulated endoluminal perspective of the air-filled distended colon. The technique uses conventional spiral or helical CT scan or magnetic resonance images acquired as an uninterrupted volume of data, and employs sophisticated post processing software to generate images that allow the operator to navigate a cleansed colon in any chosen direction. CT colonography requires a mechanical bowel prep that is similar to that needed for barium enema, since stool can simulate polyps. CT colonography has been evaluated in patients with incomplete colonoscopy and as an initial diagnostic test in patients with symptoms suggestive of CRC. In this setting, CT colonography is highly sensitive for the detection of CRC and can provide a radiographic diagnosis, although it can over call stool as masses in poorly distended or poorly prepared colons; it also lacks the capability for biopsy or removal of polyps.[5]

Systematic reviews of screening studies conducted in asymptomatic patients suggest that CT colonography and colonoscopy have similar diagnostic yield for detecting CRC and large polyps. Comparison of the benefits and costs of the two procedures depends on other factors, one of the most important of which is the need for additional investigation after CT colonography and the exposure to radiation, which is particularly important where recurrent scanning over time may be contemplated such as in screening. Abnormal results should be followed up by colonoscopy for excision and tissue diagnosis, or for smaller lesions, additional surveillance with CT colonography.[5] CT colonography should be restricted to patients who are able to pass flatus and capable of tolerating the oral preparation. For clinically obstructed patients, a gastrointestinal (GI) protocol abdominal CT scan is a good alternative to CT colonography.

The performance of diagnostic CT colonography as compared with colonoscopy in patients with symptoms suggestive of CRC has been addressed in the following studies:

- A systematic review and meta-analysis included 49 studies (11,551 patients) in which patients underwent CT colonography for the diagnosis of colorectal polyps and cancer with subsequent colonoscopy for verification of the findings; 43 studies (6668 patients) examined a symptomatic or disease-enriched population . CT colonography detected 96.1 percent of the histologically proven cancers (95% CI 93.9-97.7 percent). The sensitivity of colonoscopy was 94.7 percent (178 of 188 cancers, 95% CI 90.4-97.2 percent).[5]
- The diagnostic performance of CT colonography was directly compared with colonoscopy in the SIGGAR trial in which 1610 patients with symptoms suggestive of CRC were randomly assigned to colonoscopy (n = 1072) or CT colonography (n = 538). Detection rates for CRC and large polyps were 11 percent for both procedures. CT colonography missed 1 of 29 CRCs and colonoscopy missed none of 55. However, patients undergoing CT colonography were more than three times more likely to get additional colonic investigations (30 versus 8 percent). Only one-third of these patients were found to have CRC or a large polyp.[4]

Fecal Occult Blood- the test is almost obsolete. It is based on use of Guiac acid and an oxidizing agent which changes colour in presence of hemoglobin in stool. But this test has high false positivity rate and also false negativity rates. True positivities ar only about 50%, therefore colonoscopy has become the gold standard.[9]

Fecal immunochemical test (FIT) is also called an **immunochemical fecal occult blood test (iFOBT**). It tests for occult blood in the stool in a different way than a guaiac-based FOBT. This test reacts to part of the human hemoglobin protein, which is found in red blood cells. It is more sensitive than Guaiac-based fecal occult blood test (gFOBT), which tests blood released from large friable polyps. The false positivity rates are also high with Guaiac blood testing. Both these tests do not tell us the site of bleeding and require colonoscopy for confirmation in case any of these tests are positive.[8]

Stool DNA tests- the DNA mutations in cells passed in stool from the colorectal tumors may be detected. Some tests are being approved and are in use, though their clinical efficacy has not been proved in meta-analysis.[8]

The PillCam -A colon capsule for CRC and suspected lesions, screening has been approved by the EMA (European Medicines Agency) in Europe and by the US Food and Drug Administration. In the United States, it is

approved for use in patients who have had an incomplete colonoscopy. While its role in screening for CRC is still uncertain, it could be considered in a patient with an incomplete colonoscopy who lacks obstruction. The PillCam COLON video capsule is equipped with two miniature color video cameras (one on each end), a battery and an LED light source; it measures 12 mm X 33 mm. It is designed to be ingested by the patient and transmits 4 or 35 frames per second for approximately 10 hours to a recording device worn by the patient. Data are transferred from the device to a computer that uses RAPID software to compile the video data and enable the physician to review and report the results of the PillCam study.[9]

The risks of PillCam capsule endoscopy include capsule retention, aspiration and skin irritation. After ingesting the PillCam capsule and until it is excreted, patients should not be near any source of powerful electromagnetic fields, such as one created by an MRI device. Medical, endoscopic or surgical intervention may be necessary to address these complications, should they occur. A normal or negative capsule endoscopy examination does not exclude the possibility of colon polyps or colon cancer.[9]

Tumor markers

Serum Tumor Markers- A variety of serum markers have been associated with CRC, particularly carcinoembryonic antigen (CEA). However, all these markers, including CEA, have a low diagnostic ability to detect primary CRC due to significant overlap with benign disease and low sensitivity for early-stage disease. A meta-analysis concluded that the pooled sensitivity of CEA for diagnosis of CRC was only 46 percent (95% CI 0.45-0.47). No other conventional tumor marker had a higher diagnostic sensitivity, including carbohydrate antigen 19-9 (CA 19-9, pooled sensitivity 0.30, 95% CI 0.28-0.32).[10]

Furthermore, specificity of CEA is also limited. In the previously mentioned meta-analysis, the specificity of CEA for diagnosis of CRC was 89 percent (95% CI 0.88-0.92). Non-cancer-related causes of an elevated CEA include gastritis, peptic ulcer disease, diverticulitis, liver disease, chronic obstructive pulmonary disease, diabetes, and any acute or chronic inflammatory state. In addition, CEA levels are significantly higher in cigarette smokers than in non-smokers. [10]

An expert panel on tumor markers in breast and colorectal cancer convened by the American Society of Clinical Oncology (ASCO) recommended that neither serum CEA nor any other marker, including CA 19-9, should be used as a screening or diagnostic test for CRC.[11] A similar recommendation has been made by the European Group on Tumor Markers.[11]

However, CEA levels do have value in the follow-up of patients with diagnosed CRC. ASCO guidelines recommend that serum CEA levels be obtained preoperatively in most patients with demonstrated CRC to aid in surgical treatment planning, post-treatment follow-up, and in the assessment of prognosis:

●Serum levels of CEA have prognostic utility in patients with newly-diagnosed CRC. Patients with preoperative serum CEA >5 ng/mL have a worse prognosis, stage for stage, than those with lower levels. ●Elevated preoperative CEA levels that do not normalize following surgical resection imply the presence of persistent disease and the need for further evaluation.

Furthermore serial assay of postoperative CEA levels should be performed for five years for patients with stage II and III disease if they may be a potential candidate for surgery or chemotherapy if metastatic disease is discovered. A rising CEA level after surgical resection implies recurrent disease and should prompt follow-up radiologic imaging. Blood-based tests for early detection of CRC, or to monitor for postoperative recurrence, are under active development at present. Amongst the contenders are Sept9 and the Gemini test.[10]
CA 19-9 is a blood marker that may be elevated in colorectal cancer.[11]

Tumor markers found in tumor tissue:

- **MSI (microsatellite instability):** MSI is a way to measure a deficiency of mismatch repair (MMR) in tumor DNA. A deficiency of MMR results in an increase in mutations within the colon cells, which partly contributes to the development of colon cancer.
    - MSI can be used to identify early stage colon cancer that may require more aggressive treatment or to identify patients who should have further genetic testing due to the risk for a familial syndrome related to several cancer types.
    - MSI identifies tumors as MSI-high (MSI-H) or MSI-Stable and MSI-low.[12]
- **K-RAS mutations:** specific mutations in the K-RAS gene can predict whether or not a patient is likely to benefit from treatment with several biologic therapies.[12]

Endoluminal Ultrasound- Several meta-analyses have evaluated the staging accuracy of EUS, and some have compared the accuracy of EUS with that of magnetic resonance imaging (MRI) and CT. In general, EUS was found to exhibit high sensitivity (80%-96%) and specificity (75%-98%) for the staging of T0 to T3 disease. EUS may have higher T-staging accuracy than other cross-sectional imaging tests, but nodal staging accuracy was modest for EUS (67% sensitivity, 78% specificity) and not statistically different among the 3 imaging modalities. EUS has diagnostic role in rectal malignancies but less so for colonic malignancies.[13]

Computer Tomography Scan -In the United States and elsewhere, the standard practice at most institutions is that all patients with stage II, III, or IV CRC undergo chest, abdomen, and pelvic CT, either prior to and sometimes after resection (for residual disease or response to chemotherapy).

Abdomen and pelvis — In patients with newly-diagnosed CRC, preoperative abdominal and pelvic CT scans can demonstrate regional tumor extension, regional lymphatic and distant metastases, and tumor-related complications (eg, obstruction, perforation, fistula formation). The sensitivity of CT for detecting distant metastasis is higher (75 to 87 percent) than for detecting nodal involvement (45 to 73 percent) or the depth of transmural invasion (approximately 50 percent). The sensitivity of CT for detection of malignant lymph nodes is higher for rectal than for colon cancers; perirectal adenopathy is presumed to be malignant since benign adenopathy is typically not seen in this area in the absence of demonstrable inflammatory process (eg, proctitis, fistula, perirectal abscess).[14]

- CT scan is not a reliable diagnostic test for low-volume tumor on peritoneal surfaces. The sensitivity of CT for detecting peritoneal implants depends on the location and size of the implants. In one study, the sensitivity of CT for nodules <0.5 cm was 11 percent and it was only 37 percent for implants 0.5 to 5 cm.[15]
- The finding of liver metastases on preoperative studies may not necessarily alter the surgical approach to the primary tumor, particularly in patients who are symptomatic from their primary tumor (eg, bleeding, impending obstruction). In patients with four or fewer hepatic lesions, resection may be curative, with five-year relapse-free survival rates of 24 to 38 percent. Although most surgeons advocate resection of the primary tumor and synchronous hepatic metastases at two different operations, some approach both sites at the same time.[15]

Chest — the clinical benefit of routine clinical staging with chest CT is also controversial. At least in theory, imaging of the chest might be of more value for rectal cancer since venous drainage of the lower rectum is through the hemorrhoidal veins to the vena cava, bypassing the liver, and lung metastases might be more common.[16]

- Overall, the risk of malignancy for most patients with indeterminate pulmonary nodules (approximately 1 percent) seems sufficiently low that further preoperative diagnostic workup is unnecessary.

Liver MRI — Contrast-enhanced magnetic resonance imaging (MRI) of the liver can identify more hepatic lesions than are visualized by CT, and is particularly valuable in patients with background fatty liver changes. A meta-analysis concluded that MRI is the preferred first-line imaging study for evaluating CRC liver metastases in patients who have not previously undergone therapy. However, newer-generation CT scanners and the use of triple-phase imaging during contrast administration have improved sensitivity of CT for detection of liver metastases. In current practice, liver MRI is generally reserved for patients who have suspicious but not definitive findings on CT scan, particularly if better definition of hepatic disease burden is needed in order to make decisions about potential hepatic resection.[17]

PET scans — Positron emission tomography (PET) scans do not appear to add significant information to CT scans for routine preoperative staging of CRC. The established role of PET scanning in patients with CRC as an adjunct to other imaging modalities is described in the following settings:

●Localizing sites of disease recurrence in patients who have a rising serum carcinoembryonic antigen (CEA) level and nondiagnostic conventional imaging evaluation following primary treatment. In this setting, PET scanning can potentially localize occult disease, permitting the selection of patients who may benefit from exploratory laparotomy.

In an illustrative series, 105 such patients underwent PET scanning and subsequent abdominopelvic CT scans. Compared with CT and other conventional diagnostic studies, PET scanning had a higher sensitivity (87 versus 66 percent) and specificity (68 versus 59 percent) for the detection of clinically relevant tumor. In a second report, PET scan findings led to a potentially curative resection in 14 of 50 patients (28 percent) with elevated serum CEA levels and a completely normal or equivocal conventional diagnostic work-up.[18]

●Evaluation of patients who are thought to be present or future candidates for resection of isolated CRC liver metastases. The routine use of PET prior to attempted resection reduces the number of nontherapeutic laparotomies.[19]

However, generally, the benefit of a PET scan is to detect extrahepatic metastases in patients considered liver resection candidates, and in this situation, it is appropriate to obtain a PET prior to initiation of chemotherapy.[19]

Staging

After investigations and confirmation of CRC, the disease has to be staged and the Dukes' staging classification is now gradually being replaced by the tumor/node/metastases (TNM) classification:

- TX: primary cannot be assessed.
    - T0: no evidence of primary carcinoma in situ (Tis) - intraepithelial or lamina propria only.
    - T1: invades submucosa.

    - T2: invades muscularis propria.
    - T3: invades subserosa or non-peritonealised pericolic tissues.
    - T4: directly invades other tissues and/or penetrates visceral peritoneum.
- NX: regional nodes cannot be assessed.
    - N0: no regional nodes involved.
    - N1: 1-3 regional nodes involved.
    - N2: 4 or more regional nodes involved.
- MX: distant metastasis cannot be assessed.
    - M0: no distant metastasis.
    - M1: distant metastasis present (may be transcoelomic spread).[20]

Colorectal cancer can then be **staged** as follows:[20]

- **Stage 0:** carcinoma in situ (CIS).
- **Stage 1:** cancer growth through the inner lining of the bowel, or into the muscle wall, but no further. There is no cancer in the lymph nodes (T1, N0, M0 or T2, N0, M0).
- **Stage 2**: further local spread of the cancer but no lymph nodes are affected (N0) and the cancer has not spread to another area of the body (M0):
- ✓ **Stage 2a**: cancer growth into the outer covering of the bowel wall (T3, N0, M0).
- ✓ **Stage 2b:** cancer growth through the outer covering of the bowel wall and into tissues or organs next to the bowel (T4).
- **Stage 3**: lymph node involvement:
    - ✓ **Stage 3a**: cancer growth into the muscle layer, and between 1 and 3 nearby lymph nodes contain cancer cells (T1, N1, M0 or T2, N1, M0).
    - ✓ **Stage 3b:** cancer growth into the outer lining of the bowel wall or into surrounding body tissues or organs, and between 1 and 3 nearby lymph nodes contain cancer cells (T3, N1, M0 or T4, N1, M0).
    - ✓ **Stage 3c**: cancer growth of any local size but has spread to 4 or more nearby lymph nodes (any T, N2, M0).
- **Stage 4:** cancer has spread to other parts of the body (eg, liver or lungs) (any T, any N, M1).

Grading[20]

Colorectal cancer can also be graded according to the cancer cell differentiation:

- Grade 1 (low grade): well differentiated.
- Grade 2 (moderate grade): moderately differentiated.
- Grade 3 (high grade): poorly differentiated.

Treatment

Surgery- is the main treatment for earlier-stage colon cancers and to a certain extent for later stage carcinomas if resectable. The type of surgery used depends on the stage of the cancer, where it is, and the goal of the surgery.

Polypectomy and local excision

Some early colon cancers (stage 0 and some early stage I tumors) or polyps can be removed during a colonoscopy

- For a **polypectomy**, the cancer is removed as part of the polyp, which is cut at its stalk. This is usually done by passing a wire loop through the colonoscope to cut the polyp from the wall of the colon using diathermy
- A **local excision** is a slightly more extensive procedure that can be used to remove superficial cancers with an adequate margin
- The same procedures can be opted for undiagnosed lesions (probably benign polyps) where the biopsy itself can be diagnostic and therapeutic. Later the patient can be kept on surveillance using colonoscopy to detect new lesions.[21]

For stage 2 colon cancers surgery is the mainstay of treatment, the procedure depends on the site of tumor.
For caecum and ascending colon cancers, right radical hemicolectomy where 30 cm of distal ileum, caecum, ascending colon and medial 2/3rd of transverse colon is removed along with their draining lymphatics. The right branch of middle colic and ileocolic arteries are ligated at their origins, to enable the lymphatics to be radically removed.

For transverse colon growths, right extended hemicolectomy where the middle colic is ligated and anastomosis between ileum and descending colon is made.

For left colonic growths, left radical hemicolectomy, where the left colic artery and left branch of middle colic artery are ligated and transverse colon and rectum are anastomosed.[21]

Colectomies (surgical procedures) are indicated sometimes for benign etiologies like-

Diverticulosis- usually, the only operative indication for surgery in diverticulosis is for hemorrhage. Diverticulosis may cause a massive lower gastrointestinal (GI) bleed, and if this cannot be controlled with endoscopy or interventional radiology, surgery may be required. If the area of the bleed is localized with angiography, a segmental resection corresponding to the bleeding may be performed. In an unstable patient or one who has been transfused with more than 10 units of blood upon hospital admission or more than 6 units of blood in 24 hours or is hemodynamically unstable, an emergency subtotal colectomy may be required.[22]
Diverticulitis- The indication for colon resection is recurrent attacks or complicated diverticulitis, which is characterized by perforation, obstruction, abscess, or fistula. Here segmental resection followed by colostomy and Hartmann procedure of closing the distal rectal stump is done and stoma closure done after 4 to 6 weeks.[22]

Ulcerative colitis
Total proctocolectomy is the only curative treatment for ulcerative colitis. It is indicated when medical management fails or is intolerable owing to the side effects of the medication. In addition, surgical treatment is indicated in patients who develop dysplasia or colon cancer. Surgery alleviates symptoms and eliminates the risk of colonic adenocarcinoma As in low anterior resections, a J pouch is made using small intestine, to improve the patients' quality of life postoperatively by restoring intestinal continuity.[23]

Polyposis syndromes

a. Familial adenomatous polyposis

Patients with familial adenomatous polyposis (FAP) develop hundreds to thousands of noncancerous polyps in the colon as early as their teenage years. These polyps are premalignant and will develop into cancer. The average age at which an individual with FAP develops colon cancer is 39 years. Thus, these patients may choose to undergo prophylactic colectomy.[24]

b. Hereditary nonpolyposis colorectal cancer

Like FAP, hereditary nonpolyposis colorectal cancer (HNPCC) is an inherited colorectal cancer syndrome. Although patients with HNPCC do not develop as large a number of polyps as those with FAP do, they have an 80% lifetime incidence of colorectal cancer. Surgical resection of the entire colon is the only definitive way of preventing colon cancer. Thus, patients with HNPCC may choose to undergo prophylactic total colectomy or proctocolectomy.[25]
For stage 3- Surgery followed by adjuvant chemotherapy is the modalities of treatment for stage 3 colon cancers.. The common chemotherapy regimens being followed are.[26,27]

5-FU/leucovorin	Leucovorin 500mg/m2 given as a 2-hour infusion and repeated weekly × 6 weeks, plus 5-FU 500mg/m2 given IV bolus 1 hour after the start of leucovorin and repeated weekly × 6 weeks. Repeat cycle every 8 weeks for 4 cycles.
mFOLFOX6	Day 1: Oxaliplatin 85mg/m2 IV over 2 hours Day 1: Leucovorin 400mg/m2* IV over 2 hours Days 1–3: 5-FU 400mg/m2 IV bolus on day 1, then 1,200mg/m2/day × 2 days (total 2,400mg/m2 over 46–48 hours)† IV continuous infusion. Repeat cycle every 2 weeks.
FOLFIRI	Day 1: Irinotecan 180mg/m2 IV over 30–90 minutes Day 1: Leucovorin 400mg/m2* IV infusion to match duration of irinotecan infusion Days 1–3: 5-FU 400mg/m2 IV bolus day 1, then 1,200mg/m2/day × 2 days (total 2,400mg/m2 over 46–48 hours)† continuous infusion. Repeat cycle every 2 weeks.

For stage 4 or metastatic disease.
If the primary is resectable on imaging , radical surgery remains the mainstay of treatment. Surgery is followed by chemotherapy. Liver metastasis in colon cancer if resectable , the five-year survival rate after resection of colorectal liver metastases has reached 26%-58%. Up to 30 percent of people may be cured if metastases in the liver can be completely removed (the medical term for this is "resected").[28]

Previously more than 4 metastasis, bilobar metastasis and extrahepatic involvement were taken as unresectablity criteria for hepatic metastasis if colon cancer, involvement of hepatic pedicle lymph nodes and an inadequate resection margin of < 1 cm. The current criteria focus on what should be left after hepatic resection. Nowadays, the definition of resectability includes a complete resection with tumor-free surgical margins (R0 resection), sparing at least two liver segments having an independent inflow, outflow, and biliary drainage. The amount of the liver remnant after resection should not be less than 20% and 30% of the total liver volume in normal and cirrhotic patients, respectively. This can be accurately predicted by computed tomography (CT) or magnetic resonance imaging (MRI) during preoperative evaluation. Surgery resection margin is still improved with use of intra operative ultrasound. [28]

FIRST-LINE CHEMOTHERAPY FOR METASTATIC COLORECTAL CANCER
Conventional chemotherapy drugs and targeted agents are generally used in combination for people with newly diagnosed, previously untreated metastatic colorectal cancer. Many different combinations have been developed

and may be recommended for initial (first-line) treatment. Current chemotherapy regimens including oxaliplatin and irinotecan in addition to 5-fluorouracil (5-FU), and leucovorin (LV) have achieved improved response rates in colorectal liver metastases, with significant reduction in disease bulk in almost 50% of patients and a median survival approaching two years.[28,29]

FOLFOX, FOLFIRI, and XELOX (Oxaliplatin plus capecitabine) — several combination chemotherapy regimens may be considered for the initial treatment of metastatic colorectal cancer. Each of these regimens consists of two or three drugs, used together in a specific way.[29]

Newer approaches in chemotherapy
Different approaches are being tested in clinical trials, including:

- Testing new chemo drugs (such as trifluridine and tipiracil) or drugs that are already used against other cancers (such as cisplatin or gemcitabine).
- Looking for new ways to combine drugs already known to be active against colorectal cancer, such as irinotecan and oxaliplatin, to improve their effectiveness.
- Studying the best ways to combine chemotherapy with radiation therapy, targeted therapies, and/or immunotherapy.[30]

Targeted therapy - Other drugs that are active against metastatic colorectal cancer work by a different mechanism. These are referred to as "targeted therapy agents" since they are either antibodies (a type of protein) or drugs that work to inhibit specific proteins that are important for the growth and/or survival of colon cancer cells.
Because targeted therapy agents do not directly interfere with rapidly dividing cells, they do not have the usual side effects of conventional chemotherapy.
Targeted therapies are currently used to treat advanced colorectal cancers, but newer studies are trying to determine if using them with chemotherapy in earlier-stage cancers as part of adjuvant therapy may further reduce the risk of recurrence.[31]

Currently available targeted chemotherapy agents include:

- **Bevacizumab**– Bevacizumab binds to a protein called vascular endothelial growth factor (VEGF). VEGF is involved in the development of a blood supply within a growing cancer; this blood supply is essential for the tumor to grow and spread. Bevacizumab enhances the antitumor effect of other chemotherapy drugs. Bevacizumab is not effective when given by itself, but is generally given in combination with other drugs, such as FU (or capecitabine), oxaliplatin, and irinotecan (see below).
- Ramucirumab– Ramucirumab is a protein that binds to a receptor for VEGF (VEGFR2), thus targeting signaling through the same pathway that bevacizumab does. Like bevacizumab, ramucirumab enhances the antitumor effect of other chemotherapy drugs. In the United States, it is approved in combination with an irinotecan-based chemotherapy regimen for patients who have previously been treated with bevacizumab plus an oxaliplatin-containing regimen.
- Aflibercept– Intravenous aflibercept represents another method of interfering with a tumor's blood supply; it is a fusion protein that acts by "trapping" VEGF and preventing it from activating its receptors on the tumor cells. In the United States, aflibercept is approved, in combination with irinotecan-based chemotherapy, for patients whose tumors have progressed while receiving an oxaliplatin-containing chemotherapy regimen, with or without bevacizumab.
- Regorafenib– Regorafenib is a pill form of a drug that blocks several VEGF receptors as well as other proteins referred to as kinases. In the United States, regorafenib is approved as a single agent for the treatment of patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens as well as other targeted therapies.
- Cetuximab– Cetuximab targets a different protein, the epidermal growth factor receptor (EGFR), which is found in about 80 percent of colorectal cancers. Erbitux is effective even if EGFR is not found in an individual tumor. Cetuximab does not work for all patients. It depends on whether or not the tumor has a specific abnormality (a mutation in a set of genes called RAS genes).
  - If the tumor has a RAS gene mutation, cetuximab does not work.
  - If the tumor does not have a RAS mutation, cetuximab might work.

  Unlike bevacizumab, cetuximab is active when given alone or in combination with other drugs, like irinotecan.
- Panitumumab– Like cetuximab, panitumumab also targets the EGFR. Like cetuximab, it is effective only for tumors that do not have a specific mutation in one of the RAS genes.
- Trifluridine-tipiracil– Trifluridine-tipiracil is an oral agent that contains two components, trifluridine and tipiracil, each of which have different properties. In the United States, trifluridine-tipiracil is approved for the treatment of patients who have been previously treated with fluoropyrimidine-, oxaliplatin-, and irinotecan-containing chemotherapy regimens as well as other targeted therapies.[31]

Immunotherapy[32]
An exciting area of research is the field of immunotherapy, which is treatment that uses the body's own immune system to fight the cancer. The body normally "checkpoints" – molecules on immune cells that need to be turned on (or off) to start an immune response. Cancer cells sometimes use these checkpoints to avoid being attacked by

the immune system. These treatments work by targeting molecules that serve as checks and balances on immune responses. By blocking these inhibitory molecules or, alternatively, activating stimulatory molecules, these treatments are designed to unleash or enhance pre-existing anti-cancer immune responses. Some of the trials are ongoing and used mainly for

- For all stage IV or recurrent colorectal cancer
- For patients with stage IIa or III colorectal cancer following surgery (i.e., in the adjuvant setting)

Pembrolizumab An Anti-PD-1 Antibody

- A phase II study for patients with microsatellite unstable (MSI) tumors, including colorectal cancer (NCT01876511).
- Several stage II trials for patients with colorectal cancer (NCT02260440, NCT02437071, NCT02375672).
- Two phase I/II studies for patients with advanced cancer and advanced genitourinary cancer, including colorectal cancer (NCT02318901, NCT02268825).
- A phase I trial for patients with metastatic or advanced epithelial cancers, including colorectal cancer, in combination with **enadenotucirev**, an oncolytic virus (NCT02636036).
-

Nivolumab An Anti-PD-1 Antibody

- A phase I/II trial for patients with recurrent and metastatic colon cancer, +/- **ipilimumab**, an anti-CTLA-4 antibody (NCT02060188).
- A phase I/II trial for patients with solid tumors, including colorectal cancer, in combination with **varlilumab** (CDX-1127), an anti-CD27 antibody (NCT02335918).

Ipilimumab: An Anti-CTLA-4 Antibody

- A phase I/II trial for patients with recurrent and metastatic colon cancer, in combination with **nivolumab** (NCT02060188).
- A phase I/II trial for patients with advanced solid tumors which have spread to the liver, lung, or adrenal gland (NCT02239900).

Durvalumab: An Anti-PD-L1 Antibody

- A phase II trial for patients with colorectal cancer (NCT02227667).
- A phase II trial for patients with brain metastasis from epithelial-derived cancers, including colorectal cancer (NCT02669914).

Tremelimumab: An Anti-CTLA-4 Antibody

- A phase I trial for patients with advanced solid tumors, including colorectal cancer, in combination with **durvalumab** (MEDI4736) (NCT01975831).

Atezolizumab): An Anti-PD-L1 Antibody

- A phase I trial testing CPI-444, an oral small molecule targeting a receptor on immune cells, alone and in combination with **atezolizumab** for patients with advanced cancers, including colorectal cancers (NCT02655822).

Varlilumab :An Anti-CD27 Antibody

- A phase I/II trial for patients with solid tumors, including colorectal cancer, in combination with **nivolumab** (NCT02335918).

Monoclonal Antibodies[32]

Monoclonal antibodies are molecules, generated in the lab, that target specific antigens on tumors. Several monoclonal antibodies are currently being tested in clinical trials:

- A phase II trial of **RO5520985**, a bispecific anti-ANG-2/anti-VEGF-A antibody, in patients with untreated metastatic colorectal cancer (NCT02141295).
- A phase I/II trial testing **IMMU-132**, an antibody-drug conjugate targeting Trop-2, in patients with epithelial cancers (NCT01631552).
- A phase I/II trial of **IMMU-130**, an antibody-drug conjugate targeting CEACAM5, which is expressed on the surface of a majority of solid tumors, in patients with metastatic colorectal cancer (NCT01605318).
- A phase I study of **MGD007**, a dual-affinity re-targeting (DART) protein designed to target the glycoprotein A33 antigen, which is found on 95% of colorectal cancers, in patients with metastatic colorectal cancer (NCT02248805)
- A phase I study of **MEHD7945A**, a HER3 and EGFR antibody, in patients with locally advanced or metastatic tumors with mutant KRAS (NCT01986166)
- A phase I study of **OMP-131R10**, an anti-RSPO3 antibody, in patients with previously treated metastatic colorectal cancer (NCT02482441)

Cancer Vaccines[32]

Cancer vaccines are designed to elicit an immune response against tumor-specific or tumor-associated antigens, encouraging the immune system to attack cancer cells bearing these antigens. Tumor antigens that have been targeted in colorectal cancer include carcinoembryonic antigen (CEA), MUC1, and NY-ESO-1. Several clinical studies of cancer vaccines for colorectal cancer are open, including:

- A phase III study of **Imprime PGG®** in combination with cetuximab in subjects with recurrent or progressive KRAS wild type colorectal cancer (PRIMUS) (NCT01309126).
- A phase II study of a dendritic cell vaccine for patients with chemo-refractory metastatic colorectal cancer (NCT02615574).
- A phase II trial of a dendritic cell-based vaccine using the **NY-ESO-1** cancer antigen, given in combination with T cells genetically engineered to target the cancer-specific antigen **NY-ESO-1** (NCT01697527).
- A phase I trial to test **AVX701**, which targets the CEA antigen that has been found to be associated with colorectal cancers, in patients with stage 3 colorectal cancer (NCT01890213).
- A phase I trial of a vaccine that targets the **HER2** antigen in patients with metastatic cancer, including colorectal cancer (NCT01376505).
- A phase I study of a **HER2** vaccine in patients with HER2-expressing tumors (NCT01730118).
- A phase I trial of a personalized peptide vaccine for patients with colorectal cancer (NCT02600949).
- A phase I study of a **NY-ESO-1** vaccine, T cells genetically engineered to target **NY-ESO-1**, and the checkpoint inhibitor **ipilimumab** (NCT02070406).
- Two pilot studies testing the **GVAX** vaccine in patients with colorectal cancer (NCT01952730, NCT01966289).

Adoptive Cell Therapy[32]

In this approach, immune cells are removed from a patient, genetically modified or treated with chemicals to enhance their activity, and then re-introduced into the patient with the goal of improving the immune system's anti-cancer response. Clinical trials include:

- A phase II trial using tumor-infiltrating lymphocytes (TILs) in metastatic digestive tract cancers (NCT01174121).
- A phase II trial of T cells genetically engineered to target the cancer-specific antigen **NY-ESO-1**, given in combination with a dendritic cell-based vaccine using the NY-ESO-1 cancer antigen (NCT01697527).
- A phase II study of T cells genetically reengineered to target the **NY-ESO-1** antigen in patients with NY-ESO-1-positive cancers (NCT01967823).
- A phase I/II trial of T cells engineered to target **MAGE-A3** in patients with metastatic cancer that expresses MAGE-A3, including colorectal cancer (NCT02111850).
- A phase I/II trial of chimeric antigen receptor (CAR) T cells in patients with a **MUC1**-positive solid tumor, including colorectal cancer (NCT02617134).
- A phase I study of T cells genetically engineered to target **NY-ESO-1** in combination with the checkpoint inhibitor **ipilimumab** (NCT02070406).
- A phase I trial to test natural killer (NK) cells, important innate immune cells, in patients with advanced cancer, including colorectal cancer (NCT00720785).

Oncolytic Virus Therapies[32]

Oncolytic virus therapy uses a modified virus that can cause tumor cells to self-destruct and generate a greater immune response against the cancer.

- A phase II trial to test **Reolysin**, a virus that is able to replicate specifically in cancer cells bearing an activated RAS pathway, in patients with KRAS-mutant metastatic colorectal cancer (NCT01274624).
- A phase I trial of **enadenotucirev**, an oncolytic virus, for patients with metastatic or advanced epithelial cancers, including colorectal cancer, in combination with **pembrolizumab** (NCT02636036).

Adjuvant Immunotherapies[32]

Adjuvants are substances that are either used alone or combined with other immunotherapies to boost the immune response. Some adjuvant immunotherapies use ligands—molecules that bind to proteins such as receptors—to help control the immune response. These ligands can be either stimulating (agonists) or blocking (antagonists).

- A phase I/II trial of **epacadostat** (INCB024360), an IDO inhibitor, in combination with **nivolumab** a PD-1 checkpoint inhibitor, in patients with advanced cancer, including colorectal cancer (NCT02327078). IDO is expressed by a number of tumor types and correlates with poor prognosis.
- A phase I/II trial of tumor necrosis factor and **rintatolimod**, which binds to Toll-like receptor 3 (TLR3), in patients with recurrent resectable colorectal cancer (NCT01545141).
- A phase I trial of **motolimod** (VTX-2337), a Toll-like receptor 8 (TLR8) agonist, in patients with metastatic, persistent, recurrent, or progressive solid tumors, including colorectal cancer (NCT02650635).

Cytokines[32]

Cytokines are messenger molecules that help control the growth and activity of immune system cells.

- A phase I trial of **AM0010**, a recombinant human interleukin 10 (IL-10), in patients with advanced solid tumors, including colorectal cancer (NCT02009449).
- A phase I trial to test **interleukin 12 (IL-12)** in patients with epithelial solid tumors (NCT01417546).

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PROSTATE CANCER

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1. EPIDEMIOLOGY AND ETIOLOGY

Incidence rates show that prostate cancer (PCa) is the fifth most common malignancy worldwide and the second most common in men . Prostate cancer makes up 11.7% of new cancer cases overall, 19% in developed countries, and 5.3% in developing countries. The lowest yearly incidence rates occur in Asia (1.9 cases per 100,000 in China) and the highest in North America and Scandinavia, especially in African-Americans (249 cases per 100,000).Mortality also varies widely among countries, being highest in the Caribbean (28 per 100,000 per year) and lowest in Southeast Asia, China, and North Africa (<5 per 100,000 per year)

Epidemiological studies have shown strong evidence for a genetic predisposition to PCa, based on two of the most important factors, racial/ethnic background and family history. Genome-wide association studies have identified 100 common susceptibility loci who contribute to the risk for PCa. A small subpopulation of men with PCa (about 9%) have true hereditary PCa. This is defined as three or more affected relatives or at least two relatives who have developed early-onset disease, i.e. before the age of 55.Patients with hereditary PCa usually have a disease onset six to seven years earlier than spontaneous cases, but do not differ in other ways. Exogenous factors affect the risk of progression from so-called latent PCa to clinical PCa. Factors such as diet, sexual behaviour, alcohol consumption, exposure to ultraviolet radiation, chronic inflammation and occupational exposure have all been discussed as being aetiologically important .Hereditary factors are important in determining the risk of developing clinical PCa, while exogenous factors may have an important impact on the risk of progression. Both genetics and environment are important in the origin and evolution of prostate cancer. Most prostate cancer is polygenic, but some hereditary forms may be determined by variants in a single or relatively few genes.HPC1 is an autosomal-dominant gene with high penetrance and encodes for the enzyme RNaseL, which has both antiviral and pro-apoptotic activity. Commonly observed variants in RNaseL result in reduced enzymatic activity and have been associated with an increased risk of prostate cancer. Infectious agents, both viruses and bacteria, may be important in the genesis of prostate cancer. Other prostate cancer susceptibility genes are mediators of inflammation, DNA repair, and defenses against oxidative stress. There is, as yet, insufficient evidence to recommend lifestyle changes (such as a reduced intake of animal fat and an increased intake of fruit, cereals and vegetables) in order to decrease the risk. But such lifestyle modifications might be associated with other non-specific benefits and must therefore be encouraged.

2. CHEMOPREVENTION

Prostate cancer is an attractive and appropriate target for primary prevention, because of its incidence, prevalence, and disease-related mortality. The Prostate Cancer Prevention Trial demonstrated that finasteride reduces the period prevalence of prostate cancer by 25%. SELECT demonstrated that neither vitamin E nor selenium prevent prostate cancer. 5α-Reductase inhibitors and other hormonal agents, antioxidants, and statins are among the many agents currently being investigated in prostate cancer chemoprevention. None of the available 5-ARIs have been approved for this indication. At this moment in time no definitive recommendation can be provided for preventive measures due to the lack of conclusive data.

3. PATHOLOGY

A.PROSTATIC INTRAEPITHELIAL NEOPLASIA

Prostatic intraepithelial neoplasia (PIN) consists of architecturally benign prostatic acini or ducts lined by cytologically atypical cells and is classified as low-grade and high-grade neoplasias**Diagnostic reports shouldnot comment on low-grade PIN.** First, pathologists cannot reproducibly distinguish between low-grade PIN and benign prostate tissue. Second, when low-grade PIN is diagnosed on needle biopsy, these patients are at no greater risk of having carcinoma on repeated biopsy than are men with a benign biopsy finding. Evidence that high-grade PIN (HGPIN) is a precursor to some prostate carcinomas includes the following: There is an increase in the size and number of high-grade PIN foci in prostates with cancer compared with prostates without carcinoma; with increasing amounts of high-grade PIN, there are a greater number of multifocal carcinomas; both high-grade PIN and carcinoma preferentially involve the peripheral zone; and biomarkers and molecular changes show similarity between high-grade PIN and carcinoma. About 20% of high-grade PIN lesions harbor a *TMPRSS2-ERG* fusion gene, which is a common molecular abnormality detectable in about 50% of prostate cancers.

B. ADENOCARCINOMA

Location :-In clinical stage T2 carcinomas and in 85% of nonpalpable tumors diagnosed on needle biopsy (stage T1c), the major tumor mass is peripheral in location. In the remaining cases, tumors are predominantly located in the transition zone (i.e., periurethrally or anteriorly). Tumors that appear to be unilateral on rectal examination are bilateral in approximately 70% of cases when they are examined for pathology. Adenocarcinoma of the prostate is multifocal in more than 85% of cases.

Spread of Tumor:-Because the prostate lacks a discrete histologic capsule,*extraprostatic extension* is preferable to “capsular penetration”as the term to describe a tumor that has extended out of the prostate into periprostatic soft tissue. Peripherally located adenocarcinomas of the prostate tend to extend out of the prostate through perineural space invasion. Perineural invasion by itself in radical prostatectomy specimens does not worsen prognosis. In contrast, vascular invasion increases the risk of recurrence after radical prostatectomy. Extraprostatic extension preferentially occurs posteriorly and posterolaterally, paralleling the location of most adenocarcinomas. Further local spread of tumor may lead to seminal vesicle invasion and may also rarely involve the rectum, where it may be difficult to distinguish from a rectal primary tumor. The most frequent sites of metastatic prostate carcinoma are lymph nodes and bone. In addition to lymph nodes, bones, and lung, the next most common regions of spread of prostate cancer at autopsy are bladder, liver, and adrenal gland.

Tumor Volume :-In general, the size of a prostate cancer correlates with its stage. Extraprostatic extension is uncommon in tumors of less than 0.5 cm^3 and tumors that are less than $4cm^3$ uncommonly reveal lymph node metastases or seminal vesicle invasion. Tumor volume is also proportional to grade. The location and grade of the tumor also modulate the effect of tumor volume. For example, transition zone tumorsextend out of the prostate at larger volumes than do peripheral zone tumors, because of their lower grade and greater distance from the edge of the gland.

Grade: Although numerous grading systems exist for the evaluation of prostatic adenocarcinoma, the Gleason grading system is the most widely accepted (Gleason and Mellinger, 1974). The Gleason system is based on the glandular pattern of the tumor as identified at relatively low magnification. Cytologic features play no role in the grade of the tumor. Both the primary (predominant) and the secondary (second most prevalent) architectural patterns are identified and assigned a grade from 1 to 5, with 1 being the most differentiatedand 5 being the least differentiated .Because both the primary and the secondary patterns are influential in predicting prognosis, there is a Gleason sum or score obtained by the addition of the primary and secondary grades. If a tumor has only one histologic pattern, then for uniformity, the primary and secondary patterns are given the same grade.

2005 International Society of Urological Pathology Modified Gleason System

Pattern 1
Circumscribed nodule of closely packed but separate, uniform, rounded to oval, medium-sized acini (larger glands than pattern 3)

Pattern 2
Like pattern 1, fairly circumscribed, yet at the edge of the tumor nodule there may be minimal infiltration. Glands are more loosely arranged and not quite as uniform as Gleason pattern 1

Pattern 3
Discrete glandular units.Typically smaller glands than seen in Gleason pattern 1 or 2
Infiltrates in and amongst non-neoplastic prostate acini. Marked variation in size and shape

Pattern 4
Fused microacinarglands.Ill-defined glands with poorly formed glandular lumina.Large cribriform glands
Cribriform glands.Hypernephromatoid

Pattern 5
Essentially no glandular differentiation, composed of solid sheets, cords, or single cells.
Comedocarcinoma with central necrosis surrounded by papillary, cribriform, or solid masses.

International Society of Urological Pathology 2014 grade groups

GLEASON SCORE	GRADE
2-6	1
7 (3+4)	2
7 (4+3)	3
8 (5+3) (3+5) (4+4)	4
9-10	5

Subtypes
a. **Mucinous adenocarcinoma** of the prostate gland is one of the least common morphologic variants of prostatic carcinoma. They behave like nonmucinous prostate carcinomas, having a propensity to develop bone metastases with advanced disease.
b. **Neuroendocrine variant** -Even in ordinary adenocarcinomas of theprostate without light microscopic evidence of neuroendocrinedifferentiation, almost half show neuroendocrine differentiationon evaluation with immunohistochemistry for multiple neuroendocrinemarkers.

c. Smallcell carcinomas of the prostate are identical to small cell carcinomas of the lung . In approximately50% of the cases, the tumors are mixed small cell carcinoma andadenocarcinoma of the prostate. Although most small cell tumorsof the prostate lack clinically evident hormone production, theyaccount for the majority of prostatic tumors with clinically evidentACTH or ADH production. The average survival of patients with small cell carcinoma of the prostate is less than a year. Small cell carcinomas are not assigned a Gleason grade.

d. Ductal adenocarcinoma Between 0.4% and 0.8% of prostatic adenocarcinomas arise from prostatic ducts .Tumors are often underestimated clinically because DRE findings and PSA levels may be normal. Usually advanced stage atpresentation and have an aggressive course; they shouldbe regarded as Gleason score 4 + 4 = 8, because of theirshared cribriform morphologic features with acinaradenocarcinoma Gleason score 8 and similar prognosis.

e. Squamous carcinoma-Pure primary squamous carcinoma ofthe prostate is rare and is associated with poor survival.

f. Mesenchymal Tumors -Sarcomas of the prostate account for 0.1% to 0.2% of all malignantprostatic tumors. Rhabdomyosarcomas are themost frequent mesenchymal tumor within the prostate and areseen almost exclusively in childhood. Leiomyosarcomas are themost common sarcomas involving the prostate in adults.

g. Urothelial Carcinoma-Primary urothelial carcinoma of the prostate without bladderinvolvement accounts for 1% to 4% of all prostate carcinomas. Primary urothelial carcinomas of the prostateshow a propensity to infiltrate the bladder neck and the surroundingsoft tissue such that more than 50% of the patients present with stage T3 or T4 tumors .

GRAY-SCALE TRANSRECTAL ULTRASONOGRAPHY (TRUS)/ TRUS Biopsy

Gray-scale TRUS has become the most common imaging modality for the prostate. Endorectal probes are available in both side- and end-fire models and transmit frequencies of 6 to 10 MHz.

Indication of TRUS-Directed Biopsy

1. Diagnosis of suspected symptomatic prostate cancer (i.e., bone metastasis, cord compression)
2. Screening for prostate cancer in
   - asymptomatic patient age> 50 with a >10-year life expectancy (if strong family history or if
   - African-American, consider screening at age 45)
   - Prostate nodule or significant prostate asymmetry regardless of PSA level
   - PSA >4.0 ng/dL regardless of age
   - In men age< 60 to 65 years, consider biopsy if PSA >2.5 ng/dL
   - If PSA >0.6 ng/dL at age 40
   - Increased PSA velocity (>0.75 ng/dL/year)
   - Free PSA in considering initial biopsy with PSA <10 ng/mL: >25% no biopsy; >10% and <15%, consider biopsy; <10%, biopsy
3. Prior to intervention in symptomatic benign prostatic hyperplasia (e.g., surgical therapy or initiation of 5α-reductase inhibitors)
4. Prior to cystoprostatectomy or orthotopic urinary diversion
5. To diagnose failed radiation therapy before use of second-line therapy
6. Follow-up biopsy (3-6 months) after diagnosis of high-grade PIN or atypical small acinar proliferation

Contraindications to Prostate Biopsy

Significant coagulopathy, painful anorectal conditions, severe immunosuppression, and acute prostatitis are all contraindications of prostate biopsy.

Procedure-Cleansing Enema given before the procedure and antibiotic Prophylaxis witha dose of an oral fluoroquinolone 30 to 60 minutes before biopsy and continue therapy for 2 to 3 days.Patients are placed in the left lateral decubitus position with knees and hips flexed 90 degrees. Analgesia obtained bytopical lidocaine jelly and infiltration of local anesthesiaaround the nerve bundles .The probe is covered with a protectivecondom, the coupling medium (sonographic jelly or lubricant) is placed between the probe andthe condom, as well as between the condom and the rectalsurface.Hypoechoic foci seen on gray-scale TRUS should be considered suggestive of adenocarcinoma of the prostate and included in the biopsy specimen. A spring-driven, 18-gauge, needle core biopsy device or biopsy gun, which can be passed through the needle guide attached to the ultrasound probe, is most often used**.** The biopsy sample is typically placed in 10% formalin or perlocal protocol.

a. Sextant Biopsy-The original sextant biopsy scheme (one core, bilaterally, from the base, mid, and apex) significantly improved cancer detection for digital-directed biopsy of palpable nodules and ultrasound-guided biopsy of specific hypoechoiclesions .

b. Extended Core Biopsy Techniques

Modifications to the standard sextant biopsy scheme have focused on the importance of laterally directed cores. Numerous studies have shown improvedcancer detection rates by incorporating additional laterally directedcores into the standard systematic sextant technique, ultimatelytaking anywhere from 8 to 13 cores .

c. Repeat and Saturation Prostate Biopsy

The use of a second prostate biopsy in all cases of a negative finding on initial biopsy who have an elevated PSA nad abnormal DRE appears justified. Third and fourth repeat biopsies, however, should only be

obtained in selected patients with high suspicion of cancer and/or poor prognostic factors on the first or second biopsy. The incidence of PCa detected by saturation repeat biopsy (> 20 cores) is 30-43% and depends on the number of cores sampled during earlier biopsies.

Complications prostate biopsy:-

Complications	% of patients affected
Haematospermia	37.4
Haematuria>1 day	14.5
Rectal bleeding <2 days	2.2
Prostatitis	1.0
Fever >38.5	0.8
Epididymitis	0.7
Rectal bleeding >2days +/_surgical intervention	0.7
Urinary retention	0.2
Other complications requiring hospitalisation	0.3

Other methods of prostate biopsy-

Transperineal Prostate Biopsy-Transperineal biopsy offers an approach to the prostate in those patients lacking a rectum (e.g., surgical extirpation, congenitalanomaly).

Transurethral Prostate Biopsy-Transuretheral resection biopsy was once advocated for the diagnosisof TZ cancers or after negative TRUS sampling.

MRI guided biopsy-Endorectal magnetic resonance imaging (MRI) and MR spectroscopyas combined modalities might be able to guide and thereforelimit the number of iterative biopsies and cores for patients**.** In men with an abnormal mpMRI, MRI-Tbx had a higher detection rate of clinically significant PCa compared to TRUS biopsy (sensitivity 0.91, [95% CI: 0.87-0.94] vs. 0.76, [95% CI: 0.64- 0.84]) and a lower rate of detection of insignificant PCa (sensitivity 0.44, 95% CI: 0.26-0.64 vs. 0.83, 95% CI: 0.77-0.87).

4.SCREENING AND EARLY DETECTION

Screening for prostate cancer has recently been a matter of considerable debate. AUA Guidelines for screening are as mentioned below

Guideline Statement 1: The Panel recommends against PSA screening in men under age 40 years.In this age group there is a low prevalence of clinically detectable prostate cancer, no evidence demonstrating benefit of screening and likely the same harms of screening as in other age groups.

Guideline Statement 2: The Panel does not recommend routine screening in men between ages 40 to 54 years at average risk.For men younger than age 55 years at higher risk (e.g. positive family history or African American race), decisions regarding prostate cancer screening should be individualized.

Guideline Statement 3: For men ages 55 to 69 years the Panel recognizes that the decision to undergo PSA screening involves weighing the benefits of preventing prostate cancer mortality in 1 man for every 1,000 men screened over a decade against the known potential harms associated with screening and treatment. For this reason, the Panel strongly recommends shared decision-making for men age 55 to 69 years that are considering PSA screening, and proceeding based on a man's values and preferences.The greatest benefit of screening appears to be in men ages 55 to 69 years.

Guideline Statement 4: To reduce the harms of screening, a routine screening interval of two years or more may be preferred over annual screening in those men who have participated in shared decision-making and decided on screening. As compared to annual screening, it is expected that screening intervals of two years preserve the majority of the benefits and reduce overdiagnosis and false positives.Additionally, intervals for rescreening can be individualized by a baseline PSA level.

Guideline Statement 5: The Panel does not recommend routine PSA screening in men age 70+ years or any man with less than a 10 to 15 year life expectancy.Some men age 70+ years who are in excellent health may benefit from prostate cancer screening.

5. DIAGNOSTIC MODALITY

CLINICAL DIAGNOSIS

Prostate cancer is usually suspected on the basis of DRE and/or PSA levels. Definitive diagnosis depends on histopathological verification of adenocarcinoma on prostate biopsy.

a. ***Digital rectal examination***

Most PCas are located in the peripheral zone and may be detected by DRE when the volume is > 0.2 mL. In approximately 18% of cases, PCa is detected by suspect DRE alone, irrespective of PSA level. Suspect DRE in patients with PSA level < 2 ng/mL has a positive predictive value of 5-30%. Abnormal DRE is associated with an increased risk of higher Gleason score and is an indication for biopsy.

b. ***Prostate-specific antigen***

The use of PSA as a serum marker has revolutionisedPCa diagnosis. Prostate-specific antigen is organ but not cancer-specific, therefore, it may be elevated in benign prostatic hypertrophy (BPH), prostatitis and other non-

malignant conditions. As an independent variable, PSA is a better predictor of cancer than either DRE or transrectal ultrasound (TRUS).

PSA density

Prostate specific antigen density is the level of serum PSA divided by the TRUS-determined prostate volume. The higher the PSA density, the more likely it is that the PCa is clinically significant.

PSA velocity and doubling time

There are two methods of measuring PSA kinetics:

• PSA velocity (PSAV): absolute annual increase in serum PSA (ng/mL/year)

• PSA doubling time (PSA-DT): which measures the exponential increase in serum PSA over time

Prostate specific antigen velocity and PSA-DT may have a prognostic role in treated PCa.

Free/total PSA ratio

Free/total (f/t) PSA ratio can be used to differentiate BPH from PCa. It stratifies the risk of PCa in men with 4-10 ng/mL total PSA and negative DRE. Prostate cancer was detected by biopsy in 56% of men with f/t PSA < 0.10, but in only 8% with f/t PSA > 0.25 ng /mL. Free/total PSA is of no clinical use if total serum PSA is > 10 ng/mL or during follow up of known PCa.

Additional serum testing

A few assays measuring a panel of kallikreins in serum or plasma are now commercially available, including the FDA-approved Prostate Health Index (PHI) test, combining free and total PSA and the (-2)pro-PSA isoform (p2PSA), and the four kallikrein (4K) score test (measuring free, intact and total PSA and kallikrein-like peptidase2 [hK2]), both tests are intended to reduce the number of unnecessary prostate biopsies in PSA tested men. A few prospective multicentre studies demonstrated that both the PHI and 4K test out-performed f/t PSA PCa detection, with an improved prediction of clinically significant PCa, in men with a PSA between 2-10 ng /mL.

PCA3 marker

PCA3 is a prostate-specific, non-coding mRNA biomarker that is detectable in urine sediments obtained after three strokes of prostatic massage during DRE. The commercially available Progensa urine test for PCA3 is superior to total and percent-free PSA for detection of PCa in men with elevated PSA.

6. STAGING: - The TNM classification used to stage prostate cancer.

T - Primary tumour

TX- Primary tumour cannot be assessed
T0- No evidence of primary tumour
T1-Clinically inapparenttumour not palpable or visible by imaging
T1a-Tumour incidental histological finding in 5% or less of tissue resected
T1b-Tumour incidental histological finding in more than 5% of tissue resected
T1c-Tumour identified by needle biopsy (e.g. because of elevated prostate-specific antigen (PSA)level)
T2-Tumour confined within the prostate[1]
T2a-Tumour involves one half of one lobe or less
T2b-Tumour involves more than half of one lobe, but not both lobes
T2c-Tumour involves both lobes
T3- Tumour extends through the prostatic capsule[2]
T3a-Extracapsular extension (unilateral or bilateral) including microscopic bladder neck involvement
T3b-Tumour invades seminal vesicle(s)
T4-Tumour is fixed or invades adjacent structures other than seminal vesicles: external sphincter, rectum, levator muscles, and/or pelvic wall

N - Regional lymph nodes[3]

NX- Regional lymph nodes cannot be assessed
N0- No regional lymph node metastasis
N1- Regional lymph node metastasis[4]

M - Distant metastasis[5]

MX- Distant metastasis cannot be assessed
M0- No distant metastasis
M1- Distant metastasis
M1a- Non-regional lymph node(s)
M1b- Bone(s)
M1c- Other site(s)

1 Tumour found in one or both lobes by needle biopsy, but not palpable or visible by imaging, is classified as T1c.

2 Invasion into the prostatic apex, or into (but not beyond) the prostate capsule, is not classified as pT3, but as pT2.

3 The regional lymph nodes are the nodes of the true pelvis, which essentially are the pelvic nodes below the bifurcation of the common iliac arteries.

4 Laterality does not affect the N-classification.

5 When more than one site of metastasis is present, the most advanced category should be used.

EAU risk groups of localised and locally advanced prostatecancer/ D' Amico classification for predicting clinical outcomes.

	Low risk	*Intermediate risk*	*High risk*	
Definitions	PSA < 10 ng/mL and GS < 7 and cT1-2a	PSA 10-20 ng/mL or GS 7 or cT2b	PSA > 20 ng/mL or GS > 7 or cT2c	any PSA any GS cT3-4 or cN+
	Localised			**Locally advanced**

Partin table- The Partin Tables use clinical features of prostate cancer – Gleason score, serum PSA, and clinical stage – to predict whether the tumor will be confined to the prostate.

7. IMAGING

MRI (*Multiparametric magnetic resonance imaging (mpMRI))*

T2-weighted imaging remains the most useful method for local staging on mpMRI. At 1.5T (Tesla), mpMRI has good specificity but low sensitivity for detecting T3 stage. Multiparametric magnetic resonance imaging haspoor sensitivity since it cannot detect microscopic extraprostatic extension. Its sensitivity increases with theradius of extension within periprostatic fat. The use of high field (3T) or functional imaging in addition to T2-weighted imaging improves sensitivity for ECEor SVI detection, but the experience of the reader remains of paramount importance. Magnetic resonanceimaging, although not perfect for local staging, may improve prediction of the pathological stage when combined with clinical data.

Given its low sensitivity for focal (microscopic) extraprostatic extension, mpMRI is not recommended for local staging in low-risk patients . However, mpMRI can still be useful for treatment planning in selected low-risk patients (e.g. candidates for brachytherapy) .

PET SCAN

11C- or 18F-choline positron emission tomography (PET)/CT have good specificity for lymph node metastases, but a sensitivity of between 10-73% . 18F-fluoride PET or PET/CT shows similar specificity and superior sensitivity to bone scanning. However, unlike choline PET/CT, it does not detect lymph nodes metastases, and it is less cost-effective compared to bone scanning. Recently PSMA PET has gained attention as a promising new radiotracer for primary staging as well as restaging after biochemical recurrence.

BONE SCAN

Bone scan (BS) has been the most widely used method for evaluating bone metastases of PCa. However, it suffers from relatively low specificity. Thus, in patients with equivocal findings, the lesions need to beassessed by other imaging modalities.Bone scanning should be performed in symptomatic patients, independent of PSA level, Gleasonscore or clinical stage.

8. PELVIC LYMPHADENECTOMY

Technique of lymph node dissection

Extended LND includes removal of the nodes overlying the external iliac artery and vein, the nodes withinthe obturator fossa located cranially and caudally to the obturator nerve, and the nodes medial and lateralto the internal iliac artery. With this template, 75% of all anatomical landing sites are cleared. A recentprospective mapping study confirmed that a template including the external iliac, obturator and internal iliacareas was able to correctly stage 94% of patients. Nevertheless, in pN+ patients, this template was associatedwith a 24% incomplete clearance from positive nodes . Adding the common iliac area and the presacralarea decreased this risk to 3%. It is recommended that for each region the nodes should be sent in separatecontainers for histopathological analysis.

Complications

Pelvic eLND remains a surgical procedure that increases morbidity in the treatment of PCa. When comparingextended vs. limited LND, three-fold higher complication rates have been reported by some authors.Overall complication rates of 19.8% vs. 8.2% were noted for eLND vs. limited LND, respectively, with lymphoceles (10.3% vs. 4.6%) being the most common. Thromboembolic events occurred in less than 1% of cases.

9.DEFINITIVE THERAPY FOR PROSTATE CANCER

A) ACTIVE SURVILLENCE / WATCHFUL WAITING

There are two distinct strategies for conservative management that aim to reduce over-treatment: AS and watchful waiting (WW).Active surveillance aims to achieve correct timing for curative treatment, rather than delayed application of palliative treatment. Patients remain under close surveillance, and treatment is prompted by predefined thresholds indicative of potentially life-threatening disease, while considering individual life expectancy.Watchful waiting (WW) is also known as deferred or symptom-guided treatment. It refers to

conservative management, until the development of local or systemic progression with (imminent) disease-related complaints. Patients are then treated according to their symptoms, in order to maintain QoL
Recommended criteria for active surveillance are absence of extraprostatic disease on DRE (<T2), gleason score <6, small volume tumor (fewer than 3 biopsy cores and <50% of any core involved), PSA density<0.15 and a PSA <10ng/ml at diagnosis. It is plausible that a long PSA doubling time (>12 months) would also indicate an indolent course.

Definitions of active surveillance and watchful waiting

	ACTIVE SURVEILLANCE	**WATCHFUL WAITING**
Treatment intent	Curative	Palliative
Follow up	Predefined schedule	Patient specific
Assessment / markers used	DRE, PSA, re-biopsy, mpMRI	Not predefined
Life expectancy	>10 years	Patient specific
Aims	Minimise treatment-related toxicity without compromising survival	Minimise treatment-related toxicity
comments	Only for low risk patients	Can apply to patients with all stages

B) RADICAL PROSTATECTOMY

Radical prostatectomy (RP) involves removal of the entire prostate gland between the urethra and bladder, and resection of both seminal vesicles, along with sufficient surrounding tissue to obtain negative margins. Often,this procedure is accompanied by bilateral pelvic lymph node dissection. The goal of RP by any approach mustbe eradication of disease, while preserving continence and, whenever possible, potency. Patients shouldnot be denied this procedure on the grounds of age alone but they should have at least 10 years of lifeexpectancy. Increasing age is linked to increased incontinence risk

Surgical Approaches to Radical Prostatectomy

- Perineal
- Retropubic
- Laparoscopic.
- Robotic

Technique

The key to preserving urinary continence is to perform a meticulous dissection, avoiding injury to the external urinary sphincter. Meticulous dissection is required to preserve the neurovascular bundles. In performing nerve-sparing surgery, the neurovascular bundles are identified at the apex ofthe prostate (the dissection can also be performed in an antegrade fashion beginning at the base), and the bundles are dissected free of the posterolateral surface of the prostate gland. Hemostatic sutures or clips may be used to control bleeding from the neurovascular bundles. Use of electrocautery or a harmonic scalpel risks irreversible thermal injury to the neurovascular bundles.

Postoperative Care

Patients should ambulate with assistance beginning on the afternoon or evening of surgery. The catheter may be removed 3 to 21 days after surgery, depending on the integrity and the amount of tension on the vesicourethral anastomosis. Removal of the catheter before 7 days is associated with a 15% to 20% risk of urinary retention. After the catheter has been removed, Kegel exercises should be initiated. A protective pad is used until complete urinary control is achieved. The postoperative serum PSA level should be undetectable by 1 month after the operation.

Complications

Anatomic nerve-sparing radical prostatectomy provides excellent cancer control with an acceptable complication rate in appropriately selected patients. The overallearly complication rate after radical prostatectomy is less than 10% in experienced hands .With a careful selection of patients and performance of necessary preoperative cardiovascular evaluation, perioperative mortality has been largely avoided.

Early Complications

Early complications include hemorrhage; rectal, vascular, ureteral, or nerve injury; urinary leak or fistula; thromboembolic and cardiovascular events; urinary tract infection; lymphocele; and wound problems. It is advisable routinely to use support stockings and to ensure early ambulation. Prophylactic anticoagulation and sequential compression devices are advisable in patients at high risk for thromboembolic complications. Inadvertent injury to the obturator nerve can occur during the pelvic lymphadenectomy. When a tension free primary nerve repair is not feasible, nerve grafting can be performed by a cutaneous or genitofemoral nerve graft. However, even without a nerve repair, conservative management with physical therapy can compensate for the deficit, and therefore many patients do not have a significant thigh adductor deficit after the injury. Ureteral injury is a rare complication. A minor injury or ligation can be managed with removal of the ligature and ureteral

stenting. Mobilization of the distal ureter and reimplantation should be performed for more severe injuries. Although uncommon, a rectal injury can occur and be repaired primarily by a multiple-layer closure.

Late Complications
The most common late complications of radical prostatectomy are erectile dysfunction, urinary incontinence, inguinal hernia, and urethral stricture.

C) DEFINITIVE RADIOTHERAPY
Both external beam radiotherapy and brachytherapy have been used.

EXTERNAL BEAM RADIOTHERAPY
Intensity-modulated radiotherapy (IMRT), with or without image-guided radiotherapy (IGRT), is thegold standard for EBRT.
Several randomised studies (see below) have shown that dose escalation (range 74-80 Gy) has a significant impact on 5-year survival without biochemical relapse.

Neoadjuvant or adjuvant hormone therapy (ADT) plus radiotherapy
The combination of RT with luteinising-hormone-releasing hormone (LHRH) ADT has definitively proven its superiority compared with RT alone followed by deferred ADT on relapse, as shown by phase III randomized trials. These trials included high-risk PCa patients, mostly by virtue of locally advanced (T3-T4 N0-X) disease, though with a wide range of clinical risk factors, such as PSA level or Gleason grade (high-risk localised, T1-2, N0-X PCa). The most powerful conclusion from these studies comes from the EORTC 22863 trial, which is the basis for the combination of RT and ADT in patients with locally advanced PCa as standard practice today.

Combined dose-escalated radiotherapy and androgen-deprivation therapy
The prostate dose ranged from 64.8 to 86.4 Gy. The duration of ADT was 3 months for low-risk patients and 6 months for intermediate-risk and high-risk patients, starting at 3 months before RT.

Lymph Node Irradiation
a. Clinically N0 prostate cancer (estimated cN0): There is no level 1 evidence for prophylactic whole-pelvic irradiation, since randomised trials have failed toshow that patients benefit from prophylactic irradiation (46-50 Gy) of the pelvic lymph nodes in high-risk cases.
b. Clinical or pathological node positive, M0 disease: Outcomes in this group after RT as a sole modality are poor, and these patients should receive RT pluslong-term ADT.

BRACHYTHERAPY

Low-dose rate and high-dose rate brachytherapy
There is a consensus on the following eligibility criteria for LDR monotherapy in Stage cT1b-T2a N0, M0; Gleason score 6 with <50% of biopsy cores involved with cancer or; Gleason 3 + 4 score with < 33% of biopsy cores involved with cancer, PSA < 10 ng/mL, prostate volume of < 50 cm3, IPSS Score < 12.

In Low Dose Rate (LDR) , permanent seeds implanted uses I-125 (most common), Pd-103 or Cs-131 isotopes. Radiation dose is delivered over weeks and months and acute side effects resolve over months. Radiation protection issues for patient and carers needs to be addressed.

Whereas in High Dose Rate (HDR), temporary implantation of Ir-192 isotope introduced through implanted needles or catheters is done. Radiation dose is delivered in minutes and acute side effects resolve over weeks. There is no radiation protection issues for patient or carers.

D) Hormonal therapy

Different types of hormonal therapy
Androgen deprivation can be achieved by either suppressing the secretion of testicular androgens or inhibiting the action of circulating androgens at the level of their receptor. These two methods can be combined to achieve what is known as complete (or maximal or total) androgen blockade (CAB).

1. Testosterone-lowering therapy (castration)
Surgical castration is still considered the primary treatment modality for ADT. It leads to a considerable declinein testosterone levels: the ‘castration level’.The castrate level is < 20 ng/dL (1 nmol/L).However, the castrate level considered by the regulatory authorities and in clinical trials addressing castration in PCa is < 50 ng/dL (1.7 mmol/L).

Bilateral orchiectomy, or subcapsular pulpectomy, is a simple, cheap and virtually complication-free surgical procedure. It is easily performed under local anaesthesia and it is the quickest way to achieve a castration level which is usually reached within less than 12 hours. It is irreversible and does not allow for intermittent treatment.

2.*Oestrogens*
Treatment with oestrogens results in testosterone suppression but is not associated with bone loss .Due to thromboembolic complications, even at lower doses these drugs are not considered as standard first-line treatment.

3.*Luteinising-hormone-releasing hormone agonists*
Long-acting LHRH agonists are currently the main forms of ADT. These synthetic analogues of LHRH, are delivered as depot injections on a 1-, 2-, 3-, 6-monthly, or yearly basis. After the first injection, they induce a transient rise in luteinising hormone (LH) and follicle-stimulating hormone (FSH) leading to the 'testosteronesurge' or 'flare-up' phenomenon, which starts 2-3 days after administration and lasts for about 1 week. The different products have practical differences that need to be considered in everyday practice, including the storage temperature, whether a drug is ready for immediate use or requires reconstitution, and whether a drugis given by subcutaneous or intramuscular injection.

Achievement of castration levels:-Chronic exposure to LHRH agonists results in the down-regulation of LHRH-receptors, suppressing LH andFSH secretion and therefore testosterone production. A castration level is usually obtained within 2-4 weeks.

'Flare-up' phenomenon:-The 'flare-up' phenomenon might lead to detrimental clinical effects (the clinical flare) such as increased bone pain, acute bladder outlet obstruction, obstructive renal failure, spinal cord compression, and cardiovascular death due to hypercoagulation status. Patients at risk are usually those with high-volume, symptomatic, bony disease. Concomitant therapy with an anti-androgen decreases the incidence of clinical flare, but does not completely remove the risk.

4. *Luteinising-hormone-releasing hormone antagonists*
Luteinizing-hormone releasing hormone antagonists immediately bind to LHRH receptors, leading to a rapid decrease in LH, FSH and testosterone levels without any flare. The practical shortcoming of these compounds is the lack of a long-acting depot formulation with only monthly formulations being available.
a. Abarelix is equally effective as LHRH agonists in achieving and maintaining castration levelsand in reducing serum PSA levels. Causes allergic reactionswith its long-term use.
b. Degarelix- Monthly subcutaneous formulation.

5.Anti-androgens
These oral compounds are classified according to their chemical structure as:
• **Steroidal**, e.g. cyproterone acetate (CPA), megestrol acetate and medroxyprogesterone acetate;
• **Non-steroidal** or pure, e.g. nilutamide, flutamide and bicalutamide.

Both classes compete with androgens at the receptor level. This is the sole action of non-steroidal antiandrogens and leads to an unchanged or slightly elevated testosterone level. Conversely, steroidal antiandrogens have progestational properties leading to central inhibition by crossing the blood-brain barrier.

Steroidal anti-androgens-These compounds are synthetic derivatives of hydroxyprogesterone. Their main pharmacological side-effectsare secondary to castration (gynaecomastia is quite rare) whilst the non-pharmacological side effects are cardiovascular toxicity (4-40% for CPA) and hepatotoxicity.

a. Cyproterone acetate
b. Megestrol acetate
c. Medroxyprogesterone acetate

Non-steroidal anti-androgens:-Non-steroidal anti-androgen monotherapy has been promoted on the basis of improved QoL compared to castration. Anti-androgens do not suppress testosterone secretion and it is claimed that libido, overall physical performance and bone mineral density (BMD) are frequently preserved. Non-androgen pharmacological side-effects differ between agents, with bicalutamide showing a more favourable safety and tolerability profilethan flutamide and nilutamide. All three agents share a common potential liver toxicity (occasionally fatal) therefore; patients' liver enzymes must be monitored regularly.

a. **Nilutamide**
Nilutamide monotherapy has not been compared to castration and is not licensed for monotherapy. Nonandrogen pharmacological side-effects are visual disturbances (i.e. delayed adaptation to darkness), alcoholintolerance, nausea, and specifically severe interstitial pneumonitis (potentially life-threatening).
b.**Flutamide**
Flutamide has been studied as monotherapy. Flutamide is a pro-drug, and the half-life of the active metaboliteis 5-6 hours, leading to a three times daily use. The recommended daily dosage is 750 mg. The non-androgen pharmacological side-effect of flutamide is diarrhoea.
c.Bicalutamide
The dosage licensed for use in CAB is 50 mg/day, and 150 mg for monotherapy. The androgen pharmacological side-effects are mainly gynaecomastia (70%) and breast pain (68%). However, bicalutamide monotherapy offers clear bone protection compared with LHRH analogues and probably LHRH antagonists.

6 .*New compounds (for castrate-resistant patients only)*
During castration, the occurrence of castration-resistance (CRPC) is systematic. It is considered to be mediatedthrough two main overlapping mechanisms, which are androgen-receptor (AR)-independent and AR-dependent. In CRPC, the intracellular androgen level is increased comparedto androgen sensitive cells, and an over-expression of the AR has been observed, suggesting an adaptative mechanism. This has led to the development of two new compounds targeting the androgen axis:abiraterone acetate and enzalutamide. Both are currently approved for mCRPC only.

a.Abiraterone acetate
Abiraterone acetate (AA) is a CYP17 inhibitor (a combination of 17 hydrolase and 17-20 lyase inhibition). Byblocking CYP17, AA significantly decreases the intracellular testosterone level by suppressing its synthesis atthe adrenal level and inside the cancer cells (intracrine mechanism). This compound must be used togetherwith prednisone/prednisolone (2 x 5 mg) to prevent drug-induced hyperaldosteronism.

b.Enzalutamide
Enzalutamide is a novel anti-androgen with a higher affinity than bicalutamide for the AR receptor. While nonsteroidalanti-androgens still allow transfer of ARs to the nucleus, enzalutamide also blocks AR transfer andtherefore suppresses any possible agonist-like activity.

Cost-effectiveness of hormonal therapy options
A formal meta-analysis evaluated the cost-effectiveness of various long-term androgen suppression options in advanced PCa. For men who can accept it, bilateral orchiectomy is the most cost-effective form of ADT,providing a higher quality-adjusted survival, while CAB is the least economically attractive option, yielding small health benefits for relatively high costs. Furthermore, the greatest QoL gains and least costs may be obtainedby starting ADT when symptoms from distant metastases have occurred. Finally, once ADT is started andif a major response is obtained, intermittent androgen deprivation (IAD) may be an effective option to lower treatment costs.

10. NCCN GUIDELINES FOR STAGE WISE MANAGEMENT OPTIONS
The staging work up is used to categorise patients according to their risk of recurrence or disease progression / recurrence into those with clinically localized disease at very low, low, intermediate, or high risk or those with locally advanced at very high risk or those with metastatic disease.

Very low risk
Men with all of the following tumor characteristics are categorized in the very low risk group: clinical stage T1c, biopsy Gleason score less than equal to 6, PSA less than 10ng/ml, presence of disease in fewer than 3 biopsy cores, less than equal to 50% prostate cancer involvement in any core, and PSA density less than 0.15ng/ml/g.

Given the potential side effect of definitive therapy, men in this group have an estimated life expectancy of < 10 years should undergo observation. Unlike active surveillance, observation schedules do not involve biopsies. Men with very low risk and life expectancy of 10 to 20 years should undergo active surveillance. For patients who meet the very low risk criteria but who have a life expectancy of 20years or above, the NCCN panel agreed that active surveillance, RT or brachytherapy or radical prostatectomy are all viable options.

Low risk
The NCCN guidelines define the low risk group as patients with tumors stage T1 to T2a, low Gleason score ($\leq$ 6), and serum PSA level less than equal to 10ng/ml, life expectancy less than 10 years. If the patient's life expectancy is 10 years or more then treatment options includes 1) active surveillance 2) RT or brachytherapy or 3) radical prostatectomy with or without PLND if the predicted probability of pelvic lymph node involvement is 2% or greater. ADT as a primary treatment for localized prostate cancer due to lack of long term data comparing these treatments to radiation or radical prostatectomy.

Intermediate risk
The NCCN guidelines define the intermediate risk group as patients with any T2b or T2c cancer, Gleason score of 7, or PSA value of 10 to 20ng/ml. Patients adverse factors may be shifted to high risk category. Options for life expectancy less than 10 years include 1) observation 2) RT with or without ADT (4 to 6 months), and with or without brachytherapy 3) brachytherapy alone. Initial treatment options for patients with an expected survival of 10 years or more include 1)radical prostatectomy, including a PLND if the predicted probability of lymph node metastasis is 2% or greater ;2)RT with or without 4to6months of ADT, and with or without brachytherapy; 30brachytherapy alone for patients with favorable factors (cT1c,Gleason score 7, low volume). Active surveillance is not recommended for patients with a life expectancy of >10 years.

High risk
Men with prostate cancer that is clinically localized stage T3a, Gleason score 8 to10, or PSA level greater than 20ng/ml, are characterized as high risk. Patients with multiple adverse factors may be shifted into the very high risk category. The preferred treatment is RT in conjunction with 2 to 3 years of ADT. ADT alone is insufficient. In particular patients with low volume, high grade tumor warrant aggressive local radiation combined with typical 2 or 3 years of ADT. The combination of EBRT and brachytherapy, with or without ADT (typically 2 or 3 years), is

another primary treatment options. However the optimal duration of ADT in this setting remains unclear. Radical prostatectomy with PLND remains an option as a subset of men in the high risk group may benefit from surgery.

Very high risk
Patients at very high risk are defined as with clinical stage T3b to T4 (locally advanced).The options for this group include :1)RT and long term ADT; 2)EBRT plus brachytherapy with or without long term ADT; 3)radical prostatectomy plus PLND in selected patients with no fixation to adjacent organs; or 4)ADT for patients not eligible for definitive therapy.

Nodal and Metastatic Disease
ADT or RT of the primary tumor plus 2 or 3 years ADT are options for patients with N1 disease on presentation. ADT is recommended for patients with M1 cancer.

Biochemical Recurrence
Biochemical recurrence (BCR) after radical prostatectomy fall into three groups: 1) those PSA level fails to fall to undetectable levels after radical prostatectomy (Persistent Disease); 2) those who achieve an undetectable PSA after radical prostatectomy with a subsequent detectable PSA level that increases on 2 or more subsequent laboratory determinations (Recurrent Disease); OR 3) the occasional case with persistent but low PSA levels attributed to slow PSA metabolism or residual benign tissue.

Group 3 does not require further evaluation until PSA rises.Since PSA elevation alone does not necessarily lead to clinical failure, the work up for 1 and 2 must include an evaluation for distant metastases.The specific staging tests depend on the clinical history, but usually include a combination of PSA doubling time assessment, TRUS biopsy,bone scan, and prostate MRI.Other tests that may be useful include abdominal/pelvic CT/MRI and C-11 choline PET.

Bone scans are appropriate when patients develop symptoms or when PSA levels are increasing rapidly. IA TRUS biopsy may be helpful when imaging suggest local recurrence.The patient may be observed or undergo primary salvage RT with or without ADT if distant metastases are not suspected during biochemical recurrence.Treatment is most effective when pre-treatment PSA level is below 1.0ng/ml and PSA doubling time is slow.

ADT alone becomes salvage treatment when there is proven or high suspicion for distant metastases. Radiation alone is not recommended but may be given to the site of metastasis or symptoms in addition to ADT in specific cases, such as to weight bearing bone involvement.Observation remains acceptable for select patients. In all cases, the form of primary or secondary systemic therapy should be based on the hormonal status of the patient.

Castration resistant prostate cancer
Definition of CRPC**-**Castrate serum testosterone < 50 ng/dL or 1.7 nmol/L plus either;a) Biochemical progression: Three consecutive rises in PSA 1 week apart resulting in two 50% increases over the nadir, and a PSA > 2 ng/mL or,b) Radiological progression: The appearance of new lesions: either two or more new bone lesions on bone scan or a soft tissue lesion using RECIST (Response Evaluation Criteria in Solid Tumors)

According to AUA guidelines six index patients of CRPC and their management options are as described

Index patient 1) Asymptomatic non-metastatic CRPC:- observation with continued androgen deprivation

Index patient 2) Asymptomatic or minimally symptomatic metastatic CRPC without prior docetaxelchemotherapy:-Abiraterone+prednisolone, enzalutamide, docetaxel,sipuleucel-T

Index patient 3) Symptomatic metastatic CRPC with good performance status and no prior chemotherapy:-Abiraterone+prednisolone,enzalutamide, docetaxel, Radium-223 for symptoms from bony metastases

Index patient 4) Symptomatic metastatic CRPC with poor performance status and no prior docetaxel chemotherapy:-Abiraterone+prednisolone/enzalutamide, if patient not willing for this, then Ketoconazole+steroid or radionuclide. Docetaxel or mitoxantrone chemptherapy when performance status is directly related to the cancer.Radium 223 to patients with symptoms from bony metastases when performance status is directly related to symptoms related to bony metastases

Index patient 5) Symptomatic metastatic CRPC with good performance status with prior docetaxel chemotherapy:-Abiraterone+prednisolone, carbazitaxel or enzalutamide. Ketoconazole + steroid if above drugs not available.Radium 223 for symptomatic bony metastases without any visceral metastases.

Index patient 6) Symptomatic metastatic CRPC with poor performance status and prior docetaxel chemotherapy:-palliative care,alternatively abiraterone+prednisolone, enzalutamide, ketoconazole+steroid or radionuclide therapy may be used.

11. FOLLOW UP

Follow-up after local treatment
Local treatment is defined as RP or RT, either by EBRT or low- or high-dose BT, or any combination of these.

Recurrence occurs after primary therapy in many patients who have previously received treatment with intentto cure.The procedures indicated at follow-up visits vary according to clinical situation. Prostate specific antigen level and DRE are the only tests that should be performed routinely.

a) Prostate-specific antigen monitoring

Measurement of PSA is a cornerstone in follow-up after local treatment. Expectations differ after RP and RT, but PSA recurrence often precedes clinical recurrence. A single, elevated, serum PSA level should be confirmed before starting second-line therapy based solely on PSA elevation.

Definition of prostate-specific antigen progression-The PSA level for definition of treatment failure differs between RP and RT. International consensus defines recurrent cancer after RP by two consecutive PSA rises > 0.2 ng/mL.

Prostate-specific antigen monitoring after radical prostatectomy-Prostate-specific antigen is expected to be undetectable within 6 weeks after successful RP. Persistently elevated PSA in patients treated with RP is thought to be due to residual cancer, either micrometastases or residual pelvic disease. A rapidly increasing PSA level indicates distant metastases, whereas a later, slowly increasing, level most likely indicates local recurrence.Thus, in patients with favourable pathology (< pT3, pN0, Gleason score < 8), PSA measurement and disease-specific history could be a single test in follow-up after RP.

PSA monitoring after radiotherapy-Prostate-specific antigen level falls slowly after RT compared with RP. A nadir < 0.5 ng/mL is associated with a favorable outcome after RT, although the optimal value is controversial. The interval before reaching the nadir can be up to 3 years or more. Biochemical failure after RT is currently defined as PSA > 2 ng/ mL above the nadir (RTOG-ASTRO Phoenix conference). After RT, PSA-DT is correlated with site of recurrence: patients with local recurrence have adoubling time of 13 months compared to 3 months for those with distant failure.

b) Digital rectal examination

Local recurrence after curative treatment is possible without a concomitant rise in PSA level. However,this has only been proven in patients with unfavourable pathology, namely, undifferentiated tumours. PSA measurement and DRE comprise the most useful combination for first-line examination in follow-up after RT orRP, but PSA measurement may be the only test in cases with favourable pathology (< pT3, pN0, Gleason < 8).

Role of Imaging

Imaging techniques have no place in routine follow-up of localized PCa. They are only justified in patients with biochemical faliure or in patients with symptoms for whom the findings affect treatment decisions. Biopsy of the prostate bed and urethrovesical anastomosis are only indicated if local recurrence affectstreatment decisions.

When to follow-up?

Most patients who fail treatment for PCa do so early, even if failure only becomes clinically obvious after years.Patients should be followed-up more closely during the initial post-treatment period when risk of failure ishighest. PSA measurement, disease-specific history and DRE are recommended at 3, 6 and 12 months postoperatively,every 6 months thereafter until 3 years, and then annually.The first clinic visit is mainly to detect treatment-related complications and assist patients in copingwith their new situation. Tumour or patient characteristics may allow alterations to this schedule.

Follow-up during hormonal treatment

Follow up must be individualised as BCF(Biochemical failure) might be associated with rapid symptomatic progression or evolve without progression on imaging or symptoms over years.The main objectives of follow-up in these patients are to ensure treatment compliance, to monitor response and side effects, and to guide the treatment at the time of CRPC.

Evaluate patients at 3 - 6 months after the initiation of treatment.As a minimum, tests should include serum PSA measurement, DRE, serum testosterone, and carefulevaluation of symptoms in order to assess the treatment response and side effects. In patients undergoing intermittent androgen deprivation, monitor PSA and testosterone at fixed intervals during the treatment pause (monthly or at three month intervals).Adapt follow-up to the individual patient, according to stage of disease, prior symptoms, prognosticfactors and the treatment given. In patients with stage M0 disease with a good treatment response, schedule follow-up every6 months. As a minimum requirement, include a disease-specific history, DRE and serum PSA determination in the diagnostic work-up.In patients with stage M1 disease with a good treatment response, schedule follow-up every 3 to 6 months. As a minimum requirement, include a disease-specific history, DRE, serum PSA, haemoglobin, serum creatinine and alkaline phosphatase measurements in the diagnostic work-up.The testosterone level should be checked, especially during the first year.Counsel patients (especially with M1b status) about the clinical signs suggestive of spinal cord compression. When disease progression occurs, or if the patient does not respond to treatment, adapt/individualise follow up. In patients with suspected progression, assess the testosterone level. By definition, CRPC requires atestosterone level < 50 ng/mL (< 1 mL/L). Do not offer routine imaging to otherwise stable patients.

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Malignant Melanoma: *Changing Paradigms!*

Sunil Choudhary

Malignant Melanoma management has undergone a paradigm change due to better understanding of its genetics, histopathology, behavior and discovery of various immuno modulators and target therapies. The purpose of this article is to go beyond the basics and help surgeons to remain updated with these recent advances.

Clinical Melanoma types

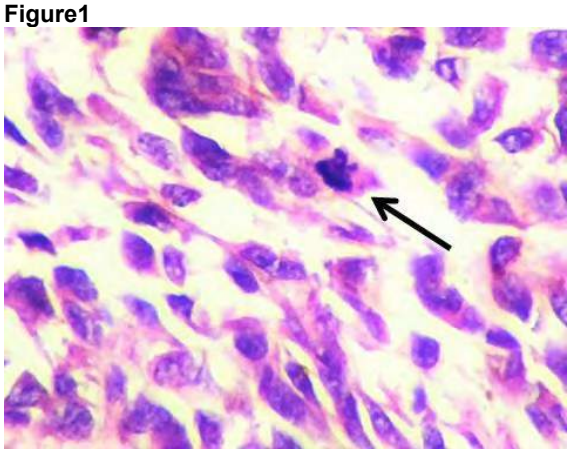
Malignant Melanomas in the Caucasians, accounts for only 3% of all cancers but accounts for 65% deaths due to skin cancers. Superficial spreading and nodular variety of Melanoma remains the most common and are mainly due to over-exposure to UV rays in Sunlight

Malignant Melanoma accounts for only 1-2% of all cancers in India but it often goes undiagnosed and remains a major cause of mortality amongst the skin cancers. Contrary to the Western countries, in India the more common varieties seen of Melanoma are Amelanotic, Acral lentiginous and Desmoplastic and they usually have no relation to UV exposure and occur often on un-exposed body areas. Mucosal and Anal Melanomas are very rare but can be treated on the same lines as cutaneous melanomas.

Staging & Prognosis

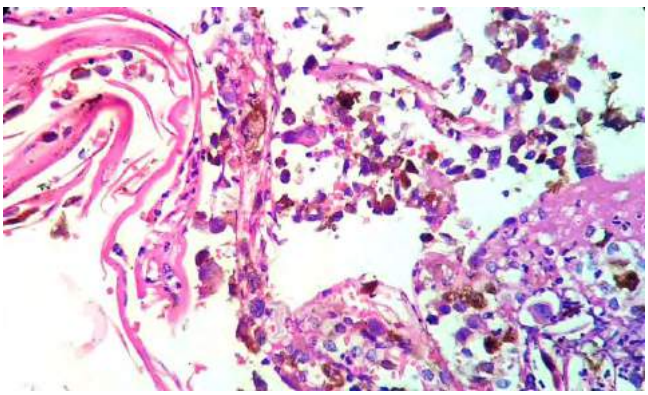
1. Clarks level of tumour invasion is NO more a part of the AJCC TNM staging.
2. Histopathology plays a crucial role in TNM staging with tumour thickness, ulceration, mitosis rate.
3. Breslow's tumour thickness in mm from histopathology forms the main basis for staging.
4. The other important staging factors are *Ulceration* and *Mitotic Rate*.
5. Mitotic rate >1/mm^2 and presence of ulceration has poorer prognosis. (Figures 1 & 2)
6. This is reflected in the new AJCC TNM staging 2010 for Malignant Melanoma. (Tables 1&2)

Figure1



Histopathology slide of Malignant Melanoma showing mitosis (marker arrow)

Figure 2



Histopathology slide showing epidermal ulceration in a case of Malignant Melanoma

Diagnosis

1. *Excision biopsy* with 1-2mm margins is the gold standard for staging.
2. Partial biopsy techniques like incisional biopsy, punch biopsy and shave biopsies may lead to inaccurate staging and possible effect on subsequent surgical treatment.
3. Full thickness incisional biopsy may sometimes be indicated in large lesions due to practical reasons but shave biopsies should be avoided as they fail to provide the information about tumour thickness necessary for proper staging. However the type of biopsy has not been shown to alter survival or recurrence.
4. Physical Examination must pay attention to other suspicious lesions, tumour satellite lesions, in-transit metastases, draining lymphnodes and systemic metastases.
5. T_1 lesions (≤1mm) are considered low risk melanomas and need no further investigations.
6. *LDH* is considered as a tumour marker designating poor prognosis if found raised in advanced melanomas.
7. *B-RAF* mutation in a proto-oncogene responsible for making a protein B-raf has been associated with poor prognosis but has also lend itself to target therapy improving outcomes.

Table 1
Seventh edition of the AJCC TNM (tumor, node, metastasis) staging categories for melanoma

T Classification	Thickness (mm)	Additional Stratification
Tis	NA	NA
T1	≤1.00	a: Without ulceration and mitoses <1/mm2 b: With ulceration or mitoses ≥1/mm2
T2	1.01–2.00	a: Without ulceration b: With ulceration
T3	2.01–4.00	a: Without ulceration b: With ulceration
T4	>4.00	a: Without ulceration b: With ulceration
N Classification	**Number of Metastatic Nodes**	**Metastatic Burden**
N0	0	NA
N1	1	a: Micrometastasis (identified on SLN biopsy) b: Macrometastasis (identified on clinical examination)
N2	2–3	a: Micrometastasis (identified on SLN biopsy) b: Macrometastasis (identified on clinical examination) c: In-transit metastases/satellites without nodal metastases
N3	4+ metastatic nodes, matted nodes, or in-transit metastases/satellites with nodal metastases	—
M Classification	**Site**	**Serum LDH Level**
M0	No distant metastases	NA
M1a	Distant skin, subcutaneous, or nodal metastasis	Normal
M1b	Lung metastases	Normal
M1c	All other visceral metastases Any distant metastasis	Normal Increased

Abbreviations: LDH, lactate dehydrogenase; NA, not available; SLN, sentinel lymph node.

Table 2
Seventh edition of the AJCC stage groupings for melanoma

Clinical Staging	T	N	M
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
III	Any T	N > N0	M0
IV	Any T	Any N	M1
Pathologic Staging			
0	Tis	N0	M0
IA	T1a	N0	M0
IB	T1b	N0	M0
	T2a	N0	M0
IIA	T2b	N0	M0
	T3a	N0	M0
IIB	T3b	N0	M0
	T4a	N0	M0
IIC	T4b	N0	M0
IIIA	T1–4a	N1a	M0
	T1–4a	N2a	M0
IIIB	T1–4b	N1a	M0
	T1–4b	N2a	M0
	T1–4a	N1b	M0
	T1–4a	N2b	M0
	T1–4a	N2c	M0
IIIC	T1–4b	N1b	M0
	T1–4b	N2b	M0
	T1–4b	N2c	M0
	Any T	N3	M0
IV	Any T	Any N	M1

Surgical Excision & Lymphnode Management

1. *Frozen sections are unreliable* for checking accuracy of resected margins as it fails to differentiate between normal melanocytes and melanoma cells.
2. Whenever possible Excision biopsy should be done with minimal margins for staging and further excision margins can be decided on the basis of Breslow thickness.
3. Table 3 shows the recommended margins of excision as per NCCN guidelines (National Comprehensive Cancer Network).

Table 3
Recommended margin of excision

Breslow Thickness (mm)	T Stage	Recommended Margin of Excision (cm)
Melanoma in situ	Tis	0.5–1
<1.0	T1	1
1.01–2.0	T2	1–2
2.01–4.0	T3	2
>4.0	T4	2

4. *Margins higher than 2cm have not been shown to give any advantage.*
5. Melanomas with 1-2mm thickness the largest possible margin should be taken as per guideline but a balance has to be struck between oncological safety and resulting deformity more so in the case of the face where usually 1cm margins are preferred over 2cm.
6. Reconstructive techniques allow generous excision margins and good functional rehabilitation.
7. Incomplete margins of excision should be treated with Re-Excision with 1-2cms margins.
8. There is no evidence to suggest that *Pregnancy* adversely affects the prognosis in Melanoma although there is more melanin production as evidenced by melasma and linea nigra.
9. Second trimester is usually preferred for any major excisions and reconstruction to decrease chances of abortion or premature labour. But if necessary general anaesthesia or local anaesthesia can be given in any trimester as none of the anaesthetic agents being used today are teratogenic.
10. *Desmoplastic Melanomas* constitute only 4% of all Melanomas but are very aggressive, mostly amelanotic, look like scar or nodular causing missed diagnosis and behave like sarcomas. They therefore have more visceral metastases than lymphnode involvement.
11. Surgical approach in many situations like *Ear melanomas* and *Limb melanomas* is becoming *'less radical' and more function preserving.*

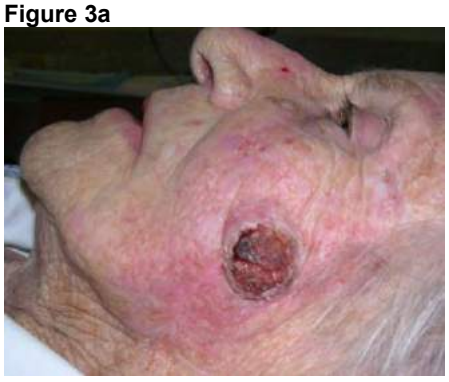
Sentinel Lymph Node Biopsy(SLND)

1. *Sentinel Lymphnode (SLND) is only a staging procedure* for N_0 neck to check the draining lymphnode basin for occult micro-metastases.
2. SLND does not improve overall survival but has been shown to improve 10yr disease free survival rates in intermediate thickness melanomas(1-4mm) and should be done in all these cases. The risk of occult lymphnode involvement in intermediate thickness melanomas is 20-40%.
3. There is also evidence that SNLD has advantage in thin melanomas >0.75mm especially when associated with high risk factors like ulceration and high mitotic rates.
4. Patients must be explained that SNLD is just a surgical staging procedure and positive cases may require Complete Lymph Node Dissection (CLND)
5. FNAC is indicated for all palpable nodes in the regional draining basin and CLND usually performed in all palpable node patients or positive SNLD N_0 is accompanied by a high complication rates especially lymphedema.
6. As only 16-23% of patients undergoing CLND after a positive SLND show metastases, the *role of CLND is also under investigation in Multicenter Selective Lymphadenectomy Trial II,* which compares CNLD against a cohort of patients who are only observed with serial ultrasound neck after a positive SNLD.
7. AJCC classifies all lymph nodes even with one melanoma cell as micro-metastases but *UICC classifies only more than 0.2mm tumour presence in the lymphnodes as micro-metastases and less than 0.2mm tumour is labeled as just 'isolated tumour cells'* (as isolated tumour cells have no typical features of metastases such as proliferation or stromal reaction and may have a better prognosis).

Reconstruction strategies

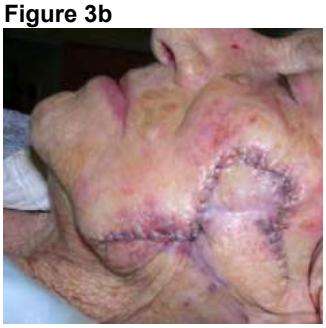
1. As surgical excisions are becoming 'less radical', reconstruction techniques using split or full thickness skin grafts and flaps are being used to do functional salvage of limbs and appendages.
2. Reconstruction also allows for extensive resections in big tumours improving disease free survival rates and also allows early adjuvant therapies due to accelerated healing of surgical sites.
3. Facial melanomas post wide local resections are reconstructed with a wide variety of advancement, transposition or pedicled flaps. Fig3 a-b
4. Ear Melanomas are increasingly being treated with perichondrium preserving techniques and skin grafting where there is no invasion into the perichondrium. In cases with such invasions wedge resection and reconstructive flap techniques like Antia-Buch advancement flaps give excellent aesthetic results without compromising on tumour clearance. Figure 4 a-b

Figure 3a



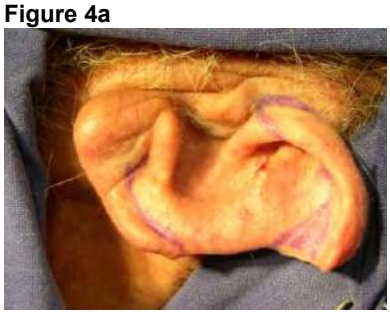
Ulcerated Melanoma cheek

Figure 3b



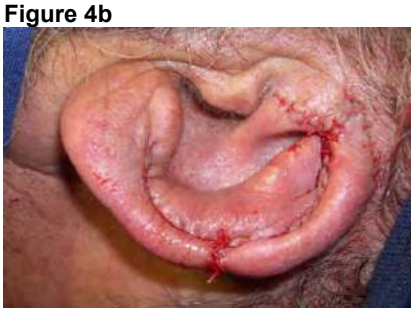
Cheek reconstructed with a Rhomboid transposition flap post wide local excision of the ulcerated melanoma seen in figure 1a.

Figure 4a



Partial rim resection of the Ear for Malignant Melanoma showing the defect

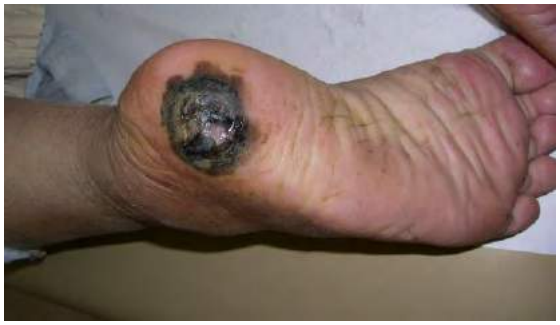
Figure 4b



Ear rim defect Reconstructed with Antia-Buch advancement flaps

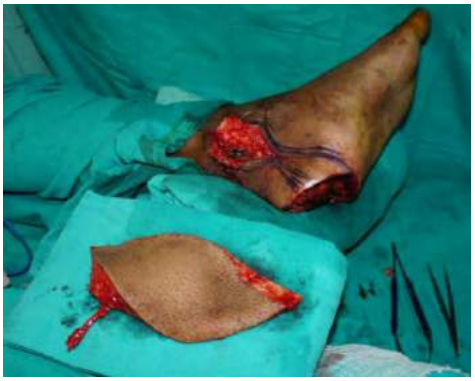
5. Subungual and limb melanomas are also not being subjected to amputations any more in most cases barring a huge tumour burden or very aggressive disease based on its physical or histopatholgical features.
6. Heel melanomas are dealt with wide local excisions and Microvascular free flap transfer reconstructions allowing normal ambulation and weightbearing in these patients. (Figures 5 a-c)

Fig 5 a



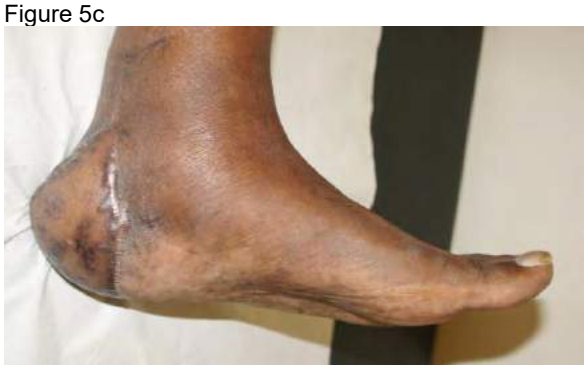
Malignant Melanoma involving the heel.

Figure 5b



Free Anterolateral thigh flap is ready to be anastomosed to posterior tibial vessels for heel reconstruction after wide local excision of Heel Malignant Melanoma.

Figure 5c



Excellent Functional Heel Reconstruction is seen that allowed the patient to walk and weight bear in a normal way.

<u>Adjuvant Therapies</u>

1. *No conclusive evidence has shown overall survival benefits of adjuvant therapies like Elective Lymph Node Dissection (ELND), Isolated limb perfusion, Radiotherapy or Chemotherapy in advanced melanomas.*
2. Surgical Excision of distant metastases if possible with minimal complications should be the preferred palliative treatment. May have survival benefits in some cases.

3. Radiotherapy plays a role in local control, pain alleviation and palliation in brain metastases, bone, soft tissue and nerve compressions.
4. Radiotherapy combined with gene target therapy or immune-modulating agents is under trials and showing promising results.
5. However *B-RAF inhibitor gene therapy agents are radio-sensitisers* and can cause increase radiation toxicity. With such patients stereotactic radiotherapy can be done instead of whole brain irradiation to decrease radiation induced complications.

Systemic Therapies for Advanced Malignant Melanomas

1. *Classic Chemotherapy like Dacarbazine and Interferon therapy is fast loosing its role* in Advanced Melanomas as two types of agents,
    1. *Gene target therapy* with monoclonal antibodies like *Vemurafenib* and *Dabrafenib* against genetic mutations of B-RAF and N-RAS genes. Thus all advanced melanomas should now be subjected to genetic testing with immunohistochemistry.
        - 40% Melanoma patients show B-RAF mutations.
        - B-RAF inhibitors and MEK (Mitogen-activated-extracellular signal regulated kinase) inhibitors can support first line therapies in patients with
            - High tumour burden,
            - Brain metastases,
            - Elevated LDH levels,
            - Inflammatory syndrome(increased CRP with neutropenia)
            - Bone marrow involvement
            - Pre-existing auto-immune disorders like Crohn's Syndrome, Rheumatoid arthritis, Wegner's granulomatosis etc. which form a contraindication for immunomodulatory agent administration.

    2. Immunomodulating agents are showing a huge promise in the rest majority 60% of advanced melanoma patients who do not show genetic mutations in histopathology
        - Anti-CTLA4 (cytotoxic T lymphocyte associated antigen-4) antibody *Ipilimulab* has shown survival benefits even in stage IV disease.
        - Anti-PDI (programmed death-I) antibodies *Pembrolizumab* & *Nivolumab* have shown promising survival benefits in advanced melanomas.
        - Combination of Ipilimulab and Nivolumab in recent trials such as *CHECKMATE 067 trial* is showing wonderful results and in spite of considerable side effects, are fast becoming standard of care.
        - Many patients on immune modulatory agents will develop *vitilago* white patches but these are considered as a marker of good response.

Followup

1. 90% melanomas recurrence happens in the first 5yrs of resection and hence the frequency of follow-up has to be *3-6monthly.*
2. If feasible *10yr* follow-up is recommended as melanomas can recur or metastasize late.
3. In thin melanomas no imaging is required
4. In thicker melanomas *ultrasound for lymph node basin* should be done as it is safe and relatively inexpensive.
5. Abdominal, chest imaging and PET-CT Scan may be required for follow up in advanced melanomas (Stage IIC and above)
6. *S-100 protein* is a tumour marker that can denote disease relapse especially relevant in advanced melanomas.

In Conclusion

The field of Malignant Melanoma is seeing constantly changing paradigms due to extensive research, clinical trials and molecular biology. New class of systemic agents targeting genes and immune modulation are fast emerging as effective medical treatments and although they serve at present an adjunct to the surgical therapy, a role reversal in future cannot be ruled out.

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Further Readings

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Soft Tissue Sarcoma of Extremity

S.V.S. Deo

Introduction

Soft tissue sarcomas (STS) are a heterogeneous group of solid neoplasm's arising from cells of mesenchymal origin. Collectively, they account for about 1% of all adult malignancies. Sarcomas are ubiquitous tumors and occur at any site throughout the body. They are diverse in histology, greatly differing between each other in biology, behaviour, and sensitivity to treatment. There are more than 50 subtypes, but pleomorphic sarcoma, liposarcoma, leiomyosarcoma, synovial sarcoma, and malignant peripheral nerve sheath tumor account for 75%. Approximately 50 % arise in the extremities, but the trunk wall, retroperitoneum and head and neck are also fairly common locations(1,2). The management of STS has evolved over the last two decades with the advances made in the fields of imaging, histopathology, molecular biology, cytogenetic and multimodality management. We will briefly review the management of extremity sarcomas and associated controversies

Management of extremity sarcoma

Optimal care in patients diagnosed with soft tissue sarcoma is the best provided by a multidisciplinary team of experts (including Surgical Oncology, Medical Oncology, Radiation Oncology, Onco-anaesthesiology, Radiology, and Physiotherapy and Rehabilitation) with experience in dealing with these types of tumors. As these tumors mainly affects young population clinical index of suspicion should be high as majority presents with painless mass with long standing history and rather than managing in inappropriate way at primary health care centres patients should be referred to speciality centres for optimal management(2,3).

Imaging in extremity sarcoma

Imaging is critical for defining the local extent of a tumor, staging, guiding biopsies, monitoring response after neo-adjuvant treatment, and detecting recurrences. Imaging should be done before any biopsy attempt as it helps in better targeting from representative area and sometimes helps pathologist in difficult situations. Magnetic resonance imaging (MRI) is preferred to Computed Tomography (CT) scan in extremity sarcoma since it has the best soft tissue discrimination and allows multiplanar imaging which helps in planning compartmental resections in extremity sarcomas. Soft tissue delineation and contrast enhancement are inferior in CT but recently various studies have shown its usefulness and apart from that it's cost effective and widely available so remains best alternative when MRI cannot be done(2,4). Lung is the most common site of metastasis accounting for 80% cases therefore, a chest CT scan is typically indicated for all patients with newly diagnosed high grade sarcomas(5). Role of functional imaging like positron emission tomography (PET) scan and MR spectroscopy (MRS) is emerging specially in post neoadjuvant response assessment and assessment of tumor grade(2).

Technique and principles of biopsy

Pre-operative biopsy is required to determine the grade and histological subtype of sarcoma. Fine-needle Aspiration Biopsy (FNAB) is mainly used only for the confirmation of recurrence rather than for the primary diagnosis. Core-needle Biopsy has a diagnostic accuracy of 93% and now is the preferred modality for taking biopsy. For tumors located near critical structures and solid cystic tumors an image guided core biopsy can be considered. Incisional Biopsy is performed only when core biopsy specimens yield non-diagnostic findings. In certain small, superficial located and less than 3 cm tumors excision biopsy can be performed. Inappropriate biopsy scar can turn a limb salvage surgery into amputation so outmost care should be given when performing the biopsy. Preferably it should be performed at centre where definitive management is planned and by surgeon or his team member who are directly involved in management. Incision should be placed in a way that it can be removed en bloc during surgery without sacrificing extra skin or any vital structure. Longitudinal incisions should be used for extremities. No skin flaps should be raised and haemostasis should be good to avoid tumor contamination(6). Availability of large number of immuno-histochemical (IHC) markers has contributed in better delineation of certain sarcomas and helps in planning various neoadjuvant treatments(2).

Staging and grading of soft tissue sarcoma

Various staging systems have been proposed including AJCC system, MSKCC staging and Enneking staging system of musculoskeletal society. Tumor size, location (superficial or deep) and grade are main factors in most of the systems.

Surgical management of extremity sarcoma

Surgical resection remains the mainstay of overall treatment in extremity STS. Over the past three decades, tremendous progress has been made in limb-sparing treatment of extremity STS including improvement in surgical techniques and multimodality approach. The goal of limb salvage surgery (LSS) is to preserve an extremity that is more functional than its prosthetic equivalent without compromising the patient's oncologic outcome. Surgical procedures range from skin grafts, pedicled and free flaps for coverage of extensive skin and soft tissue losses to vascular reconstructions, tendon transfers, nerve grafts, arthrodeses, and bone allografts.

Amputation versus limb salvage surgery

Last three decades witnessed major shift from amputation towards limb salvage surgery for extremity STS management. Rosenberg et al in a randomized trial proved that although local recurrence is greater in those undergoing limb-sparing operation plus irradiation than in those undergoing amputation, disease free survival is not different(7). Majority of cancer centres worldwide now reports limb salvage rate of 80-90% with optimal oncological outcomes(2,3,8). Amputations are now reserved only for recurrent and locally advanced tumors where limb salvage cannot be performed. Optimal margins for extremity STS are defined as 1-2 cm margins of grossly normal tissues all around the tumor. In few circumstances it may increase or decrease according to histological subtypes and proximity to critical structures. Enneking described a classification system to describe margin status. In Intralesional excision margin runs through tumor and therefore tumor remains. In marginal excision surgical plane runs through pseudocapsule (reactive zone). Both these procedures are associated with local recurrence rates of 40% and not recommended now. In wide resection surgical plane remains in normal tissue but in the same compartment as the tumor while in radical resection the tumor is removed including affected compartments. Wide resection and radical resections are procedure of choice in limb salvage surgery(9). Given the choice, most but not all patients and families would select limb salvage over amputation. With advancement in surgical and reconstructive techniques now only few contraindications exists. Relative contraindications include major neurovascular involvement, immature skeletal age, pathological fracture, extensive soft tissue involvement with no reconstruction options and sarcoma in diseased limb(8).

Role of Pulmonary metastasectomy in extremity STS

Despite achieving good local control by surgery and radiation approximately 50% of extremity high grade STS develop lung metastasis. Retrospective studies have shown 30-40% five year survival in patients undergoing pulmonary metastasectomy. Various factors like post treatment recurrence free interval, number of metastatic nodules, histology, tumor biology, site of primary and presence of other visceral metastasis should be taken into consideration before taking surgical decision(2,3).

Role of radiotherapy in extremity STS

Adjuvant radiotherapy (RT) has become standard treatment now and should be added to the surgical resection for most deep, large (>5 cm), high grade sarcomas if the excision margin is close, particularly with extramuscular involvement, or if a local recurrence would necessitate amputation or the sacrifice of a major neurovascular bundle. Superficial lesions and smaller contained lesions confined to individual muscles may be managed with surgery alone. Radiotherapy can be given either pre or post operatively with no difference in terms of local control and survival. Advantages of preoperative RT include reduced field irradiation, lower dose and improved margin negative resection. Main drawback of preoperative RT is postoperative wound morbidity but results of Canadian trial have shown that acute wound complications were higher in preoperative group at 3 and 12 months. Updated results have shown that postoperative late tissue sequels (fibrosis and edema) after two years were significantly higher in postoperative arm(2,8,10). However post operative RT remain preferred modality in most of the centres in view of availability of complete tumor related information including type, grade and margin status with minimal post operative morbidity. Role of brachytherapy is increasing for high grade sarcomas with tight margins either as sole treatment or for tumor bed boost with EBRT(2,8).

Role of chemotherapy in extremity STS

Apart from paediatric sarcomas, use of chemotherapy apart in patients with resectable STS remains controversial. More than 15 studies of adjuvant therapy for soft tissue sarcoma have been performed but most of them were small and therefore lack statistical power to detect small changes in overall survival. And also due to rarity and heterogeneity of these tumors accrual of patients is difficult for further studies. In updated results of one of the largest metaanalysis by sarcoma metaanalysis collaboration (SAMC) including 18 trials and 1953 patient's, chemotherapy was associated with significantly lower risk of local recurrence. Overall survival was not significantly improved by single agent doxorubicin, but it was improved with doxorubicin and ifosfamide combination(11). Neoadjuvant chemotherapy has been successful with paediatric sarcomas such as rhabdomyosarcoma and ewing sarcoma, and there is substantial benefit for synovial sarcoma and myxoid-round cell liposarcoma which are moderately chemo sensitive(2,8).

Role of isolated limb perfusion in extremity sarcoma

Isolated limb perfusion is a special technique of delivering high dose chemotherapy to involved limb sparing the normal body. These techniques can be used in advanced and recurrent extremity sarcomas not suitable for LSS. Hyperthermia has been used along with chemotherapy (cisplatin, melphelan) with good outcomes in some studies. However, isolated limb perfusion requires substantial expertise and specialized dedicated equipment(2).

Palliative surgery in extremity sarcomas

In cases of metastatic settings a palliative resection or amputation is required in cases of bleeding, fungation, infection or intractable pain.

Conclusion

Extremity soft tissue sarcoma is a rare but challenging clinical entity. These patients should be treated by a experienced multidisciplinary team for optimal outcomes. Quality control surgery, coupled with adjuvant treatment

when required, provides safe and effective treatment of extremity soft tissue sarcoma with a high limb salvage rates, good loco-regional control and good long term survival.

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Diaphragmatic Hernias in Adults

Sabyasachi Bal

Although the diaphragm is a relatively simple organ compared with other structures, the diaphragm serves important anatomic and functional roles necessary for proper respiratory function. It is an organ of little irregularity or disease, and easily manipulated in the operating room by those who have a basic understanding of its anatomic details.

Embryology

The development of the diaphragm begins in the seventh week of gestation and is complete by the tenth week. It is derived from four embryologic precursors: the septum transversum, the right and left pleuroperitoneal membranes, and the dorsal mesentery of the esophagus . The septum transversum is an anterior structure that becomes the central tendon and fuses with three dorsal structures to form the primitive diaphragm. The dorsal mesentery, containing the primitive aorta, inferior vena cava, and esophagus, becomes the posteromedial portion of the diaphragm. Myoblasts migrate into this structure, forming the crura bilaterally. The right and left pleuroperitoneal membranes grow medially and anteriorly to fuse with the central tendon. The final phase of diaphragmatic development is the formation of the neuromuscular component. The muscle fibers migrate from the third, fourth, and fifth cervical myotomes of the body wall. The phrenic nerves arising from the third, fourth, and fifth cervical nerves migrate distally, completing the final phase of diaphragmatic development.

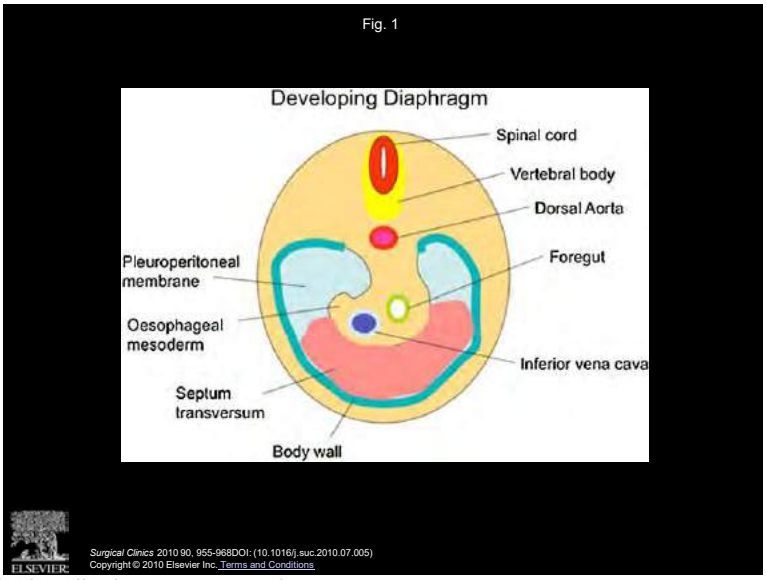
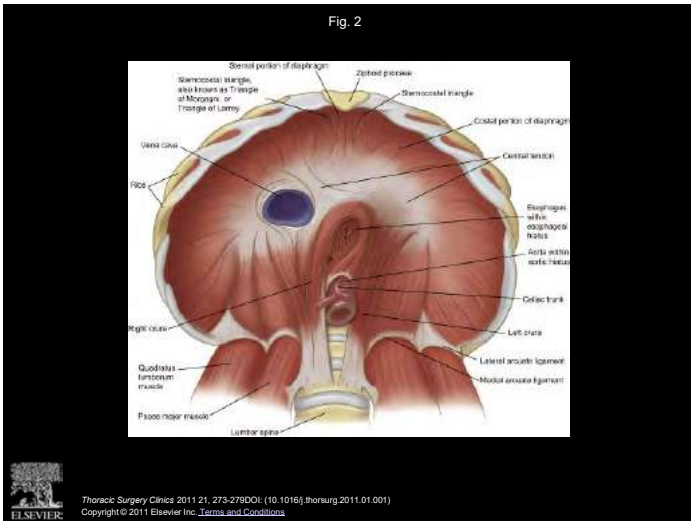


Diagram of the developing diaphragm at 7 weeks.
(Respiratory Dev © Dr Mark Hill 2008 Slide 30; Available at: http://embryology.med.unsw.edu.au. with permission.)

The importance of understanding embryologic development for a surgeon lies in gaining an understanding of the common variants and uncommon congenital defects that are encountered in surgical practice. Fortunately,the diaphragm is a very consistent organ and has no normal variations. However, several common abnormalities result from faulty embryologic development, including congenital diaphragmatic hernias and eventration.

Anatomy



Blood supply and Nerve supply –these are well known and will not be discussed further.

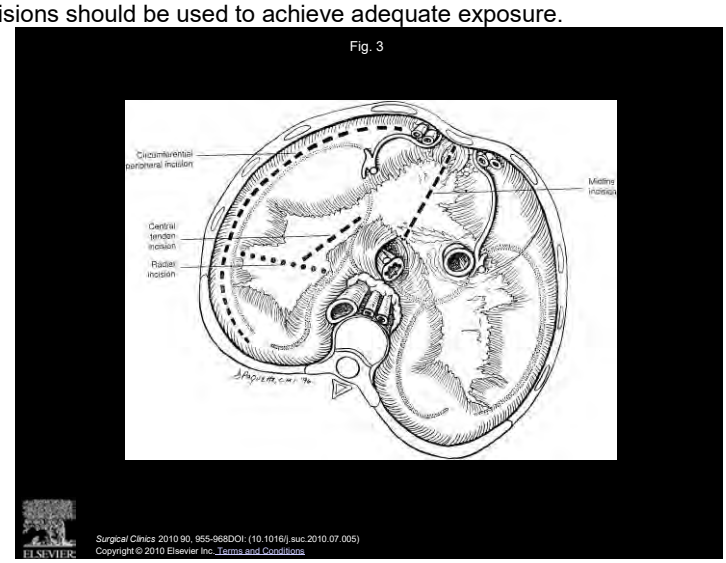
Surgical considerations

Preservation of at least one phrenic nerve is critical during any surgical procedure. The nerve courses posteriorly in the lateral compartment of the neck and can be inadvertently injured during posterior neck dissections. As it courses through the thoracic cavity, it transitions from a posterior to anterior position and can be seen on the anterior surface of the pericardium before it pierces the diaphragm. Care must be taken to identify the course of the nerve before opening the pericardium. The nerve is often involved in tumors of the chest wall and mediastinum, and may need to be sacrificed. More commonly, the nerve is drawn up toward the tumor from peritumoral inflammation and may be salvageable with careful, often tedious dissection of the nerve away from the bulky tumor.

When opening of the diaphragm is necessary, for either access or excision of the muscle, an understanding of how the nerve traverses across the diaphragm is helpful. The figure shows the course of the nerve and where incisions should be placed to preserve nerve function. Circumferential incisions should be placed parallel to the edge of the muscle to avoid nerve injury. Radial incisions traverse from the central tendon outward toward the

chest wall and should be placed so that only the distal branches of the nerve are transected. Combinations of these two types of incisions should be used to achieve adequate exposure.

Fig. 3



Surgical Clinics 2010 90, 955-968DOI: (10.1016/j.suc.2010.07.005)

Diaphragmatic Hernias

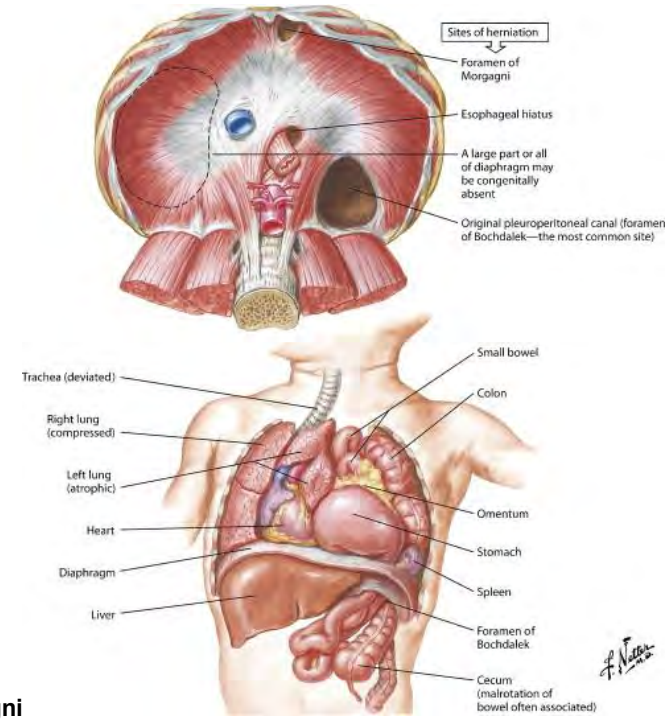
1. Congenital- Most of these are diagnosed in the newborn or early childhood.A small percentage reach adulthood before diagnosis
2. Acute
3. Chronic
4. Eventration

Imaging

Many pathologic conditions affect the diaphragm, both anatomically and functionally. Precise localization and characterization of tumors and diaphragmatic injury may be necessary, and identifying functional abnormalities before and after surgery is often helpful. Chest radiography is a useful screening tool for diaphragmatic abnormalities. hernia defects and functional defects can be seen easily. Cross-sectional imaging with ultrasound, high-resolution CT, and MRI can illustrate intrinsic pathology and assist in the evaluation of peridiaphragmatic masses.

The latter two modalities, especially, clearly delineate the complex anatomic relationships that the diaphragm shares with major intrathoracic and intra-abdominal organs. MRI has the added advantage of showing relationships of the diaphragm to neurovascular structures.

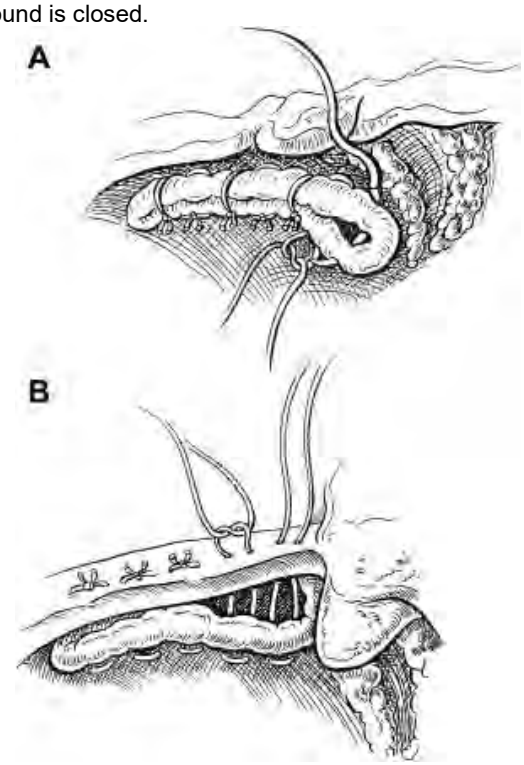
Congenital defects



Hernia of Morgagni

Surgical correction of a hernia of Morgagni is undertaken at initial diagnosis and even in the absence of symptoms. Neglect can lead to bowel obstruction, ischemia, and necrosis in some cases. Observation is reserved for debilitated patients. Patients are prepared for surgery with a liquid diet for 24-hours in advance. A complete bowel preparation is not necessary. A nasogastric tube is placed to help with bowel decompression. The repair is performed using an abdominal approach: either an upper midline or subcostal incision. Laparoscopic approaches have also been undertaken with success.

Transthoracic repair is appropriate when the contents of the hernia are fixed in position at or above the level of the carina. Reduction of these structures can be difficult using the abdominal approach because of dense adhesions, and so a transthoracic approach is preferred under these circumstances. The hernia sac is identified, its contents are reduced, and the sac is resected. The defect in the diaphragm is evaluated for size and location. Small defects that are surrounded entirely by a rim of muscle may be repaired primarily with heavy nonabsorbable interrupted mattress sutures .A defect with an incomplete muscular rim is repaired by attaching the free edge of the muscle to the costal margin . Defects that are too large to close primarily without resulting tension should be closed with a nonabsorbable mesh interposed between the muscular rim and the chest wall. A chest tube is placed and the wound is closed.



Repair of a Hernia of Morgagni. (*A*) Anterior rim of tissue is present. (*B*) Anterior rim of tissue is absent.
(*From* Daly BD, Feins NR. The diaphragm. In: Kaiser LR, Kron IL, Spray TL, editors. Mastery of cardiothoracic surgery. Philadelphia (PA): Lippincott-Raven, Lippincott, Williams and Wilkins; 1998. p. 203; with permission.)

Hernia of Bochdalek

Up to 85% of neonates born with this condition will be in critical condition at delivery,and up to 60% will not survive past the neonatal period. Bochdalek's hernia constitutes 90% of all diaphragmatic hernias and occurs in approximately 1 of every 2200 to 12,500 births every year. In contrast to hernias of Morgagni, these defects are commonly associated with other congenital abnormalities, especially those that are cardiac in nature. They occur more commonly in men than women, by a ratio of 3:2, and are left-sided 85% of the time . The diagnosis is usually made with a prenatal ultrasound.. After delivery, the infant is supported by mechanical ventilation until repair is undertaken. Mechanical ventilation alone can often restore adequate gas exchange so that surgery can be delayed. Extracorporeal membrane oxygenation (ECMO) is used in infants for whom mechanical ventilation is unsatisfactory. ECMO is often sustained until the infant is decannulated after surgical repair, but this is institution biased. Often other defects must be emergently addressed in an operative setting, and the hernia is repaired simultaneously. In other instances, emergent repair is not necessary, and aggressive neonatal resuscitation has proven to be beneficial in the survival of these infants. Despite early diagnosis and advanced intensive care management, the operative mortality approaches 50%.

Acute Diaphragmatic Hernias

Motor vehicle accidents are the leading cause of blunt diaphragmatic injury, whereas penetrating injuries result from gunshot or stab wounds. Among patients admitted to the hospital for trauma, 3% to 5% have a diaphragmatic hernia. They occur more commonly in men than women, at a ratio of 4:1, with most presenting in the third decade of life. Upwards of 75% of patients have tears from penetrating injuries, whereas fewer than 2%

of patients have rupture from blunt injuries. Approximately 69% of hernias are left-sided, 24% are right-sided, and 15% are bilateral. Nonetheless, blunt injuries are far more common and account for 75% of acquired defects. Other rare causes of traumatic rupture include labor in women who have had prior diaphragmatic hernia repair[26] and barotrauma during scuba diving in patients with a history of nissen fundoplication.

Acquired diaphragmatic hernias affect physiology in many ways. Circulatory and respiratory depression occur as a result of decreased diaphragmatic function, compression of the lungs from intra-abdominal contents, shifting of the mediastinum, and cardiac compromise. Smaller diaphragmatic hernias are often not discovered until months or years later, when patients present with strangulation of intra-abdominal organs, dyspnea, or nonspecific gastrointestinal complaints.

In the acute setting, patients present with respiratory distress, decreased breath sounds on the affected side, auscultation of bowel sounds in the chest, palpation of abdominal contents during insertion of a chest tube, paradoxic motion of the abdomen with breathing, or abdominal pain. Patients often present asymptomatically or have distraction injuries. Increased clinical acumen by the treating physician is necessary to detect this injury.
Traumatic rupture of the diaphragm requires surgical intervention whether the patient presents immediately or sometime after the trauma. Repair of the acute diaphragmatic rupture from trauma is directed by other injuries that may be present. In the absence of intrathoracic injuries, the high incidence of concomitant intra-abdominal injuries dictates the need for emergency abdominal exploration in the acute trauma setting after initial resuscitation is accomplished. Before induction of anesthesia, a nasogastric tube should be inserted to help bowel decompression and reduce the chance of aspiration on induction. A midline incision is made so that a complete abdominal exploration is possible. Critical injuries are controlled and the diaphragmatic defect is assessed for size and viability. Areas of nonviable tissue are resected. Small defects are closed primarily with interrupted horizontal mattress sutures. Larger defects are patched with mesh. A running suture may be used to approximate the mesh to the central tendon. When nerve injury has occurred and functional impairment is imminent, the mesh repair should be taut to prevent paradoxic movement.

Chronic Diaphragmatic Hernias
Chronic diaphragmatic hernias are acquired defects that remain asymptomatic for months to years after initial injury. Patients who present in the latent phase or long after trauma require repair because the hernia contents may become strangulated, leading to ischemia or necrosis of the gut, stomach, liver, spleen, or other organs. The surgical approach has traditionally been through a thoracotomy incision in the 7th or 8th intercostal space. With the advent of video-assisted surgery, however, laparoscopic and thoracoscopic repair is acceptable. Thoracoscopic repair should be reserved for small defects, because the contents of a large hernia will obscure an adequate view. If preoperative imaging shows hernia contents above the level of the inferior pulmonary vein, an intrathoracic approach is preferred and safest. Unlike acute hernias, chronic hernias form dense adhesions to surrounding structures that are difficult and unsafe to divide using an abdominal approach. The principles involved in the surgery are reduction of hernia contents back into the abdomen, excision of the entire hernia sac, and repair of the diaphragmatic defect. Small defects may be repaired primarily, whereas large defects should be closed with a mesh patch to avoid tension on the repair and postoperative disruption.

If a thoracoscopic approach is planned, the patient is placed into the lateral decubitus position with single lung ventilation secured. A camera port is placed into the midaxillary line at the 4th intercostal space. Two additional ports are placed strategically to triangulate onto the dome of the diaphragm: one posterior to and one anterior to the midaxillary line. Once the hernia sac is reduced, a moist laparotomy sponge can be placed through the diaphragm to keep the abdominal contents reduced while closure is underway. It is then removed before securing the final sutures.

The laparoscopic approach requires a camera port just above the umbilicus in the midline. For left-sided defects, a Nathanson liver retractor is placed just below the xiphoid process and two working ports are placed into the right and left subcostal positions. For right-sided defects, a paddle liver retractor is placed in the right lower quadrant and working ports are placed into the left subcostal and left paraumbilical positions. Additional ports may need to be placed to help reduce the hernia sac and enable adequate visualization during the repair.

Diaphragmatic eventration and Paralysis
The broader definition of *eventration* is the abnormal elevation of the hemidiaphragm. It can be classified into congenital and acquired forms. The acquired form is usually caused by phrenic nerve injury. In the strictest sense, however, eventration refers to the congenital abnormality that occurs from failure of the fetal diaphragm to muscularize. A narrow rim of muscle is present peripherally that contracts with electrical stimulation, resulting in a thin, pliable central portion of the hemidiaphragm. It is frequently associated with other congenital abnormalities of the spine and chest, hypoplastic lungs, extrapulmonary sequestration, and transposition of the viscera. Children born with this defect are often in cardiopulmonary distress and on mechanical ventilation or ECMO. In these infants, immediate repair is undertaken. Delayed repair is safe for infants who are not in extremis.

Whether congenital or acquired, repair of diaphragmatic eventration is best performed through a thoracotomy incision in the 7th or 8th intercostal space. The goal of the operation is to tighten the diaphragm and restore it close to its intended anatomic location. The diaphragm is incised near its costal attachments and stretched out. It

is reattached with interrupted nonabsorbable sutures placed in a horizontal mattress fashion. Thoracoscopic repair is gaining favor. A 10-mm camera port is placed in the 5th intercostal space posteriorly and a 5-mm port is placed in the 5th intercostal space anteriorly. A mini-thoracotomy incision is made over the 9th or 10th intercostal space. First, a running suture is used to invaginate the eventration. A second running suture is then used over the top of the first to adjust to the desired tension. Other thoracoscopic and laparoscopic techniques have been described to avoid the mini-thoracotomy[6]; however, the principles of repair remain the same.

Diaphragmatic paralysis

Diaphragmatic paralysis can result from direct injury to the diaphragm or injury to the phrenic nerve. I**n** adults, diaphragmatic injury almost always occurs on the left side and is attributed to hypothermia during cardiopulmonary arrest. The overall incidence is approximately 2% and is more commonly associated with open procedures and reoperations. Most often the paralysis is temporary. Paralysis may also result from direct invasion of the phrenic nerve by tumors of the lung and mediastinum and trauma associated with sudden deceleration. In these instances, paralysis is often permanent. Paralysis has also been associated with neuromuscular disorders, difficult births, cervical osteoarthritis, a substernal thyroid, an aortic aneurysm, von Recklinghausen disease, Lyme disease, and viral, bacterial, syphilitic, and tuberculous infections. Noncardiac thoracic or cervical operations also may cause paralysis from direct injury to the nerve, traction on the nerve, pressure from a retractor, or use of cautery near the nerve. Unilateral diaphragmatic paralysis is not associated with a significant respiratory dysfunction in most patients, but can lead to dyspnea and affect ventilatory function. An initial reduction in vital capacity and total lung capacity of 20% to 30% usually returns to normal after 6 months. It has been documented that most patients reporting an initial symptom of cough or chest pain experienced improvement of these symptoms on follow-up, whereas in two thirds of patients whose primary complaint was dyspnea on exertion, these symptoms remained unchanged or deteriorated. The prognosis is usually good in unilateral paralysis in the absence of neurologic or pulmonary processes. Patients with bilateral paralysis, although rare, present with marked reduction in vital capacity and flow rates and may show excessive accessory muscle movement. The prognosis for patients with bilateral paralysis is usually poor and often leads to long-term mechanical ventilation through a permanent tracheostomy.

In adults, diaphragmatic plication should be considered in symptomatic patients whose phrenic nerve has irreversible injury, generally after 1 year. Plication alters the shape of the diaphragm and allows vital capacity and lung capacity to increase. These increases can continue for up to a year, along with increases in residual volume, diffusing capacity, and partial arterial oxygen. A thoracotomy through the 7th or 8th intercostal space is recommended. The lateral and posterior portions of the diaphragm are gathered in pleats and sutured with interrupted, pledgeted, horizontal mattress sutures. Thoracoscopic repair has also been described, although long-term results are not well studied.

**** All pictures used in this text have been reproduced after necessary permission. All sources are duly acknowledged.**

Further Reading
1. Anatomy of the Normal Diaphragm
Robert Downey, MD
Thoracic Service, Department of Surgery, Memorial Sloan-Kettering Cancer Center, 1275 York Avenue, C-871, New York, NY 10065, USA
DOI: http://dx.doi.org/10.1016/j.thorsurg.2011.01.001
2.. Surgical Conditions of the Diaphragm: Anatomy and Physiology
Masaki Anraku, MD, Yaron Shargall,
DOI: http://dx.doi.org/10.1016/j.thorsurg.2009.08.002
3. SURGICAL EMBRYOLOGY AND ANATOMY OF THE DIAPHRAGM WITH SURGICAL APPLICATIONS
Volker Schumpelick, MD,Gerhard Steinau, MD, Ingo Schlüper, MD,Andreas Prescher, MD
DOI: http://dx.doi.org/10.1016/S0039-6109(05)70403-5

Advances in Radiotherapy: What a general surgeon should know

Rambha Pandey

Radiotherapy plays an an important role in the multimodal management of cancer with approximately 50 % of all cancer patient receiving radiation therapy during their course of illness; it contributes towards 40% of curative treatment. Radiotherapy has evolved over the period of time moving from conventional 2 Dimensional technique where only rectangular or square field were used for treating cancer to conformal radiotherapy technique such as 3DCRT(3 Dimensional Radiotherapy), IMRT(Intensity Modulated Radiotherapy), IGRT(Image Guided Radiotherapy), Stereotactic Radiotherapy and Stereotactic Radiosurgery These technique allows more precision in Radiotherapy dose delivery to the tumor as well as reduces the radiation to the adjacent normal

structures and critical strucures, thus reducing the acute and late radiation toxicities. The progress in Radiotherapy delivery technique continues to be boosted by advances in imaging technique(from two Dimensional imaging to 4 Dimensional Imging allowing us real time tumor tracking), computerized treatment planning System, radiation treatment Machines as well as improved understanding of the radiobiology of radiotherapy.

Technological Advances in Radiotherapy:

3Dimensional Radiotherapy:
Three-dimensional conformal radiotherapy (3DCRT) is a complex process that begins with the creation of individualized, 3D digital data sets of patient tumors and normal adjacent anatomy. These data sets are then used to generate 3D computer images and to develop complex plans to deliver highly "conformed" (focused) radiation while sparing normal adjacent tissue. Because higher doses of radiation can be delivered to cancer cells while significantly reducing the amount of radiation received by surrounding healthy tissues, the technique should increase the rate of tumor control while decreasing side effects.

Intensity Modulated Radiotherapy
This is a technique of conformal radiotherapy optimizing the the delivery of irradiation to irregularly shaped volume whilst simultaneously avoiding critical organs. IMRT is made possible through : a) inverse Planning software and b) computer controlled intensity modulation of multiple radiation beam during radiation delivery. Thus the therapeutic ratio for tumors can be improved

Image Guided Radiotherapy(IGRT)
As the treatment margin becomes tighter, potential to miss tumor due to organ motion and patient setup variation become greater. When the critical organs are close to tumor a slight positional error may lead to inadvertent radiation to the normal organ

IGRT is a technique aimed at increasing the precision of radiotherapy by frequently imaging the target or normal tissue just before the treatment or by real time tracking during the treatment and thus enhancing the therapeutic ratio for the tumor and reducing the error arising from the internal organ motion or patient set up. Present era's linear accelerators have inbuilt KV/ MV Imaging, Cone Beam CT and US imaging system enabling the IGRT possible.

Stereotactic Radiosurgery(SRS) and Radiotherapy(SRT)
SRS and SRT are techniques to administer precisely directed, high dose irradiation that tightly conforms to an intracranial target to create a desired radiobiological response while minimizing radiation dose to surrounding normal tissue, thus reducing the risk of radiation toxicity

The term stereotactic refers to using precise three dimensional mapping technique to guide a procedure.
Stereotactic radiosurgery (SRS) is used for stereotactically guided conformal irradiation of a defined target volume in single session. SRS can be delivered with Gamma Knife(where Gamma rays from multiple Co-60 sources are utilised for treating the tumor or functional brain disease) or X X ray knife(X rays produced in modified LINAC radiosurgery system, including Cyberknife, Novalis Tx are used for treating functional brain diseases or Brain tumors), and protons beam therapy.

Stereotactic Radiotherapy refers to stereotactically guided delivery of highly conformal radiation to adefined target volume in multiple fractionstypically using non invasive positioning technique

Stereotactic Body Radiotherapy(SBRT)
SBRT is the term applied by the American Society of Therapeutic Radiology and Oncology (ASTRO) for the management and delivery of image-guided high-dose radiation therapy with tumor-ablative intent within a course of treatment that does not exceed 5 fractions.

SBRT for early staged Lung cancer and SBRT for Hepatocellular carcinoma in surgically unfit patient has given promising result and randomized trials in surgically Fit patients are still awaited.
SBRT spine has evolved as a much effective technique increasing the therapeutic ratio for tumor control and symptom relief.

Particle Beam therapy: (Electron, proton and neutron beam therapy)
Electron beam produced from linear accelerators are commonly used to treat superficial tumors as they do not penetrate deeply into the tissues. External beam radiotherapy is also carried out with heavy particles such as neutrons produced by neytrons generators or cyclotrons; protons produced from cyclotrons and synchrotrons; and heavy ions(helium, carbon, nitrogen, argon and neon) produced by synchrocyclotrons

Proton beams are newer form of particle beam irradiation used to treat deep seated cancer. It delivers very high dose to tumor and minimal dose to s normal structure in their path due to its characteristic absorption profile in tissues called Bragg's peak. Intensity modulated proton therapy(IMPT) allows modulation of the Bragg's peak of

protons of different energies making it ideal for deep seated tumors at skull base, brain and spinal cord and also paediatric tumors

Advances In Radiotherapy Delivery System:
The First linear accelerator principle was invented by Rolf Wideroe in 1930 which was followed by development of first linear accelerator for therapy in 1949 by Newberry developed first linear in England. Then the first linearcompact linear accelerator was developed by Varian /Electa system in 1950s. The basic linear accelerators were of single photon energy and they had basic collimator rendering them fit for conventional radiotherapy only Linear accelerators have undergone various upgradation over the decades, resulting in present day linear accelerator with dual photon energy, multiple electron energies, enabled with multileaf collimators, KV and MV imaging and cone beam CT , exac trac, USG imaging system making IMRT , IGRT, SRS, SRT and SBRT possible.

Apart from the External beam Radiotherapy delivery system, Brachytherapy delivery system has also evolved over the period of time from manual loading to manual afterloading and then remote afterloading technique and thus reducing the radiation hazards to the radiation workers. In present era incorporation of USG, CT scan and MRI based brachytherapy treatment planning renders effective tumor control and reduces the radiation induced toxicities.

Summary
In present era, technological advances in radiotherapy conforms the radiation to the target lesion reducing the dose to the surrounding critical organs. As a dose escalation in radiotherapy becomes feasible enhancing the therapeutic ratio for the tumor. Concurrent chemordiotherapy has evolved as an alternative to surgery in many head and neck tumors, Bladder cancer, Limb salvage surgeries strengthening the principle of organ preservation.

Suggested readings:

1. **PRINCIPLE AND PRACTICE OF RADIATION ONCOLOGY by Perez and Brady's**
2. **CANCER: Principle and practice of Oncology by DeVIta, Hellmanand Rosenberg**
3. **Leibel's TEXT BOOK OF RADIATION ONCOLOGY by Phillips, Hoppe and Roach**

Assessment of response to chemotherapy

A. K. Dhar

History
Objective response of a tumour to cancer therapy were made in the early 1960s. In the mid- to late 1970s, the definitions of objective tumour response were widely disseminated and adopted when it became apparent that a common language would be necessary to report the results of cancer treatment in a consistent manner. The World Health Organization (WHO) published a handbook in 1979 which used common definitions and criteria of response used by various investigators[1]. However because of some problems, modification of WHO criteria was made which later on led to origin of RECIST criteria.

Introduction
Tumour response is a fundamental concept in clinical oncology but perhaps the least understood. In fact, the need to classify tumours as responding or non-responding can be seen as a direct consequence of our currently limited understanding of tumour biology. In essence, tumour response simply describes the phenomenon whereby some patients benefit from a particular therapy whereas others, despite apparently identical clinical and histopathological characteristics, do not. Monitoring tumour response to therapy is therefore a crucial part of clinical oncology. The definitive proof of the effectiveness of a therapy is improvement in clinical symptoms and survivorship. Current response assessment is based primarily on changes in tumour size as measured by CT scan or other anatomic imaging modalities. Criteria for tumour response have been refined over more than 25 years but fundamental limitations remain. The aim of this article is to describe accurate methods for monitoring tumour response to therapy.

TUMOUR RESPONSE TO THERAPY
There are various methods by which tumour response can be assessed. These methods range from clinical to molecular markers for prediction of response depending upon tumour type.

Clinical examination. By Clinical examination we can find site, size and nature of lesion. These lesions will only be considered measurable when they are superficial (e.g., skin nodules and palpable lymph nodes). For the case of skin lesions, documentation by colour photograph and measurement by a ruler is recommended.

Chest x-ray. Lesions on chest x-ray are acceptable as measurable lesions when they are clearly defined and surrounded by aerated lung. However, CT scan is preferable.

CT scan and MRI. CT and MRI are the best currently available and most reproducible methods for measuring target lesions selected for response assessment. Conventional CT and MRI should be performed with contiguous cuts of 10 mm or less in slice thickness. Spiral CT should be performed by use of a 5-mm contiguous reconstruction algorithm; this specification applies to the tumours of the chest, abdomen, and pelvis, while head and neck tumours and those of the extremities usually require specific protocols.

Ultrasound

Ultrasound measures objective response evaluation. .Ultrasound may be used as a possible alternative to clinical measurements for superficial palpable lymph nodes, subcutaneous lesions, and thyroid nodules. Ultrasound might also be useful to confirm the complete disappearance of superficial lesions usually assessed by clinical examination. It should not be used to measure tumour lesions that are clinically not easily accessible.

Endoscopy and laparoscopy. The utilization of these techniques for objective tumour evaluation has not yet been fully or widely validated. Their uses in this specific context require sophisticated equipment and a high level of expertise that may be available only in some centres. Therefore, utilization of such techniques for objective tumour response should be restricted to validation purposes in specialized centres.

Tumour Markers

Tumour markers alone cannot be used to assess response. However, if markers are initially above the upper normal limit, they must return to normal levels for a patient to be considered in complete clinical response when all tumour lesions have disappeared.

Cytology and histology. Cytological and histological techniques can be used to differentiate between partial response and complete response in rare cases (e.g., after treatment to differentiate between residual benign lesions and residual malignant lesions in tumour types such as germ cell tumours).

Molecular Markers for Prediction of Response

There are various molecular markers for prediction of response in various malignant disorders like HER 2 Over expression in Breast cancer, KRAS Mutation in colorectal cancer and Specific somatic mutations of the EGFR kinase domain which greatly increase the sensitivity of non–small cell lung cancer (NSCLC) cells to EGFR kinase inhibitors such as gefitinib and erlotinib. Therefore, EGFR kinase mutations may be a prognostic marker in NSCLC.

Serum Markers for Monitoring Response

In clinical practice , two approaches have been used to monitor tumour response to therapy. One is to measure markers specifically secreted by cancer cells into the blood; the other approach, which is much more common, uses changes in tumour size as a criterion for tumour response. The use of changes in serum markers as a measure of tumour response to therapy is appealing because it is non invasive, can be repeated frequently, and has a relatively low cost. Furthermore, it offers the opportunity to measure tumour response at multiple sites with a single parameter. In some of the malignant tumours, tumour markers (prostate-specific antigen in prostate cancer, CA125 in ovarian cancer, and thyroglobulin in thyroid cancer) are frequently used to monitor tumour response for patient management.

MONITORING RESPONSE BY MOLECULAR IMAGING

Because of these well-recognized limitations of current approaches for monitoring tumour response to therapy, there has been considerable interest in new functional or molecular imaging techniques. This interest has been further stimulated by a growing number of alternative treatment regimens. For many malignant diseases, several treatment regimens have become available, acting on different targets in the tumour tissue. For treatment of metastatic colon cancer, ten chemotherapy combinations are listed in the Physician Data Query database of the National Institutes of Health, which summarizes evidence-based treatment options for all malignant diseases. Among several pursued molecular imaging approaches for treatment monitoring, such as dynamic contrast-enhanced MRI, diffusion-weighted MRI, MR spectroscopy, optical imaging, and contrast-enhanced ultrasound , PET with the glucose analogue 18F-FDG are currently routinely used as molecular imaging for monitoring response in malignant tumours.

RESPONSE EVALUATION CRITERIA IN SOLID Tumours (RECIST Criteria)

RECIST criteria explores the definitions, assumptions, and purposes of tumour response criteria. The guidelines that are offered may lead to more uniform reporting of outcomes in tumour response assessment[2]. The tumour response can be evaluated by following methods.

Assessment of overall tumour burden and measurable disease.
To assess objective response, it is necessary to estimate the overall tumour burden at baseline to which subsequent measurements will be compared. Only patients with measurable disease at baseline should be included in protocols where objective tumour response is the primary end point. Measurable disease is defined by the presence of at least one measurable lesion .

Baseline documentation of "target" and "non-target" lesions

All measurable lesions up to a maximum of five lesions per organ and ten lesions in total, representative of all involved organs, should be identified as target lesions and recorded and measured at baseline. Target lesions should be selected on the basis of their size (those with the longest diameter) and their suitability for accurate repeated measurements (either by imaging techniques or clinically). A sum of the longest diameter for all target lesions will be calculated and reported as the baseline sum of longest diameter.

Response Criteria

1. Evaluation of target lesions. Evaluation of target lesions can be done by defining the criteria used to determine objective tumour response for target lesion. Complete response is defined as the disappearance of all target lesions; partial response—at least a 30% decrease in the sum of the longest diameter of target lesions, taking as reference the baseline sum of longest diameter; progressive disease—at least a 20% increase in the sum of the longest diameter of target lesions, taking as reference the smallest sum of longest diameter recorded since the treatment started or the appearance of one or more new lesions; stable disease—neither sufficient shrinkage to qualify for partial response nor sufficient increase to qualify for progressive disease, taking as reference the smallest sum of longest diameter since the treatment started.

2. Evaluation of non-target lesions. The evaluation of tumour response for non-target lesions include: complete response—the disappearance of all non target lesions and normalization of tumour marker level; incomplete response/stable disease—the persistence of one or more non-target lesion(s) and/or the maintenance of tumour marker level above the normal limits; and progressive disease—the appearance of one or more new lesions and/or unequivocal progression of existing non-target lesions.

Evaluation of best overall response. The best overall response is the best response recorded from the start of treatment until disease progression/recurrence (taking as reference for progressive disease the smallest measurements recorded since the treatment started). In general, the patient's best response assignment will depend on the achievement of both measurement and confirmation criteria.

Frequency of tumour re-evaluation. Frequency of tumour re-evaluation while on treatment should be protocol specific and adapted to the type and schedule of treatment. However, in the context of phase II studies where the beneficial effect of therapy is not known, follow-up of every other cycle (i.e., 6–8 weeks) seems a reasonable norm.

Confirmation. The main goal of confirmation of objective response is to avoid overestimating the response rate observed. This aspect of response evaluation is particularly important in nonrandomized trials where response is the primary end point. In this setting, to be assigned a status of partial response or complete response, changes in tumour measurements must be confirmed by repeat assessments that should be performed no less than 4 weeks after the criteria for response are first met. In the case of stable disease, measurements must have met the stable disease criteria at least once after study entry at a minimum interval (in general, not less than 6–8 weeks) .

Duration of overall response. The duration of overall response is measured from the time that measurement criteria are met for complete response or partial response (whichever status is recorded first) until the first date that recurrent or progressive disease is objectively documented (taking as reference for progressive disease the smallest measurements recorded since the treatment started). The duration of overall complete response is measured from the time measurement criteria are first met for complete response until the first date that recurrent disease is objectively documented.

Duration of stable disease. Stable disease is measured from the start of the treatment until the criteria for disease progression is met (taking as reference the smallest measurements recorded since the treatment started). The clinical relevance of the duration of stable disease varies for different tumour types and grades. Therefore, it is highly recommended that the protocol should specify the minimal time interval required between two measurements for determination of stable disease. This time interval should take into account the expected clinical benefit that such a status may bring to the population under study [3].

Conclusion: This article has described a standard approach to solid tumour measurement and definitions for objective assessment of patients suffering from cancer. It is expected that these criteria will be useful in all solid tumours where objective response is the primary study endpoint, and where assessment of stable disease,

tumour progression or time to progression analyses are undertaken. The article has provided definitions and criteria for assessment of tumour response. It has also provided guidelines and recommendations regarding standard reporting of the results that utilise tumour response as an endpoint.

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Surgery for chronic pancreatitis

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Chronic pancreatitis (CP) is a progressive, chronic inflammatory and debilitating condition characterized by disabling pain and is associated with development of exocrine and endocrine pancreatic insufficiency. It usually affects younger population which leads to enormous socio-economic burden to the patient and his family due to loss of working hours because of pain. These patients usually have a poor quality of life and a shortened life expectancy due to the development of secondary complications.
Ongoing pancreatic inflammation can lead to formation of a mass in the head of pancreas in about 30-50% of the patients. The disease can be complicated with the development of biliary (about 30%) or rarely duodenal (5-7%) obstruction, porto-mesenteric compression (8-10%) and splenic vein thrombosis (3-5%).

Indication of Surgery
Majority of the patients during the course of disease require surgical intervention. **Pain is the most common indication of surgery**. Failure of medical and endoscopic management to provide adequate pain relief is the classical indication of surgery.

Other indications of surgery:
- Development of an inflammatory mass
- Multiple strictures in pancreatic duct unsuitable for endotherapy
- Development of biliary or duodenal stenosis
- Suspicious of malignanacy

Rationale of Surgery in Chronic pancreatitis

Intra-ductal and interstitial hypertension have been the proposed as the mechanisms of pain in chronic pancreatitis. This situation is quite similar to the occurrence of compartment syndrome in pancreas. Both the etiologies can be very effectively addressed by the surgical decompression and adequate drainage of the pancreas.

Pancreas head has been found to be enlarged in about half of the patients with chronic pancreatitis due to the ongoing inflammatory process. **Pancreatic head** has been considered as a **'pacemaker of pain'** in chronic pancreatitis. Head mass is often addressed with resectional procedures.

In a randomized controlled trial, surgery has been proved to be superior to endoscopic treatment of chronic pancreatitis in terms of long term complete pain relief and increase in body weight at 5 years. However, development of de novo diabetes was similar in both the arms. Another randomized trial comparing surgery and endotherapy was terminated early after interim analysis on the basis of significant improvement of pain score and better quality of life favoring surgical interventions.

Timing of Surgery
Surgical intervention should be performed early in the course of the disease. Not only does it achieve a better pain relief but also it can delay the onset of insufficiency in these patients. It can slow down the ongoing inflammatory process by providing surgical decompression. It is imperative to have intervention before the changes become irreversible to cause permanent damage to the pancreas.

Surgical options
The main aim of the surgical intervention is to provide a lasting pain relief and at the same time preserve endocrine and exocrine function. Surgical procedures can be divided as (table 1)

Table 1: Classification of Surgical Procedures for Chronic Pancreatitis

Resectional procedures	Drainage procedures	Hybrid procedures
1.Pancreaticoduodenectomy 2. PPPD 3. Total pancreatectomy with or without duodenum preservation 4. Total pancreatectomy with islet cell autotransplantation 5. Left sided resection	1. Duval's procedure 2. Puestow–Gillesby procedure 3. Partington–Rochelle variant of the Puestow procedure	1. Head Coring and drainage (Frey's procedure) 2. DPHR(Beger's Procedure) 3. Izbicki (Hamburg) modification 4. Berne modification

PPPD pylorus preserving pancreaticoduodenectomy, DPHR Duodenum preserving pancreatic head resection

Preoperative assessment
Proper patient selection is essential for an excellent outcome. Components of assessment includes:
a) Confirmation of the diagnosis of chronic pancreatitis and to establish the benig nature of the head mass if present
b) Define the anatomy of pancreatic duct, head mass and parenchyma
c) Evaluation for biliary and duodenal obstruction
d) Ascertain the patency of spleno-porto-mesenteric axis
e) Assessment of exocrine and endocrine function
f) Pain assessment in terms of severity and opioid dependence
g) Assessment of nutritional, medical and psycho-social co-morbidities.

RESECTIONAL PROCEDURES
Partial or total resection of pancreas is an attractive and permanent solution for pain associated with CP, however, it is associated with the risk of developing permanent pancreatic insufficiency.

Pancreaticoduodenectomy
Kausch-Whipple pancreaticoduodenectomy (PD) entails the resection of pancreatic head along with the entire duodenum, distal third of the stomach, bile duct, and proximal jejunum. With increasing safety of the procedure, it is being done for the benign disease as well.

Classical PD is associated with nutritional sequelae associated with distal gastrectomy, so it is not the preferred for chronic pancreatitis. Pylorus-preserving procedure (PPPD) on the other hand does not entail the removal of stomach and has evolved as the preferred procedure for chronic pancreatitis.

The major advantage of PD is the resection of an unrecognized adenocarcnoma in a patient with head mass. The procedure in itself is sufficient to address the patients with duodenal and distal bile duct stricture.

Pancreatico-duodenectomy, provides long term pain relief has been reported in 85% of the patients. However, it is associated with more than 50% incidence of new onset of diabetes and almost half of the patients developing exocrine insufficiency at a follow up of ten years.

Distal Pancreatectomy
This is suitable only small percentage patients (5-15%) have focal disease confined to the body and tail of pancreas. This happens in patients with isolated duct stricture, pseudocyst, or both at the neck of the pancreas. Since head is the pacemaker of pain in CP, this procedure leaves major portion of the gland untreated. Therefore it is associated with a significant incidence of recurrence and is not widely advocated in the management of CP.

95% Distal Pancreatectomy
The procedure entails removal of almost entire pancreas leaving a very thin rim of tissue over the duodenum. This tissue accounts for only 5% of the pancreatic parenchymal tissue. This in turn helps in preserving the pancreaticoduodenal arcade and intrapancreatic portion of the bile duct. This helps in the preservation of the entero-duodenal axis.

The procedure was able to achieve a pain relief of more than 80% at long term follow up. However, majority of the patients will develop brittle diabetes and endocrine insufficiency. So the procedure of 95% distal pancreatectomy didn't become popular.

DRAINAGE PROCEDURES
Duval and Zollinger et al in separate studies reported distal pancreato-splenectomy with caudal pancreaticojejunostomy as a drainage procedure for chronic pancreatitis. The procedure provided drainage of

only a small distal segment of the duct without addressing the strictures. So it failed to provide a lasting pain relief in the presence of classical 'Chain of lakes' appearance.

The procedure was later modified by **Puestow and Gillesby** by the addition of longitudinal pancreaticojejunostomy from the caudal end with implantation of the divided tail into the Roux en Y limb of the jejunum. This was done to have a larger drainage of the duct particularly in the body and tail of pancreas. This procedure to decompress the head region as the jejunum limb was not brought beyond the superior mesenteric vessels. So the failure rate in terms of recurrence of pain was high.

In 1960, **Partington and Rochelle** later modified the procedure by fashioning a side to side anastomosis with jejunum after longitudinally incising the anterior surface of pancreas to expose the duct. This procedure did not require posterior mobilization of the pancreas and had an advantage of avoiding distal pancreatectomy and splenectomy. In addition it had an advantage of decompressing the pancreatic duct in the head region as well. So, this procedure has been widely popularized over the years and i salso known as Lateral Pancreatico Jejunostomy (LPJ).

Technique of Lateral Pancreatico Jejunostomy (LPJ):
A dilated duct, with chain of lakes appearance in the absence of a head mass is suitable for this procedure.
A midline or a bilateral subcostal incision is preferred. Gastrocolic omentum is divided so as to expose the pancreas in its entire extent. Hepatic flexure is taken down to expose the pancreatic head. Anterior pancreaticoduodenal and gastroduodenal veins are suture ligated and divided. Pylorus and the first part of the duodenum should be lifted of the pancreas head. The head should be palpated for any suspicious mass and frozen biopsy should be sent if required. The superior and inferior borders of pancreas are delineated anteriorly so as to facilitate the subsequent placement of sutures during anastomosis.
Pancreatic duct can be identified easily by palpation in the neck or body region where it is superficial, as thin parenchyma overlies a dilated duct. In patient with duct packed with stones, the needle can be used to sound the stone for subsequent opening of the duct. Once the duct is located, it is confirmed by aspiration. Small ductotomy is made to gain sufficient access to place a fine instrument into the duct. The ductotomy is extended towards the left till about 1 cm short of the tip of tail. The calculi n the pancreatic duct can be removed as and when they are encountered while opening the duct. Towards, the right, the ductotomy is extended just short of duodenum. Intra-parenchymal cyst if encountered is incorporated into the ductotomy and drained into the jejunum. Bleeding from the pancreatic margin is usually controlled with diathermy or a fine non absorbable suture.

About 15 cm from ligament of Trietz, jejunum is divided with a stapler cutter device. Jejunojunostomy is fashioned 45-50 cm down-stream in a side to side fashion. Roux limb is brought up through retro-colic route usually to the left of middle colic artery.

Jejunum is placed over the pancreatic surface and opened longitudinally serially to match the length of dutotomy. Usually a single layer continuous anastomosis with a long lasting fine monofilament suture is performed. Full thickness jejunal bites are sutured with pancreatic capsule taking partial thickness of parenchyma. No attempt is made to sew directly the mucosa of pancreatic duct except the tail region where the parenchyma is very thin. Deep bites into the parenchyma can occlude the side branches of the gland and may limit the drainage.

Results of LPJ:
Relief of pain is the primary end point of the operation. With LPJ it has been seen from 48% to 91%. Despite early pain relief in more than 80% of the patients, about 30-35% of patients develop pain at a follow up of 3-5 years. There is no evidence to suggest that this procedure worsens the pancreatic insufficiency as it is associated with minimal loss of the functioning pancreatic parenchyma.

HYBRID PROCEDURES
Frey Procedure
With about one thirds of patients developing recurrence of pain, there was a need to develop new procedure. As pancreatic head is a pacemaker for pain, so without excising the head, it is difficult to achieve pain relief in patients with inflammatory head mass. Frey and Smith described a procedure which combines partial excision of head as well as the drainage of duct.

In patients with dilated duct, 30-50% patients have as associated inflammatory head mass. Partial excision of the head improves the ductal drainage and better clearance of calculi. Due to the more posterior location of main pancreatic duct in the head region there is presence of thick pancreatic tissue between the posteriorly placed duct and medial duodenal wall. It is important to excise this tissue for adequate drainage of duct.

Surgical technique: The exposure of pancreas and opening of the pancreatic duct is performed as described for lateral pancreatico-jejunostomy.

Head Coring:
The location of mesenteric vessels in relation to pancreas is identified as pancreas at this point will not be divided and careful coring out is performed in this area. After the duct is opened till the neck of pancreas, coring of

pancreatic tissue in small bites is performed in the head region. Pancreaticoduodenal groove is preserved as it contains the vasculature of the duodenum. Marking sutures are placed on the pancreas, 5mm parallel and medial to the inner aspect of duodenum to limit the medial extent of resection. The pancreatic tissue is removed in small bits, and one should secure hemostasis after removal of each and every bit. While coring out the pancreatic tissue, care should be exercised to avoid injuring common bile duct. Panccreatic duct is the posterior-most limit of the coring. At the end of coring, a thin rim of pancreatic tissue should remain over the duodenum to preserve the superior and inferior arcade. The cored out head is in continuity with the main pancreatic duct and drained in a Roux en Y limb of the jejunum as done in LPJ. In the head region, the jejunum is sutured with the rim of pancreatic tissue left on the duodenal wall.

Complications: it can be performed with a mortality of less than 2%. Other complications like pancreatic fistula, intra-abdominal collection, haemorrhage, pulmonary complications, occur in 7 to 40%. Anastomotic failure occurs in 2 - 3%. Outcome: Pain relief in 70% to 100% of the patients. New onset diabetes occurs in 8 to 34% while exocrine insufficiency occurs in 60 to 80%. Improved quality of life and improved nutritional status is reported in more than 90% of the patients.

Modifications of Hybrid Procedures

Beger's Procedure (Duodenum preserving head resection)

The procedure entails 95% resection of pancreatic head. The pancreas is transected at the neck region after separating it from porto-mesenteric axis and medially leaving a small rim of pancreatic tissue along the medial duodenal wall. The pancreas remnant is drained in the Roux limb of the jejunum. This allows the preservation of entero-duodenal axis which has the major advantage over pancreaticoduodenectomy. However this is associated with loss of pancreatic tissue leading on to the development of brittle diabetes. Complete or partial pain relief is achieved in 70 – 100% of the patients.

Bern Modification: This is a technical simplification of the Beger-procedure with equivalent outcome. The excavation of the pancreatic head is performed identical to that of Berger-procedure. However, separation of pancreas from the porto-mesentric axis is not required as it doesn't mandate transaction of the pancreatic neck. This makes the procedure technically easy and safer. The procedure is ideal for patients with a dominant inflammatory head mass without left side stenosis.

Izbicki Modification: The procedure is most suitable for patients with small duct pancreatitis as defined by duct diameter of less than 3 mm. The procedure entails removal of a longitudinal triangular cavity along the ventral aspect of pancreas. This V-shaped excision provides adequate drainage of secondary and tertiary order pancreatic ducts. Subsequently, this V shaped cavity is anastomosed to a Roux-en-Y loop jejunum in a side-to-side manner. This achieves a complete pain relief in 75%, weight gain in 89%, improved quality of life and return to work.

Conclusions

Pain is the dominant symptom for which surgical intervention is needed. The surgical should be selected as per the stage of the disease and patho-morphology of the pancreas. Choice of surgical procedure is determined by the main pancreatic duct diameter and the presence inflammatory head mass as described in the table 2. Pain relief is similar for hybrid procedures and pancreaticoduodenectomy. Resectional procedures should be avoided as far as possible as it leads to the permanent loss of functioning parenchyma. Development of endocrine or exocrine dysfunction occurs as a part of the natural course of the disease.

Table 2: Choice of surgical procedure in Chronic pancreatitis

Procedure	**Patho-morphology**
Dranage procedures	
Caudal drainage (Duval) Puestow Procedure	Obsolete, replaced by newer procedures
Lateral pancreaticojejunostomy	Dilated main pancreatic duct without presence of inflammatory head mass
Resection Procedures	
PD/ PPPD	Suspected neoplasia Presence of fixed duodenal stenosis
Distal Pancreatectomy	Focal disease localized to the body and tail region of pancreas
Total pancreatectomy	Only as a salvage procedure; Caution of brittle diabetes
Total pancreatectomy with AIT	Preserves endocrine function Caution severe exocrine insufficiency
Hybrid procedures	Exclude malignancy by frozen section
Frey procedure	Ductal obstruction with a small inflammatory head mass
Beger procedure	Large Inflammatory head mass without a distal stricture
V shaped excision	Small duct pancreatitis (< 3 mm)

AIT autologous islet cell transplantation

Further reading

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Approach to a patient with obstructive jaundice

Anubhav Vindal, Keshav Mishra

Jaundice (French word 'jaune' meaning yellow) refers to yellowish discoloration of skin, mucus membrane and sclera due to excess bile pigment in serum and tissues. Jaundice is a symptom that may be the manifestation of several pathologies. Jaundice may be classified in several different ways – the most commonly used of which is based on the pathophysiology. By convention, the non obstructive causes of jaundice are labeled as medical jaundice, where as the obstructive causes are known as surgical jaundice.

Causes of jaundice:

1. Medical jaundice
    a. Increased production of bilirubin
    b. Impaired hepatocyte uptake of bilirubin
    c. Impaired conjugation of bilirubin
    d. Impaired transport or excretion of bilirubin into bile canaliculi
2. Surgical jaundice
    a. Obstruction of intrahepatic or extrahepatic biliary tree

The present discussion will be limited to the approach to the history and examination of a patient with obstructive (surgical) jaundice.

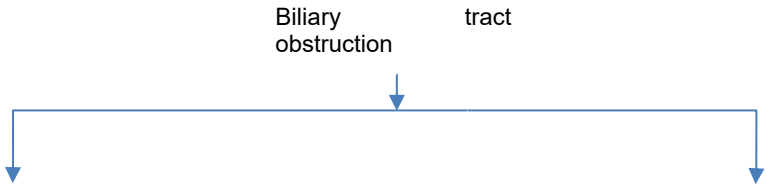
Causes of obstructive jaundice

Complete obstruction (Progressive Jaundice)	**Intermittent obstruction (Intermittent Jaundice)**	**Chronic incomplete obstruction**
• Ca head of pancreas • Cholangiocarcinoma • Common bile duct ligation	• Choledocholithiasis • Periampullary carcinoma • Duodenal diverticulum • Choledochal cyst • Biliary parasites • Haemobilia	• Strictures of CBD • Traumatic (iatrogenic) • Sclerosing cholangitis • Stenosis of biliary-enteric anastomosis • Chronic pancreatitis • Sphincter of Oddi stenosis

Pathophysiology of obstructive jaundice

All the signs and symptoms in obstructive jaundice can be explained by two mechanisms of causation central to the pathophysiology of biliary tract obstruction:

1) Absence of bile constituents in intestinal lumen
2) Overflow of biliary constituents into systemic circulation



Absence of bile constituents in intestinal lumen

1) Malabsorption of lipids – steatorrhoea
2) Malabsorption of fat soluble vitamins
   Vitamin A – Xerophthalmia
   Vitamin D – Osteomalacia and Osteoporosis
   Vitamin E
   Vitamin K – impaired carboxylation of clotting factors in liver - deranged PT and CT
3) Decreased bile pigments in intestinal lumen – pale stools (decreased stercobilins)

Overflow of biliary constituents into systemic circulation

1) Increased bile pigment in blood – hyperbilirubinemia (jaundice)
2) Conjugated bilirubin in blood (water soluble) – excreted in urine- high coloured urine
3) High circulating bile salts - pruritus

Approach to the History in a patient with obstructive jaundice

While eliciting the history in a patient with suspected obstructive jaundice, the following points deserve special attention:

1) Characteristics of Jaundice

   a. Fluctuating/intermittent jaundice:

      The intensity of the jaundice waxes and wanes during the course of the disease. It is usually due to partial or incomplete obstruction to the biliary tract – when the pent up secretions are released into the duodenum, the intensity of jaundice comes down.

      This is commonly seen in:
      - Choledocholithiasis
      - Carcinoma of ampulla of vater
      - Primary sclerosing cholangitis
      - Choledochal cyst
      - Biliary parasites
      - Haemobilia

   b. Progressive jaundice:
      The intensity of the jaundice keeps on increasing as the obstruction follows an unrelenting course.

      This is commonly seen in:
      - Periampullary carcinoma
      - Cholangiocarcinoma
      - Ca Gall bladder
      - Strictures of extrahepatic billiary tree
      - Chronic pancreatitis
      - Cystic fibrosis
      - Sphincter of oddi stenosis

   c. Resolving jaundice:

      The intensity of the jaundice is already on a decline when the patient presents. It is an indication that the cause of obstruction has had a natural cure. Such a course is seen when a patient has passed out a small CBD calculus.

2) High coloured urine
   The colour of the urine become dark yellowish – brown due to presence of conjugated bilirubin (water soluble) in urine. This is associated with a low urinary urobilinogen as the conversion of bilirubin into

urobilinogen which takes place in the intestines, does not occur. The urine is sometimes called 'tea coloured urine'.

A high coloured urine can also be seen in hepatic and cholestatic causes of jaundice due to presence of conjugated bilirubin in the blood.

3) Steatorrhoea
The patient passes clay coloured, bulky, foul smelling stools in obstructive jaundice. The colour of the stool corresponds with the intensity of biliary tract obstruction. Due to the absence of emulsifying function of bile in the gut, there is fat malabsorption. Such a stool floats on water and is difficult to flush due to its increased fat content.

4) Viatmin deficiency
Steatorrhoea is also associated with malabsorption of fat soluble vitamins (A, D, E and K) and the consequent symptoms of vitamin deficiency like easy bruisability and prolonged bleeding time (Vit K) and xerophthalmia (Vit A).

5) Generalized pruritus
Itching is a very common and characteristic symptom seen in almost 80%-100% of patients presenting with obstructive jaundice. The intensity shows a circadian rhythm with the highest intensity in evening and night. The patient is often unable to sleep due to the severe itching at night. Bile salts, particularly chenodeoxycholate and deoxycholate, accumulate in the blood due to overflow from the bile canaliculi. As they get deposited in the skin, they stimulate the release of histamine from mast cells, resulting in itching

6) Melaena
Melaena is passage of black, tarry, foul smelling stools. It is a very specific symptom suggestive of upper gastrointestinal bleed (proximal to ligament of Treitz). The stools become black and tarry due to the conversion of haemoglobin in blood to acid haematin. In general melaena in a patient with obstructive jaundice is suggestive of a periampullary carcinoma.

7) Pain
Intermittent pain predominantly in right upper and upper abdomen is a frequent complaint in patients with calculus disease. The pain is colicky/ gripping in nature and moderate to severe in intensity. A constant dull aching/ boring pain radiating to back is suggestive of a malignancy (carcinoma head of pancreas) or a benign condition (chronic pancreatitis).

8) Loss of weight/appetite
Significant loss of weight (more than 10% weight loss over 6 months) and loss of appetite with obstructive jaundice is suggestive of a malignant cause of obstruction. However weight loss can also occur in long standing obstructive jaundice due to fat malabsorption.

9) Fever
Fever in a patient with jaundice indicated presence of infection in the biliary system. Usually such a patient has high grade fever with associated chills and rigors. Presence of Charcot's triad – intermittent pain, fever with chills and intermittent jaundice is suggestive of cholangitis and is more commonly seen in choledocholithiasis than malignancy.

10) Past history
The past history in a patient with obstructive jaundice should specifically aim at finding history of any previous hepatobiliary surgery (iatrogenic biliary injury leading to stricture, anastomotic stricture) or any intervention on biliary tract like ERCP/ES with CBD stenting.

At the end of the history, one should be able to answer the following questions:

a) Is the patient having obstructive jaundice?
b) What is the most likely pathology causing it?
c) What is the stage in the natural history of the disease the patient has presented in?

Approach to the Examination in a patient with obstructive jaundice

The idea of examining a patient with suspected obstructive jaundice is to confirm the points elicited in the history and to gather more cues to narrow down the diagnosis out of a possible list of differentials arrived at after the history.

The following are the important points to note while examining a patient with obstructive jaundice:

1) Icterus

Icterus is the yellowish discolouration of the various body tissues due to an accumulation of bile pigments. The colour is best seen in daylight and may be missed under artificial light. It may range from pale yellow to dark olive greenish yellow, depending on the extent and duration of obstruction. Icterus can be seen in sclera (usually best seen in the upper sclera above the superior limbus), undersurface of tongue, hard palate, mucous membranes and skin. It is earliest appreciable against the white background of sclera as the bilirubin has high affinity to elastin fibres present in sclera. It must be differentiated from a muddy sclera by examining the unexposed part of the sclera underneath the superior palpebra.

2) Pulse
Relative bradycardia is seen in patients with obstructive jaundice due to an effect of bile salts on sino-atrial node. However, in patients who are febrile or septic, this sign may not be present.

3) Clubbing
Clubbing of fingernails can be seen in a patient with Primary biliary cirrhosis, Hepatocellular carcinoma and chronic liver disease.

4) Enlarged Virchow's node (left supraclavicular lymph node)
This node is palpable between the two heads of sternocleidomastoid muscle on the left side. The sign is known as Troisier's sign and it indicates metastatic disease. It is usually seen in malignancy of hepatobilliary tract, pancreas, stomach, ovary, testis and breast.

5) Signs of liver failure/portal hypertension
Patients may have signs of advanced liver disease in form of spider angiomas, palmar erythema, leucomychia, gynaecomazia (in males), testicular atrophy (in males), loss of body hair (in males). Patients may also have signs of portal hypertension like splenomegaly and caput medusae.

6) Abdominal examination:
May be unremarkable in many cases of obstructive jaundice. However, the skin may show presence of icterus and itch marks.

7) Gall bladder
The gall bladder may be distended and palpable. It may or may not be tender. The feel of the gallbladder on palpation (soft/hard) may give a clue to the diagnosis. Courvoisier's law states that if the gallbladder is palpable in a patient of obstructive jaundice, it is unlikely to be due to gallstones. It is usually due to a downstream obstruction due to malignancy. A hard gall bladder is suggestive of carcinoma of gall bladder.

8) Hepatomegaly
Liver enlargement and liver span should always be checked in a patient with obstructive jaundice. Characteristics of liver that should be noted are enlargement, tenderness, suface (smooth or nodular) and edge (sharp or rounded).

9) Splenomegaly
Spleen may be enlarged in a jaundiced patient due to haemolytic anaemia, portal hypertension secondary to liver cirrhosis and SMV or portal vein thrombosis.

10) Ascites
Free fluid may be present in the peritoneal cavity of a patient with obstructive jaundice. The causes can be due peritoneal spread of malignancy, chronic liver disease or portal hypertension.

Small amount of fluid may be tested for by the puddle sign, whereas larger amounts of fluid can be checked by shifting dullness and fluid thrill.

11) Sister Mary Joseph's nodule
A palpable nodule bulging into the umbilicus is indicative of metastatic intra peritoneal malignancies like carcinoma of stomach, pancreas, colon and ovarian and uterine malignancies.

12) Rectal examination
No abdominal examination is complete without a per rectal examination. In a patient with obstructive jaundice, a rectal examination may reveal thickening of the rectovaginal pouch (Blummer's shelf) due to deposition of malignant cells by transperitoneal spread.

A proper approach to history and examination of a patient with obstructive jaundice helps in arriving at a scientifically sound differential diagnosis and at the same time also helps in the next step of selecting appropriate investigations to aid the diagnosis and management of the patient.

Fistula in Ano management

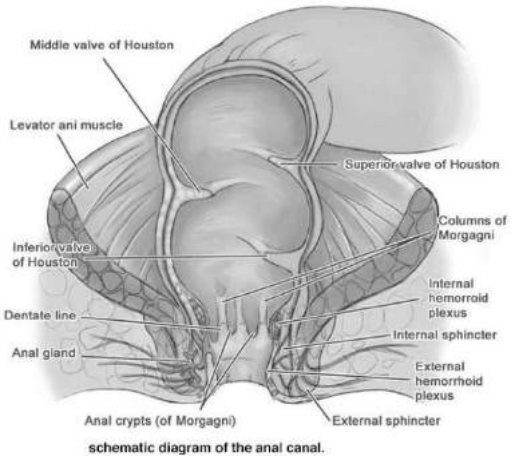
Pawan Lal

Ano-Rectal Anatomy

The pelvic diaphragm, pelvic cavity, and ischioanal fossae are complex structures beyond the scope of this tutorial. In practice, the general surgeon (in the ambulatory setting), will deal with much more superficial anatomy. Therefore, a more superficial approach to the anatomy of this area will be presented.

Anal Canal

The anal canal (approximately 2.3-3.5 cm long) is the terminal part of the large intestine, extending from the upper aspect of the pelvic diaphragm to the anus. Surrounded by internal and external sphincters, it descends posteroinferiorly between the anococcygeal ligament and the perineal body.



schematic diagram of the anal canal.

The internal anal sphincter is an involuntary sphincter supplied by parasympathetic fibers which pass through the pelvic splanchnic nerves. This sphincter relaxes in response to pressure (gas or feces) distending the rectal ampulla.

The external anal sphincter is a voluntary sphincter innervated primarily by S4 through the inferior rectal nerve.
Within the anal canal, the uppermost portion of the canal is dominated by a series of mucosal ridges called anal columns. These columns contain the terminal branches of the superior rectal artery and vein, and it is here (at their superior ends) that the division of the rectum from the anus is defined.

The Pectinate Line

The Pectinate Line (also known as the Dentate or Mucocutaneous Line) is a clinically important landmark due to the fact that it is visible and approximates the level of certain anatomic changes that will be discussed below. It lies at the inferiormost level of the anal columns and indicates the junction of the superior part of the anal canal (derived from the embryonic hindgut) and the inferior part (derived from the embryonic proctodeum). It is this difference in embryonic origin which gives rise to differing arterial, venous, and nervous connections (above and below this line)

Blood Supply and Nerves

The superior portion of the anal canal (that is, superior to the pectinate line) is supplied by the superior rectal artery. Below the pectinate line, the inferior rectal arteries supply the inferiormost part of the anal canal. Between the two, the middle rectal arteries form anastomoses with each to assist in the blood supply.

A plexus of veins branch around the anal canal. Above the pectinate line, this internal rectal plexus drains into the superior rectal vein. Below, the plexus drains into the inferior rectal vein. Similar to the arterial system, a middle rectal vein exists, which mainly drains the muscularis externa, and anastomoses with the superior and inferior veins.

Although not pictured, the lymphatic drainage differs above and below the pectinate line. Above it, the lymphatics drain into the internal iliac lymph nodes. Below, the vessels drain into the superficial inguinal lymph nodes.

Lastly, the anal canal also has differing nervous innervations above and below the line. Above the pectinate line, the nerve supply is visceral, coming from the inferior hypogastric plexus. As is it visceral, this part of the anal canal is only sensitive to stretch. Below the pectinate line, the nerve supply is somatic, receiving its supply from the inferior rectal nerves (branches of the pudendal). As it is somatically innervated, it is sensitive to pain, temperature, and touch.

A fistula-in-ano is an abnormal hollow tract or cavity that is lined with granulation tissue and that connects a primary opening inside the anal canal to a secondary opening in the perianal skin; secondary tracts may be multiple and can extend from the same primary opening. It should be differentiated from the following processes, which do not communicate with the anal canal:

- Hidradenitis suppurativa
- Infected inclusion cysts
- Pilonidal disease

- Bartholin gland abscess in females

Most fistulas are thought to arise as a result of cryptoglandular infection with resultant perirectal abscess. The abscess represents the acute inflammatory event, whereas the fistula is representative of the chronic process. Symptoms generally affect quality of life significantly, and they range from minor discomfort and drainage with resultant hygienic problems to sepsis.

Etiology

In the vast majority of cases, fistula-in-ano is caused by a previous anorectal abscess. Typically, there are eight to 10 anal crypt glands at the level of the dentate line in the anal canal, arranged circumferentially. These glands penetrate the internal sphincter and end in the intersphincteric plane. They provide a path by which infecting organisms can reach the intramuscular spaces. The cryptoglandular hypothesis states that an infection begins in the anal canal glands and progresses into the muscular wall of the anal sphincters to cause an anorectal abscess.

After surgical or spontaneous drainage in the perianal skin, a granulation tissue–lined tract is occasionally left behind, causing recurrent symptoms, formation of a fistula tract after anorectal abscess drainage occurs in 7-40% of cases.

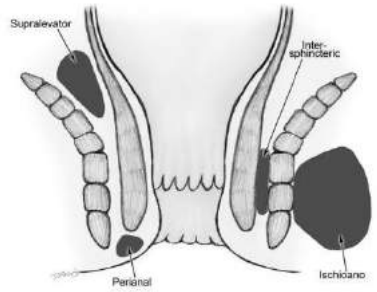
Other fistulas develop secondary to trauma (eg, rectal foreign bodies), Crohn disease, anal fissures, carcinoma, radiation therapy, actinomycoses, tuberculosis, and lymphogranuloma venereum secondary to chlamydial infection.

Incidence

The true prevalence of fistula-in-ano is unknown. The incidence of a fistula-in-ano developing from an anal abscess ranges from 26% to 38%.

Anorectal Abscesses

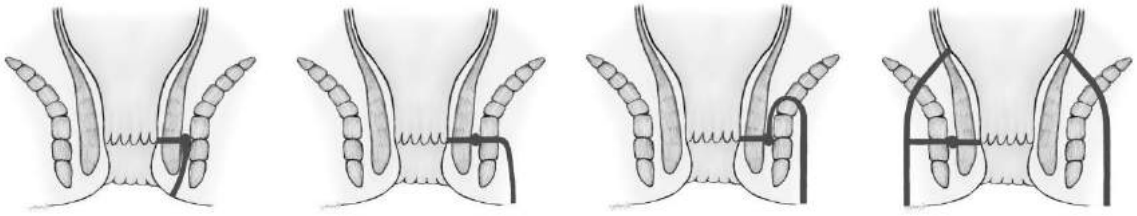
There are five types of anorectal abscesses described: perianal (60%), ischiorectal (30%), intersphincteric (5%), supralevator (4%) and submucosal (1%). Anorectal abscesses usually arise from infection of the cryptoglandular epithelium along the anal canal.



Parks Classification System

The classification system developed by Parks, Gordon, and Hardcastle (generally known as the Parks classification) is the one most commonly used for fistula-in-ano. This system defines four types of fistula-in-ano that result from cryptoglandular infections, as follows:

- Intersphincteric
- Transsphincteric
- Suprasphincteric
- Extrasphincteric



Intersphincteric fistula-in-ano is characterized as follows:

- It is the result of a perianal abscess
- Common course - It begins at the dentate line, then tracks via the internal sphincter to the intersphincteric space between the internal and external anal sphincters, and finally terminates in the perianal skin or perineum
- Incidence - 70% of all anal fistulas
- Other possible tracts - No perineal opening; high blind tract; high tract to lower rectum or pelvis

A **trans-sphincteric fistula-in-ano** is characterized as follows:

- In its usual variety, this fistula results from an ischiorectal fossa abscess
- Common course - It tracks from the internal opening at the dentate line via the internal and external anal sphincters into the ischiorectal fossa and then terminates in the perianal skin or perineum
- Incidence - 25% of all anal fistulas
- Other possible tracts - High tract with perineal opening; high blind tract

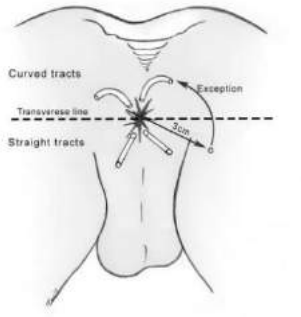
A **suprasphincteric fistula-in-ano** is characterized as follows:
- It arises from a supralevator abscess
- Common course - It passes from the internal opening at the dentate line to the intersphincteric space, tracks superiorly to above the puborectalis, and then curves downward lateral to the external anal sphincter into the ischiorectal fossa and finally to the perianal skin or perineum
- Incidence - 5% percent of all anal fistulas
- Other possible tracts - High blind tract (ie, palpable through rectal wall above dentate line)

An **extrasphincteric fistula-in-ano** is characterized as follows:
- It may arise from foreign body penetration of the rectum with drainage through the levators, from penetrating injury to the perineum, from Crohn disease or carcinoma or its treatment, or from pelvic inflammatory disease
- Common course - It runs from the perianal skin via the ischiorectal fossa, tracking upward and through the levator ani muscles to the rectal wall, completely outside the sphincter mechanism, with or without a connection to the dentate line
- Incidence - 1% of all anal fistulas

Current procedural terminology for fistula in ano includes the following:
- Subcutaneous
- Submuscular (intersphincteric, low transsphincteric)
- Complex, recurrent (high transsphincteric, suprasphincteric and extrasphincteric, multiple tracts, recurrent)

Parks classification system developed by Parks et al does not include the subcutaneous fistula. These fistulas are not of cryptoglandular origin but are usually caused by unhealed anal fissures or anorectal procedures (eg, hemorrhoidectomy or sphincterotomy).

Goodsall's Rule



If the external opening is anterior to an imaginary line drawn horizontally through the anal canal, the fistula usually runs directly into the anal canal.
If the external opening is posterior to the line, the fistula usually curves to the posterior midline of the anal canal.
It should be noted that application of this rule is often unreliable in anterior fistulas and those with underlying disease

Presentation

History
Patients often provide a reliable history of previous pain, swelling, and spontaneous or planned surgical drainage of an anorectal abscess. Signs and symptoms of fistula-in-ano, in order of prevalence, include the following:
- Perianal discharge
- Pain
- Swelling
- Bleeding
- Diarrhea
- Skin excoriation
- External opening

Physical examination
No specific laboratory studies are required in the diagnosis of fistula-in-ano, instead, physical examination findings remain the mainstay of diagnosis.

The examiner should observe the entire perineum, looking for an external opening that appears as an open sinus or elevation of granulation tissue. Spontaneous discharge of pus or blood via the external opening may be apparent or expressible on digital rectal examination.

Digital rectal examination (DRE) may reveal a fibrous tract or cord beneath the skin. It also helps to delineate any further acute inflammation that is not yet drained. Lateral or posterior induration suggests deep postanal or ischiorectal extension.

The examiner should determine the relationship between the anorectal ring and the position of the tract before the patient is relaxed by anesthesia. The sphincter tone and voluntary squeeze pressures should be assessed before any surgical intervention to determine whether preoperative manometry is indicated. Anoscopy is usually required to identify the internal opening. Proctoscopy is also indicated in the presence of rectal disease (eg, Crohn disease or other associated conditions).

Imaging Studies

Radiologic studies are not performed for routine fistula evaluation, because in most cases, the anatomy of a fistula-in-ano can be determined in the operating room. However, such studies can be helpful when the primary opening is difficult to identify or when recurrent or persistent disease is present. In the case of recurrent or multiple fistulas, such studies can be used to identify secondary tracts or missed primary openings. Several imaging diagnostic modalities are available to evaluate fistula-in-ano..

Fistulography
This technique involves injection of contrast via the internal opening, which is followed by anteroposterior, lateral, and oblique radiographic images to outline the course of the fistula tract.

Fistulography is relatively well tolerated but it can be painful when injecting the contrast material into the fistulous tract. It requires the ability to visualize the internal opening. Questions have been raised about its accuracy, which has been reported to range from 16% to 48%.

Because of these limitations, fistulography is generally reserved for cases in which there is a concern about a fistulous connection between the rectum and adjacent organs such as the bladder, where it may be slightly more useful than a careful examination under anesthesia.

Endoanal or endorectal ultrasonography
Endoanal or endorectal ultrasonography involves the passage of a 7- or 10-MHz ultrasound transducer into the anal canal to help define the muscular anatomy and thereby help differentiate intersphincteric from transsphincteric lesions. A standard water-filled balloon transducer can facilitate evaluation of the rectal wall for any suprasphincteric extension.

Investigations have shown that the addition of hydrogen peroxide via the external opening can aid in outlining the course of the fistula tract. This may be useful for helping to identify missed internal openings.

Endoanal/endorectal ultrasonography has been reported to be 50% better than physical examination alone in helping to detect an internal opening that is difficult to localize. This modality has not been used widely for routine clinical fistula evaluation.

Magnetic resonance imaging
Findings on magnetic resonance imaging (MRI) show 80-90% concordance with operative findings when a primary tract course and secondary extensions are observed. MRI is the investigation of choice for the evaluation of complex fistulas and recurrent fistulas. It has been shown to reduce recurrence rates by providing information on otherwise unknown extensions.

St James's University Hospital Classification for MRI of fistula in Ano
The MR imaging–based classification - the St James's University Hospital classification, consists of five grades and relates the Parks surgical classification to anatomy seen at MR imaging in both axial and coronal planes.

Grade 1: Simple Linear Intersphincteric Fistula.—In a simple linear intersphincteric fistula, the fistulous track extends from the skin of the perineum or natal cleft to the anal canal, and the ischiorectal and ischioanal fossae are clear. There is no ramification of the track within the sphincter complex. The enhancing track is seen in the plane between the sphincters and is entirely confined by the external sphincter. Fistulous tracks arising behind the transverse anal line, which are by far the most common type, enter the anal canal in the midline posteriorly.

Grade 2: Intersphincteric Fistula with Abscess or Secondary Track.—Intersphincteric fistulas with an abscess or secondary track are also bounded by the external sphincter. Secondary fistulous tracks may be of the horseshoe type, crossing the midline, or they may ramify in the ipsilateral intersphincteric plane. Even

when there is abscess formation, this process is confined within the sphincter complex regardless of imaging plane or sequence.
On T2-weighted images, pus has high signal intensity and thus cannot be reliably distinguished from edema and inflammation, but gas within abscesses has a low signal intensity similar to that of the anorectal lumen. On these contrast-enhanced images, the pus in the central cavity has low signal intensity and is surrounded by a brightly enhancing rim. A horseshoe fistula, in which the process extends to the opposite side, is best demonstrated in the axial plane.

Grade 3: Trans-sphincteric Fistula.—Instead of tracking down the intersphincteric plane to the skin, the trans-sphincteric fistula pierces through both layers of the sphincter complex and then arcs down to the skin through the ischiorectal and ischioanal fossae. Thus, a trans-sphincteric fistula may disrupt the normal fat of the ischiorectal and ischioanal fossae with secondary edema and hyperemia. These fistulas are distinguished by the site of the enteric entry point in the middle third of the anal canal (i.e. corresponding to the position of the dentate line), as seen on coronal images. Because these fistulas disrupt the integrity of the sphincter mechanism, their tracks must be excised by dividing both layers of the sphincter, thus risking fecal incontinence.

Grade 4: Trans-sphincteric Fistula with Abscess or Secondary Track within the Ischiorectal Fossa.—A trans-sphincteric fistula can be complicated by sepsis in the ischiorectal or ischioanal fossa. Such an abscess may manifest as an expansion along the primary track or as a structure distorting or filling the ischiorectal fossa. Axial and coronal dynamic contrast-enhanced MR imaging clearly depicts a trans-sphincteric abscess, which characteristically has a central focus of low-signal-intensity pus. As with grade 3 lesions, the key anatomic discriminator of a grade 4 fistula is the track crossing the external sphincter. The track or its associated abscess clearly involves the ischiorectal or ischioanal fossa. In some cases, the track assumes a “dumbbell” configuration spanning the external sphincter.

Grade 5: Supralevator and Translevator Disease.—In rare cases, perianal fistulous disease extends above the insertion of the levator ani muscle. Suprasphincteric fistulas extend upward in the intersphincteric plane and over the top of the levator ani to pierce downward through the ischiorectal fossa. Extrasphincteric fistulas reflect extension of primary pelvic disease down through the levator plate. These fistulas pose problems for management because further assessment is needed to detect pelvic sepsis. Coronal dynamic contrast-enhanced MR imaging elegantly demonstrates breaches of the levator plate, which is clearly shown in this plane. In some translevator fistulas, horseshoe ramifications to the contralateral side may occur.

Computed tomography
Computed tomography (CT) is more helpful in the setting of peri-rectal inflammatory disease than in the setting of small fistulas because it is better for delineating fluid pockets that require drainage than for delineating small fistulas. CT requires administration of oral and rectal contrast. Muscular anatomy is not well delineated.

Barium enema/small bowel series
These studies may be useful for patients with multiple fistulas or recurrent disease to help rule out inflammatory bowel disease.

Anal Manometry
Anal manometry is rarely used in the evaluation of patients with fistula-in-ano. However, pressure evaluation of the sphincter mechanism is helpful in certain patients for operative planning, including the following:

- Patients in whom decreased tone is observed during preoperative evaluation
- Patients with a history of previous fistulotomy
- Patients with a history of obstetrical trauma
- Patients with a high transsphincteric or suprasphincteric fistula (if known)
- Very elderly patients

If a decrease in pressure is found, surgical division of any portion of the sphincter mechanism should be avoided.

Diagnostic Procedures

Examination under anesthesia
Examination of the perineum, digital rectal examination (DRE), and anoscopy are performed after the anesthesia of choice is administered. This must be done before surgical intervention is initiated, especially if outpatient evaluation causes discomfort or has not helped to delineate the course of the fistulous process.

Several techniques have been described to help locate the course of the fistula and, more important, identify the internal opening. They include the following:

- Inject hydrogen peroxide, milk, or dilute methylene blue into the external opening and watch for egress at the dentate line; in the authors' experience, methylene blue often obscures the field more than it helps identify the opening

- Traction (pulling or pushing) on the external opening may also cause a dimpling or protrusion of the involved crypt
- Insertion of a blunt-tip crypt probe via the external opening may help to outline the direction of the tract; if it approaches the dentate line within a few millimeters, a direct extension likely existed (care should be taken to not use excessive force and create false passages)

Treatment Indications and Contraindications

Indications
Therapeutic intervention is indicated for symptomatic patients. Symptoms usually involve recurrent episodes of anorectal sepsis. An abscess develops easily if the external opening on the perianal skin seals itself.

Crohn disease of the perineum with multiple and often complex fistulas requires careful surgical treatment. Acute perianal abscess requires incision and drainage. Definitive repair of fistulas in these patients requires that the intra-abdominal disease be under control with medical therapy. If the disease is controlled, routine therapy is warranted. Recurrent fistulous disease to the rectum and perineum with persistent anorectal sepsis is an indication for pan-proctocolectomy.

Studies have identified a role in Crohn disease for fistula therapy with infliximab, with 50-60% response rates for perianal fistulas. Adipose-derived stem-cell therapy is currently being studied for use in the treatment of Crohn fistula and other complex fistulas.

Contraindications
If patients are without symptoms and a fistula is found during a routine examination, no therapy is required.
Surgery for fistula-in-ano should not be performed for definitive repair of the fistula in the setting of anorectal abscess (unless the fistula is superficial and the tract is obvious). In the acute phase, simple incision and drainage of the abscess are sufficient. Only 7-40% of patients will develop a fistula. Recurrent anal sepsis and fistula formation are twofold higher after an abscess in patients younger than 40 years and are almost threefold higher in non-diabetics.

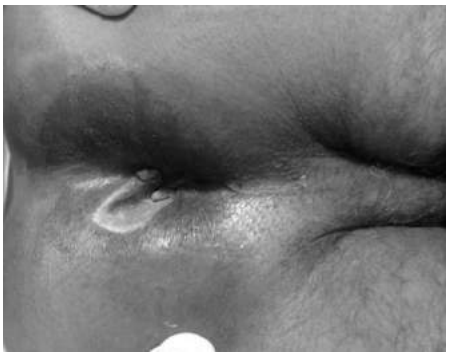
Perioperative Considerations

Preoperative considerations include the following:
- Rectal irrigation with enemas should be performed on the morning of the operation
- Anesthesia can be general, local with intravenous sedation, or a regional block
- Administer preoperative antibiotics
- The prone jackknife position with buttocks apart is the most advantageous position

Intraoperative considerations include the following:
- Examine the patient under anesthesia to confirm the extent of the fistula
- Identifying the internal opening to prevent recurrence is imperative
- A local anesthetic block at the end of the procedure provides postoperative analgesia

After the operation, most patients can be treated in an ambulatory setting with discharge instructions and close follow-up care. Sitz baths, analgesics, and stool-bulking agents (eg, bran and psyllium products) are used in follow-up care. It is important to ensure that the internal wound does not close prematurely, causing a recurrent fistula. Digital examination findings can help distinguish early fibrosis. Wound healing usually occurs within 6 weeks.

Fistulotomy
The laying-open technique (fistulotomy) is useful for 85-95% of primary fistulas (ie, submucosal, intersphincteric, and low transsphincteric).



A probe is passed into the tract through the external and internal openings. The overlying skin, subcutaneous tissue, and internal sphincter muscle are divided with a knife or electrocautery, and the entire fibrous tract is thereby opened.

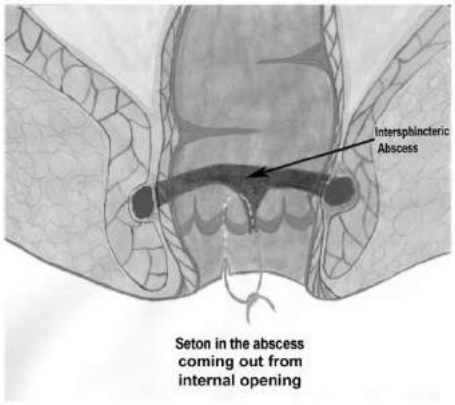
At low levels in the anus, the internal sphincter and subcutaneous external sphincter can be divided at right angles to the underlying fibers without continence being affected. This is not the case if the fistulotomy is performed anteriorly in female patients. If the fistula tract courses higher into the sphincter mechanism, seton placement

should be performed. Curettage is performed to remove granulation tissue in the tract base.
Opening the wound out on the perianal skin for 1-2 cm adjacent to the external opening with local excision of skin promotes internal healing before external closure. Some advocate marsupialization of the edges to improve healing times. Perform a biopsy on any firm, suggestive tissue.

Complete fistulectomy creates larger wounds that take longer to heal and offers no recurrence advantage over fistulotomy.

Seton Placement
A seton can be placed alone, combined with fistulotomy, or in a staged fashion. This technique is useful in patients with the following conditions :

- Complex fistulas (ie, high transsphincteric, suprasphincteric, extrasphincteric) or multiple fistulas
- Recurrent fistulas after previous fistulotomy
- Anterior fistulas in female patients
- Poor preoperative sphincter pressures
- Patients with Crohn disease or patients who are immunosuppressed



Beyond giving a visual identification of the amount of sphincter muscle involved, the purposes of setons are to drain, to promote fibrosis, and to cut through the fistula. Setons can be made from large silk suture, silastic vessel markers, or rubber bands that are threaded through the fistula tract. The Ayurvedic seton also called as kshar sutura has alkaline plant derivatives coated around it which causes intense fibrosis.

Single-stage seton (cutting)
Pass the seton through the fistula tract around the deep external sphincter after opening the skin, subcutaneous tissue, internal sphincter muscle, and subcutaneous external sphincter muscle. The seton is tightened down and secured with a separate silk tie.

With time, fibrosis occurs above the seton as it gradually cuts through the sphincter muscles and essentially exteriorizes the tract. The seton is tightened on subsequent office visits until it is pulled through over 6-8 weeks. A cutting seton can also be used without associated fistulotomy.

Recurrence and incontinence are important factors to consider when this technique is employed. The success rates for cutting setons range from 82-100%; however, long-term incontinence rates can exceed 30%.

Two-stage seton (draining / fibrosing)
Pass the seton around the deep portion of the external sphincter after opening the skin, subcutaneous tissue, internal sphincter muscle, and subcutaneous external sphincter muscle.

Unlike the cutting seton, the seton is left loose to drain the intersphincteric space and to promote fibrosis in the deep sphincter muscle. Once the superficial wound is healed completely (2-3 months later), the seton-bound sphincter muscle is divided.

Once wound healing is complete, the seton is removed without division of the remaining encircled deep external sphincter muscle.

Mucosal Advancement Flap
A mucosal advancement flap is reserved for use in patients with chronic high fistula but is indicated for the same disease process as seton use. Advantages include a one-stage procedure with no additional sphincter damage. A disadvantage is poor success in patients with Crohn disease or acute infection.

This procedure involves total fistulectomy, with removal of the primary and secondary tracts and complete excision of the internal opening.

A rectal mucomuscular flap with a wide proximal base (two times the apex width) is raised. The internal muscle defect is closed with an absorbable suture, and the flap is sewn down over the internal opening so that its suture line does not overlap the muscular repair.

Plugs and Adhesives
Advances in biotechnology have led to the development of many new tissue adhesives and biomaterials formed as fistula plugs. By their less-invasive nature, these therapies lead to decreased postoperative morbidity and risk

of incontinence, but long-term data are lacking for eradication of disease, especially in complex fistulas, which carry high recurrence rates.

Reported series exist of fibrin glue treatment of fistula-in-ano, with 1-year follow-up showing recurrence rates approaching 40-80%. The Surgisis fistula plug has also had mixed long-term results. Early success rates have been reported for newer materials, such as acellular dermal matrix and the bioabsorbable Gore Bio-A fistula plug, in low fistulas and good animal model data. Assessment of long-term success rates with plug techniques for complex disease is still lacking.

A combined sphincter-sparing repair that includes both an anal fistula plug and a rectal advancement flap has been proposed for the treatment of transsphincteric fistula-in-ano.

LIFT Procedure
Ligation of the intersphincteric fistula tract (LIFT) is a sphincter-sparing procedure for complex transsphincteric fistulas first described in 2007. It is performed by accessing the intersphincteric plane with the goal of performing a secure closure of the internal opening and by removing the infected cryptoglandular tissue.

The intersphincteric tract is identified and isolated by performing meticulous dissection through the intersphincteric plane after making a small incision overlying the probe connecting the external and internal openings. Once isolated, the intersphincteric tract is hooked with a small right-angle clamp, and the tract is ligated close to the internal sphincter and then divided distal to the point of ligation. Hydrogen peroxide is injected through the external opening to confirm the division of the correct tract. The external opening and the remnant fistulous tract are curetted to the level of the proximity of the external sphincter complex.
Finally, the intersphincteric incision is loosely reapproximated with an absorbable suture. The curettaged wound is left opened for dressing.

Further randomized surgical trials are needed to determine whether this technique is a viable—or, possibly, a better—alternative to the other previously mentioned procedures for the treatment of fistula-in-ano.

Diversion
In rare cases, the creation of a diverting stoma may be indicated to facilitate the treatment of a complex persistent fistula-in-ano. The most common indications include, but are not limited to, patients with perineal necrotizing fasciitis, severe anorectal Crohn disease, reoperative rectovaginal fistulas, and radiation-induced fistulas. Fecal diversion alone is effective in these select patients to control sepsis and symptoms; however, long-term success rates after reanastomosis are low because of recurrence from the underlying disease. Thus, this approach should be avoided unless the underlying fistula-in-ano disease process is repaired or has healed completely, which is unlikely.

Complications

Early postoperative complications may include the following:

- Urinary retention
- Bleeding
- Fecal impaction
- Thrombosed hemorrhoids

Delayed postoperative complications may include the following:

- Recurrence
- Incontinence (stool)
- Anal stenosis - The healing process causes fibrosis of the anal canal; bulking agents for stool help to prevent narrowing
- Delayed wound healing - Complete healing occurs by 12 weeks unless an underlying disease process is present (ie, recurrence, Crohn disease)

Postoperative rates of recurrence and incontinence vary according to the procedure performed, as follows:

- Standard fistulotomy - The reported rate of recurrence is 0-18%, and the rate of any stool incontinence is 3-7%
- Seton use - The reported rate of recurrence is 0-17%, and the rate of any incontinence of stool is 0-17%
- Mucosal advancement flap - The reported rate of recurrence is 1-17%, and the rate of any incontinence of stool is 6-8%

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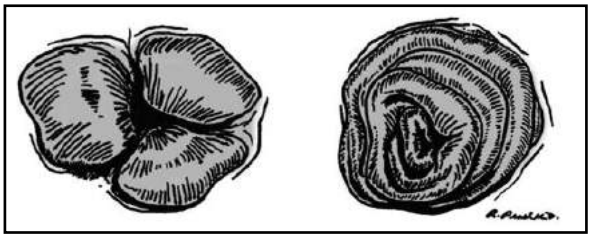
Rectal Prolapse

Manoj Andley

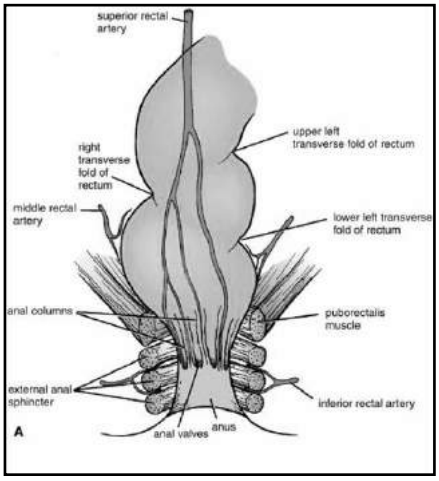
Rectal prolapse is the protrusion of either the rectal mucosa or the entire wall of the rectum. First described by Ebers Papyrus in 1500 BC also described honey containing suppositories, laxatives and enema for treatment. Ancient Greeks used the method of hanging by feet and shaking to reduce prolapse. Rectal prolapse was recognized as an intussusception of the colon in the 18th century.

True rectal prolapse should be distinguished from rectal mucosal prolapse and hemorrhoidal disease. On examination, the former has thick, concentric, circumferential folds while the latter has radial folds often shaped like a three-pointed star.

Anatomy



- 18-20 cm long
- Begins –from rectosigmoid junction
- Ends-At anorectal junction
- Follows curve of sacrum
- Three lateral curvatures:
  - Upper/Lower-Convex to right
  - Middle-Convex to left
- Rectum is divided in three parts:
  - Upper third: covered on all sides by peritoneum.
  - Middle third: covered anteriorly and laterally by peritoneum.
  - Lower third: not covered on any side by peritoneum, fully extraperitoneal.
- Anterior Fascia: Fascia of Denonvillers.
- Posterior Fascia: Waldeyers fascia.



Pathophysiology

The anatomic defect of complete rectal prolapse is relatively easy to describe. The pathophysiology, however, has been more difficult to define. The development of rectal prolapse occurs over a period of years, making it difficult to identify a specific cause. Several findings have been associated with rectal prolapse like weak levator ani and anal sphincter muscles, a redundant rectosigmoid colon, a deep cul-de-sac, and loss of fixation of the rectum to the sacrum. Numerous diseases have been linked to rectal prolapse including connective tissue disorders, pelvic outlet obstruction, pelvic floor laxity, spina

bifida, multiple sclerosis, cystic fibrosis, anorexia and bulimia nervosa, and excess straining or Valsalva maneuver. A history of mental illness has been linked to rectal prolapse, with a fourfold higher rate in that population. Straining at stool is often associated with rectal prolapse. A history of constipation is seen in up to 67% of patients and diarrhea in 15%. Paradoxically, incontinence is reported to be present in up to 70% of patients with rectal prolapse. Women are six times more likely than men to develop rectal prolapse. There is also a different age distribution in women and men, with men presenting in their twenties and thirties while women present more commonly after the sixth decade.

Etiology

Congenital	Redundant rectosigmoid
Acquired	Deep pouch of douglas
Poor bowel habits	Patulous anus
Neurological diseases	Defect in pelvic floor
Cauda equine lesion	**After surgery**-Piles surgery, fistulotomy
Spinal cord injury	Free mesentry to entire rectum
Spina Bifida	Lack of fixation of sacrum to rectum
M:F = 1:6	Torn perineum-Straining at micturition
Nulliparity	Young men with psychiatric disorders

History and Examination

The typical patient with complete rectal prolapse will present with a **history of bleeding** and a "**bulge**" in the anal region after bowel movements. The rectum is often obvious on inspection. Occasionally, the prolapse may become evident only when asking the patient to squat or strain on a toilet. An evaluation of **resting anal tone** and **squeeze pressures** is important in the workup. Identification of other concomitant pelvic floor defects including rectocele, cystocele, vaginal prolapse, and enterocele is important and may influence the operative approach.

Investigations

1. **Anorectal physiology testing** refers to the systematic evaluation of anal canal resting and squeeze pressures, anal reflexes, pudendal nerve conduction velocities, and electromyographic muscle fiber recruitment.[1] Measurement of anal canal pressures (manometry) involves the use of water-filled balloons attached to catheters and transducers placed in the anal canal. The measurement of resting and squeeze pressures at various points in the anal canal reflects the strength, tone, and function of the internal and external sphincter. Normal resting and squeeze values are 40 to 80 mm Hg. Resting pressure reflects the function of the internal sphincter, whereas squeeze pressure measures external sphincter (voluntary muscle) contributions.

2. **Defecography** is determining the precise nature of various pelvic floor abnormalities. Barium paste is placed in the vagina and rectum after the patient ingests a water soluble contrast agent to opacify the small bowel. As the patient evacuates the rectal barium paste, abnormalities occurring during the act of defecation can be recorded with fluoroscopic videotaping. A vast amount of functional and anatomic information can be gathered from this test. The presence of multiple anatomic abnormalities, such as rectocele, enterocele, and vaginal vault prolapse, can be efficiently evaluated.

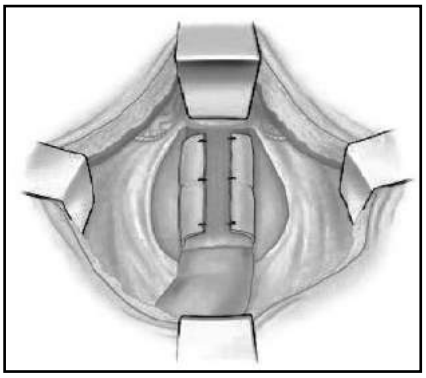
3. Plain radiograph of sacrum to see for spina bifida.

4. **Colonoscopy** is essential to rule out synchronous or causative neoplasm prior to a planned surgical repair. Colonic transit time should be evaluated with marker studies for patients with a history of constipation and rectal prolapse.

Treatment

Acute complete rectal prolapse involves early reduction. Often, especially in the mentally ill in whom persistent straining or Valsalva has contributed to the prolapse, the rectum will immediately reprolapse. Gentle constant pressure is often successful in reducing the prolapse and if the rectum continues to prolapse after

reduction, taping the buttocks together may help temporarily. If the prolapse has been neglected or unrecognised for a prolonged period, it may not easily reduce. Unless the rectum is frankly nonviable or necrotic, a few techniques may help return the bowel to its anatomic position. Sedation, placing the patient in the Trendelenburg position, and placement of salt or sugar topically can reduce the prolapse.

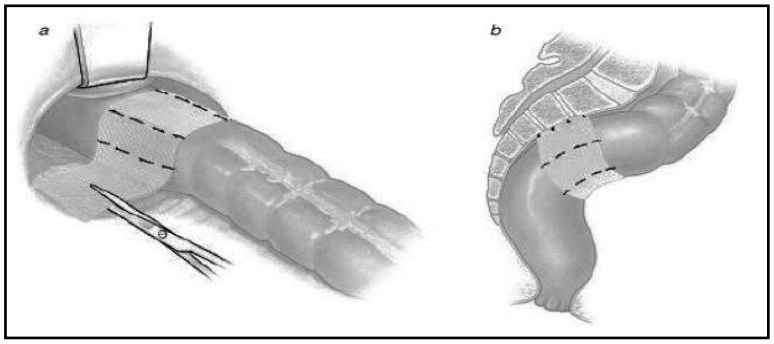


Surgical Treatment: More than 100 different procedures or modifications have been described in the medical literature. In fact, newer innovations continue to appear in the literature.[2-6] The spectrum of current operative techniques includes both abdominal and perineal procedures. The laparoscopic approach has gained popularity, as surgeons have become comfortable operating on the colon laparoscopically. Patients who can tolerate laparotomy should be offered an abdominal approach to correct their prolapse, while elderly or debilitated patients are better managed with a perineal procedure. The exception may be young men who may prefer to accept the higher risk of recurrence of their prolapse with a perineal procedure to the increased risk of impotence or infertility with an abdominal procedure.

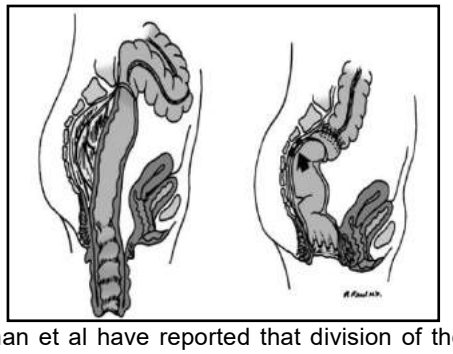
General anaesthesia is usually employed, but regional anaesthesia has also been successfully used. Patients are placed in low dorsal lithotomy position for all laparoscopic or open laparotomy procedures. For laparoscopic approaches, the patients' arms are tucked at the side.

1. **Open Approach**	
Abdominal Approach: a) Ripstein Modification b) Wells Modification (Ivalon Sponge Repair) c) Resection Rectopexy (Fuykwan Procedure)	Perineal Approach: a) Altemeiers (Perineal Proctosigmoidectomy) b) Delorme (Anorectal Mucosectomy with muscular plication) c) Thiersch wiring (Anal Encirclement)
2. **Laparoscopic Approach**	

Ripstein Approach: Ripstein's approach was to wrap a 5-cm-wide non absorbable polytetrafluoroethylene (Teflon) mesh around the anterior rectum, then suture it to the pre sacral fascia on the sides of the rectum 5 cm below the sacral promontory.



Wells Approach: Also called as Ivalon Sponge Repair, Ivalon sponge is placed posteriorly and wrapped around rectum after pulling rectum. A 2 cm gap is left anteriorly for rectal compliance.



Successful rectopexy has been described simply using non absorbable suture or metal staples to fix the rectum to the sacrum and thus re-creating the normal rectal angulation.

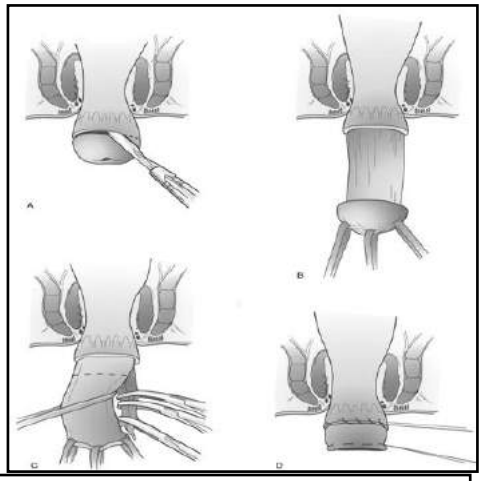
Recently it has been suggested that mobilization of the rectum itself is sufficient to produce enough fibrotic scar to fix the bowel to the sacral curvature.[7] Patients with constipation preoperatively will have worsening of their symptoms with rectopexy alone, because it results in acute angulation of the rectosigmoid by allowing the sigmoid colon to fall anteriorly into the pelvis. Spearman et al have reported that division of the

lateral stalls will allow for better rectal mobilization and fixation and prevent recurrence but at a cost of worsening constipation.[8]

Resection Rectopexy: Through a low midline or transverse incision or laparoscopically, the rectum is mobilized to the level of the coccyx to produce fibrotic fixation to the sacrum upon healing. Next, the redundant sigmoid colon and rectum are resected and reanastomosed. The anastomosis should be at the level of the sacral promontory. Resection-rectopexy has the advantage of removing excess bowel and restoring the normal rectal angulation. There are reports that this approach improves symptoms of both incontinence and constipation.[9]

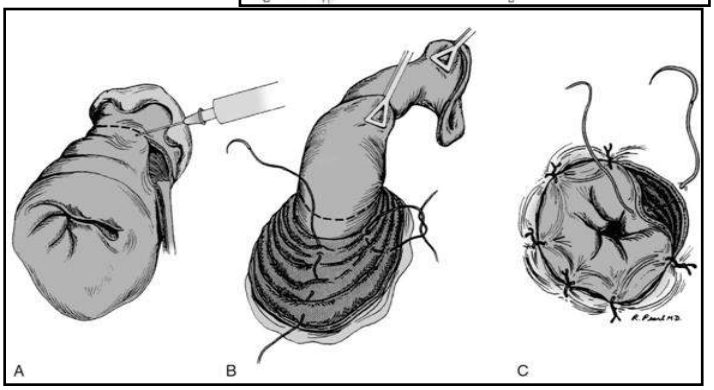
The laparoscopic approach to rectal prolapse has gained popularity as surgeons have obtained expertise at laparoscopic colon surgery in general and as safety concerns have abated.[10-14] Proponents describe a lower perioperative morbidity than open procedures.[13] The key steps of the operation should be comparable to the open technique. Randomized, controlled trials by Solomon et al[12-13,1] comparing laparoscopic and open rectopexy showed both a lower cost and improved clinical outcome with the laparoscopic technique. The low recurrence and lack of deterioration of functional outcome were durable with long-term followup.[15] A recent metaanalysis of published studies comparing the two surgical modalities showed no difference in morbidity, mortality, or functional results, though an earlier Cochrane Review showed fewer complications with laparoscopic rectopexy compared to open rectopexy.[16-17]

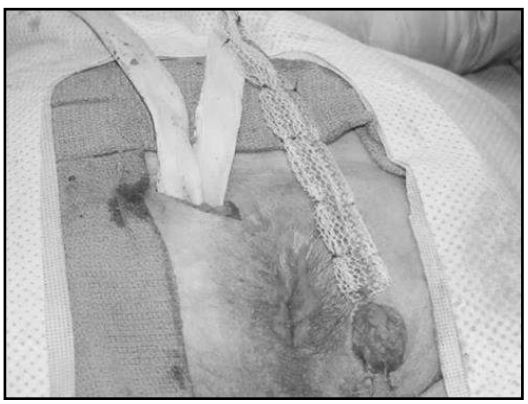
Perineal Proctosigmoidectomy: Altemeier popularised the technique of resecting the prolapsed bowel directly.[18-19] The Prasad modification is the only surgical approach to correct each of the anatomic defects associated with rectal prolapse.[18] The first step is to completely prolapse the redundant rectum by gently pulling on the rectal wall. The dentate line will be easily visible on the everted rectum. A dilute epinephrine solution is injected 1 to 2 cm proximal to the dentate line in the prolapsed rectal wall. Next, the rectal wall is incised full thickness, circumferentially, with electrocautery at the level of the injection. The vascular supply to the splenic flexure should not be mobilized as lack of left upper quadrant fixation may theoretically contribute to recurrence of the prolapse. Resection procedures tend to alleviate preoperative constipation symptoms.



Anorectal Mucosectomy With Muscular Plication (Delorme):

The advantage of the procedure is that no bowel resection and anastomosis are needed.[6,20,21] Once the bowel is completely prolapsed, a dilute epinephrine solution is injected in the submucosal plane. The mucosa is circumferentially incised 1 cm proximal to the dentate line with electrocautery. The incision is deepened only to the level of the submucosa. The muscular layers are left intact. The mucosa is then stripped off the rectal wall musculature, continuing proximally to the apex of the redundant bowel. The mucosal sleeve is then excised. Longitudinal plicating sutures are placed along the length of the rectal wall musculature approximately 1 cm apart. The sutures are tied once all six to eight rows have been placed. Next, the proximal mucosal edge is resutured to the initial mucosal incision with absorbable sutures. A modification utilizing a double purse-string suture and a circular stapler has been described.[3] The Delorme procedure can be combined with posterior levatorplasty[6] in an attempt to improve continence.





Anal Encirclement (Thiersch): Anal encirclement[22,23] is a procedure that should be relegated to historical interest only. However, for the bedridden patient with short life expectancy, multiple comorbidities, and possible dementia or Alzheimer disease and those who may not

tolerate even a perineal resection of rectal prolapse, the Thiersch technique can still be useful. It may also have a place after failure of the perineal procedures. This simple procedure can be performed quickly, with very low morbidity. Two perianal skin incisions 180 degrees apart and lateral to the midline are made. The incisions are connected with a tunnel through the ischiorectal fossa. A strip of polypropylene mesh 1.5 cm wide is placed around the deep external sphincter. The mesh is passed around the anus from one incision to the second and then back to the first to completely encircle the anus. The mesh is tightened and sutured to itself allowing an anal diameter only large enough to admit one finger in the anus. The risks of the procedure include erosion of the mesh into the rectum, infection of the mesh, recurrence of the prolapse, and impaction secondary to tight encirclement.

Procedure	Major Risk	Major Benefit	Best for
Rectopexy	Higher operative risk, Presacral bleeding, Pelvic abscess	Lower recurrence rate	Young, healthy patient without redundant sigmoid or constipation
Resection-rectopexy	Higher operative risk Anastomotic leak Presacral bleeding Pelvic abscess	Lower recurrence Correction of constipation	Young, healthy patient with redundant sigmoid and constipation
Perineal Proctosigmoidectomy and levatorplasty (Altmeier)	Higher recurrence Technique unfamiliar to many surgeons	Lower operative risk Correction of incontinence May be combined with pelvic floor reconstruction	Older patient with comorbidities and long-segment rectal prolapse
Rectal mucosectomy with muscular plication (Delorme)	Higher recurrence Technique unfamiliar	Lower operative risk Correction of incontinence May be combined with pelvic floor reconstruction	Older patient with comorbidities and short-segment rectal prolapse
Anal encirclement (Thiersch)	Higher recurrence Mesh infection Erosion into bowel	Lower operative risk	Elderly patient with comorbidities and short life expectancy

Results and Patient Selection

Abdominal rectopexy in its various forms claim lower recurrence rates (0% to 5%) than perineal procedures (10% to 15%). Surgeons with a preference for perineal proctosigmoidectomy and Delorme procedure point to their relative safety and ease of reoperation in the event of recurrence. Most likely, each clinical situation will favor one approach from the other. Caution must be employed if a perineal approach is contemplated for recurrent rectal prolapse previously treated with an abdominal resection or, alternatively, if an abdominal resection is planned after a perineal resection. Unless the prior anastomotic line is resected there is a risk of ischemia, and necrosis of the intervening bowel between the two anastomoses can occur.[24]

Recurrent rectal prolapse is seen in 10%-20% of patients after mean time of 3 years. Early recurrence within first year are due to technical factors. **IMP:** If a patient treated with perineal proctectomy after failed anterior resection or vice versa will develop ischemia and sloughing of the intervening rectum between two anastomosis unless the previous anastomosis is resected or superior hemorrhoidal artery was perserved in abdominal procedure.

Robotic Rectopexy: Advantage of 3D vision, instrument stability, wrist like movements provides a lot of ease. No advantage seen over open or laparoscopic approaches. Operating time and cost are increased.[25]

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Recent advances in management of carcinoma rectum

NK Shukla

Introduction

Colorectal cancer constitutes third common cancer worldwide. 40,000 new cases of rectal cancer were diagnosed in past one year in US. In last three decades many advances have taken place in the management of rectal cancer including better understanding of molecular biology, advances in diagnostic and staging modalities, changing concepts of surgical resection as understanding zone of upward spread, concept of total mesorectal excision and higher sphincter preservation. Impressive advances have taken place in the field of adjuvant therapy both radiation and chemotherapy with development of new drugs and evolution of targeted therapy.[1]

Advances in molecular biology

These advances have led to predict the response to adjuvant therapy and development of targeted agents. They include DNA sequencing of microsatellite instability, detection of oncogenes, proteins and growth factors. KRAS and P53 positivity indicates poor prognosis. Vascular endothelial growth factor receptor (VEGFR) and epithelial growth factor receptor (EGFR) are targeted by monoclonal antibodies leading to the development of Bevacizumab, Cetuximab and Panitumumab. Tyrosine kinase receptor is targeted by agent like Regorafinib.

Changing concepts in surgical resection

Treatment of early cancer (T1N0M0)
Early lesions are treated by surgery in form of transanal local excision, transanal endoscopic microsurgery (TEMS) and endoscopic mucosal resection (EMR). The selection criteria for local surgery includes superficial tumors less than 3 cm, located in middle and lower rectum, well differentiated histology, no neurovascular invasion and compliance with aggressive post operative surveillance. Currently EMR is the most preferred approach.[2]

Treatment of locally advanced cancer (T2-3, N1-3, M0)
Surgery is the cornerstone of curative therapy for locally advanced cancer. Primary goal is complete removal of primary tumor and secondary goal is preservation of anorectal sphincter function and bowel continuity whenever possible.

Principles of resection

Wide excision of the primary tumor achieving histological negative margins proximal, distal and circumferential along with total mesorectal excision is performed. This is done along with resection of lymph nodes up to inferior mesenteric artery pedicle. The preservation of anorectal sphincter is only done if histological negative distal margin can be achieved.

Distal margin
Earlier recommended distal margin was 5 cm hence there was high rate of abdominoperineal resection (APR). Recently mostly accepted distal margin is 2 cm along with TME. With the improvement in surgical techniques and incorporation of neoadjuvant chemotherapy (CT) and radiotherapy (RT) a negative margin of 1 cm or less is acceptable and it compares 2 cm margin in terms of loco regional recurrence rate.[3,4]

Circumferential resection margin (CRM)

To achieve a negative CRM total mesorectal excision (TME) including complete removal of mesorectal fascia enveloping fat pad around the rectum containing terminal branches of IMA, lymphatics and perirectal lymph nodes. TME has become standard of surgical care for cancers of middle and lower rectum. Sharp meticulous dissection is done in the avascular (Holy) plane between presacral fascia and mesorectal fascia. Blunt dissection previously performed can damage mesorectal fascia leading to higher loco regional recurrence. Distance of mesorectal fascia from the tumor 2 mm or less it is called threatened involvement and is an indication for neoadjuvant treatment. A positive CRM leads to higher loco regional recurrence and poor five-year survival. [5,6]

The length of mesorectum removed beyond the tumor margin should be 3 to 5 cm.[7] For tumors of upper rectum TME includes removal of mesorectum 5 cm distal to the tumor, for middle and lower rectum complete TME is done till the pelvic floor. TME with negative CRM improves loco regional control rate to 4-7% and better survival.[8] TME also preserves pelvic autonomic nerves and decrease genitor urinary dysfunction. According to NCCN and ASCO guidelines at least 12 lymph nodes should be removed with TME.[9]

Sphincter sparing resection
It is indicated for histologically proven distal resection margin. Procedures include low anterior resection (LAR) and very low (ultra) low anterior resection. Temporary diversion stoma decreases clinically relevant anastomotic leaks.[10]

Abdominoperineal resection (APR)
APR is indicated if histologically negative distal resection margin cannot be achieved. It is also indicated as salvage surgery for recurrence of sphincter saving procedure and local resection.

Laparoscopic assisted APR and LAR
Radical surgery for rectal cancer can also be done by minimal invasion surgery. The procedure is safe even after neoadjuvant CT/RT.[11] The quality of oncological resection is equal to open surgery. It causes less post operative ileus and pain. The length of hospital stay is decreased.

The colorectal cancer laparoscopic or open **trial COLOR II** [12] has shown similar completeness of resection, equivalent rates of positive lymph nodes, CRM and median tumor distance of distal margin.

Robotic assisted resection of rectum
With this emerging technology and high quality three dimensional vision the rectal resection can be safely done. TME is safe and feasible. Less postoperative pain and faster recovery are advantages of the procedure but high cost, long intraoperative set up time and long procedure time are disadvantages.

Exenteration procedures

In advanced rectal cancers with involvement of urinary bladder, prostate, uterus and vagina exenteration procedures are recommended. If posterior or total pelvic exentration can be done provided the tumor is not invading the lateral pelvic wall and there are no internal iliac lymph nodes.

Cytoreductive surgery with hyperthermia intraperitoneal chemotherapy (HIPEC)
This procedure has recently shown promising results in peritoneal metastasis from rectal cancer.

Neoadjuvant therapy in the combined modality approach in rectal cancer

Though the surgical resection is cornerstone of managing locally advanced carcinoma rectum, last two decades have shown better results when it is combined with neoadjuvant therapy. Indication of neoadjuvant therapy include

1. Presence of T3 or T4 tumors
2. Presence of lymph nodes in the mesorectum as shown by MRI or TRUS
3. Invasion of mesorectal fascia or threatened mesorectal invasion neoadjuvant therapy decreases positive CRM
4. Neoadjuvant therapy can increase the sphincter preservation. It can convert candidates thought for APR to sphincter preservation by 20-40%. In **German trial** sphincter preservation with neoadjuvant therapy was 39% as compared to those without neoadjuvant CT/RT (19%).[13]

Neoadjuvant RT / Preoperative RT
In Swedish trial short course preoperative radiotherapy in the dose of 25Gy in 5 fractions over one week with rectal resection after 3-6 weeks compared with no RT have shown significant improvement in local control (89% versus 73%) and overall survival (58% versus 48%).[14] **The Dutch trial** have also shown better results with preoperative short course RT with local recurrence of 5% versus 11%.[15]

Neoadjuvant CT-RT versus postoperative CT-RT
The German rectal cancer trial has also shown that neoadjuvant CT-RT gives better results as compared to postoperative CT-RT, local recurrence rate 6% versus 13%, DFS 68% versus 65%.[13]

Preoperative RT versus neoadjuvant CT-RT
Polish trial has compared neoadjuvant CT-RT with preoperative RT and has shown higher pathological CR rates with neoadjuvant CT-RT (16% versus 1%), CRM positive rate 4% versus 13% and loco regional recurrence rate 9% versus 14% indicating superiority of neoadjuvant CT-RT as compared to preoperative RT.[16] The radiotherapy was given 45 Gy in 25 fractions over 5 weeks and surgery was performed after 4-6 weeks.

The drugs used for NACT-RT were 5FU which is the gold standard and newer drugs like oxaliplatin, irinotecan, capecitabine. The targeted therapy along with chemotherapy gives better results. Monoclonal antibodies like Bevacizumab, Cetuximab and Panitumumab are used.

Metastatic rectal cancer

Usual metastatic site is liver. The metastasis can be synchronous or metachronous. In synchronous metastasis if resectable primary the options are

A. Neoadjuvant CT-RT followed by surgery for both primary and metastasis followed by adjuvant chemotherapy
B. Surgery for the primary rectal tumor followed by chemotherapy and letter removal of liver metastasis
C. Chemotherapy with targeted therapy for 2-3 moths than surgical resection of primary and metastasis followed by adjuvant chemotherapy.

Summary

The recent advances in the management of rectal cancer have taken place by improvising surgical resection and addition of neoadjuvant chemotherapy, radiotherapy and targeted therapy. TME has become the standard practice in all locally advanced rectal cancer patients. Distal resection margin has receded from 5 cm to 1 cm provided it is histologically negative. Importance of negative CRM has been realized. Incorporation of neoadjuvant chemotherapy has decreased local recurrence and decreased distal resection margin thereby increasing sphincter saving surgery and quality of life. Laparoscopic assisted APR and LR emerged as alternative approach to open surgery. Targeted therapy has added efficacy to chemotherapy. Thus management of rectal cancer has moved from a pure surgical treatment to a real multimodality management.

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Granulomatous Bowel Disease

Sundeep Singh Saluja, Hari Govind S

Granulomatous disease of the bowel include intestinal tuberculosis and Crohn's disease. Even though the incidence of Crohn's disease (CD) is much less than intestinal tuberculosis (ITB), it is very important to differentiate between the two as the management for both is different. Type of surgery depends upon the extent of the disease and the complication that has occurred. Diagnosis of CD becomes difficult in countries like India which are endemic for TB as differentiating CD and ITB still remains an uphill task. So this text covers the important aspects on the two common granulomatous bowel diseases – Intestinal TB and Crohn's disease.

INTESTINAL TUBERCULOSIS

Intestinal TB is prevalent in developing countries like India due to low living standards and poor literacy. In 2010, there were about 2 million cases reported from India. Usually time is lost in investigations and evaluating patients with non specific symptoms . So high index of suspicion is needed to diagnose intestinal TB to avoid morbidity and mortality due to the disease.

Etiopathogenesis

The 4 routes of infection in intestinal TB are :

(1) Hematogenous from primary pulmonary focus
(2) Swallowing of infected bacilli from active pulmonary TB
(3) Local spread from adjacent viscera
(4) Ingested milk

Most cases of intestinal tuberculosis is caused by mycobacterium tuberculosis. Nowadays with pasteurization of milk, Mycobacterium Bovis has become rare. M Avium is a major pathogen in HIV positive patients. The pathological changes that occur in these patients are mentioned in Table 1.

Table 1 Pathological changes in Intestinal TB

Pathology	Effect
Inflammatory cell infiltration, LN enlargement	Mass formation
Endarteritis and caseous necrosis	Transverse mucosal ulceration
Fibroblastic activity	Strictures

Pathological changes

Ephitheloid cell granulomas with peripheral rim of lymphocyte and plasma cell, langerhans gaint cell and central caseous necrosis are hallmark of tuberculosis. These granulomas are usually of variable sizes, confluent and are mainly seen in submucosal layer. In 8-48% of patients, granulomas are seen in the colonoscopic biopsy (1). Ileocecal valve is the most common site of granuloma. Sometimes these are seen only in mesenteric lymphnodes especially in those who have received antitubercular treatment. Fibrosis and calcification is seen in lymph nodes indicating healing lesions.

Hoon et al (2) classified the intestinal lesions into ulcerative , ulcerohyperproliferative and hypertrophic variants. Hypertrophic form is seen in reasonably well nourished subjects which may be attributed to the strong host resistance, while ulcerative lesions are seen in malnourished patients. Small bowel usually presents with ulcerative or stricturous lesions whereas colonic and ileocecal lesions are usually ulcerohypertrophic.

Clinical Features

Intestinal TB usually occurs in young adults (20-40 years) . Ulcero hypertrophic is the most common type of intestinal tuberculosis. In children peritoneal and nodal are more common form than intestinal type, while in immunocompromised patients disseminated form with involvement of solid organs and lymph node is seen more often. These patients usually present with abdominal pain, loose stools, alternating bowel habits or abdominal mass. Constitutional symptoms including low grade fever, night sweats, malaise, anorexia and weight loss are more commonly seen either in ulcerative variety of intestinal tuberculosis or ascitic variety of peritoneal tuberculosis. Around 20% of patients with intestinal TB have active pulmonary disease. While 10% of women will have concomitant genital TB. Sometimes abdominal tuberculosis may present as acute abdomen most commonly in form intestinal obstruction followed by perforation, pancolitis, acute lower GI bleed rarely acute peritonitis without perforation. Isolated colonic TB is seen in 9 % patients with abdominal TB.

Investigations

Blood investigations usually reveal anemia and hypoalbuminemia secondary to chronic disease and malnutrition. Leucocytosis with relative lymphocytosis , raised ESR, raised CRP may be seen. Tuberculin skin test may be of limited value as it may be frequently false positive. Chest radiograph reveals changes in 15 – 50 % of cases (3,4)**.** Plain X ray abdomen shows features of intestinal obstruction if present.

Barium studies are useful but may not sometimes differentiate between Crohn’s disease and intestinal TB. Multiple strictures with segmental dilatation, increased intestinal transit and hypersegmentation of barium column may be seen in small bowel barium study. Barium enema may show the following features in patients with tuberculosis – thickened incompetent ileocecal valve with narrowing of terminal ileum (Fleischner sign), thickened mucosal folds, pulled up contracted and deformed ceacum (conical ceacum), straightening of Ileocecal valve, dilated terminal ileum which appears to be suspended from deformed caecum (gooseneck deformity), persistent narrow stream of barium suggestive of stenosis (string sign) and absence of barium retention in inflammed segments of ileum, cecum and ascending colon with normal column in between (Sterlin sign) (5). Both sterlin and string sign are not specific for tuberculosis as these may be seen in Crohn's disease.

USG abdomen may demonstrate sliced bread sign due to interbowel loop fluid and pseudokidney sign due to pulled up ileocecal mass in subhepatic space. Computed tomography may reveal evidence of abdominal lymphadenopathy, circumferential thickening of bowel and thickenend nodular mesentery. It may useful in differntaiting from peritoneal carcinomatosis. CT enteroclysis is useful in differentiating from Crohn's disease.

Demonstration of acid fast bacilli on microscopy and culture is considered gold standard for diagnosis. But its yield in abdominal tuberculosis is low. It may be increased with immunohistochemical staining with monoclonal antibodies. Colonoscopy with retrograde ileoscopy is a useful diagnostic modality in 60 to 80 % with histology and culture.

Classically, the tubercular ulcers are superficial and transverse with undermined edges. Mucosal nodules of 2-6 mm size with friability, pseudopoylps, cobblestoning and strictures may also be seen (6). Disease may be multifocal in 50 % of patients and pancolitis is seen in 4 to 8 %. The yield of biopsy is low as the disease involves the submucosa. Polymerase chain reaction is a non-invasive method and can provide rapid diagnosis with 100 % specificity.

Complications
Most common complications are intestinal obstruction, perforation, abscess and GI bleeding. The Incidence of obstruction ranges from 12 to 30 % in India. It could be secondary to narrowing of lumen in hypertrophic variety, presence of strictures, adhesions, kinking or extrinsic compression. TB perforation is usually single just proximal to stricture and pneumoperitoneum is seen in 50 % of cases. Incidence varies from 1-15% in India. Tuberculosis account for 4% of lower GI bleed in India. Malabsorption may occur due to decreased absorption in ulcerated areas, lymphatic and lymph node involvement and bacterial overgrowth resulting in deconjugation of bile salts.

Management
Most physicians recommend ATT after demonstration of caseating granulomas on histopathology. The usual regimen is 4 drugs (Isoniazid, rifampicin, pyrazinamide and ethambutol) given for 2 months followed by 4 month therapy of isoniazid and rifampicin. The peritoneal, lymphnodal and solid organ respond well to ATT. Gastrointestinal variety respond well but may require intervetion secondary to complication. Balasubramanium R et al in his RCT reported equivalent cure rates (99% vs 94%) with 6 months short course and 12 months standard therapy (7). Complaince to treatment in most important factor to avoid MDR Tb. Second line drugs like fluoroquinolones, ethionamide , cycloserine and PAS may be effective in treatment of multidrug resistant TB. Surgical management may be warranted in complications of TB such as obstruction not responding to conservative management, perforation, massive GI bleed and when malignacy cannot be ruled out. Limited ileocecal resection may be done in obstructing lesions. Resection is preferred to primary closure in cases with intestinal perforation.

CROHN'S DISEASE

Crohn's disease (CD) is an inflammatory disorder involving focal and transmural involvement of bowel. It occurs as a result of interaction of different aetiological factors – host immune response, genetic and environmental factors and microbiological agents. The incidence of CD is increasing in developing countries like India (8).

Clinical Features
CD commonly presents with chronic diarrhoea, abdominal pain, bleeding per rectum, recurrent episodes of subacute intestinal obstruction, fever, anorexia, weight loss and perianal fistulae. Extraintestinal features (musculoskeletal , ocular and dermatological) may occur simultaneously or before the onset of CD. Acute terminal ileitis may also present with acute abdomen .

Investigations
Apart from routine blood investigations CRP has been shown to correlate with disease activity. Other biomarkers of disease activity are fecal calprotectin and fecal lactoferrin. Presently they have role in predicting relapse rather than establishing diagnosis. Workup to rule out ITB should also be done. Ileocolonoscopy with biopsy is the investigation of choice. Full length colonoscopy should be avoided in presence of severe active disease. The common colonoscopic appearances are :

(1) Discontinuous involvement of colon.
(2) Longitudinal and aphthous ulcers
(3) Cobblestoning
(4) Perianal lesions

Capsule endoscopy may detect lesions that have been missed by standard endoscopic methods. Normal capsule endoscopy has high negative predictive value in excluding the diagnosis. Indications include high suspicion of diagnosis with normal routine endoscopy, determine extent of disease in proven cases and assess healing of lesions on therapy. CI include presence of stricture or fistula. Prerequisite before its use is assessment of patency either by CT enteroclysis or small bowel series. Double balloon enteroscopy has the advantage of obtaining biopsies from lesions.

Histopathological features are useful in diagnosis and assessment of the disease activity in patients with CD. These include architectural and inflammatory changes. (table 2) Among these focal or patchy inflammation and granulomas are most important histological features. Granulomas are usually small size (<200 μ), discrete and small in number (<5) in CD. They are submucosal in location and away from the active crypt injury. They are more commonly seen in large bowel compared to small bowel and in younger patients with shorter disease duration. Presence of necrosis and giant cells are rare in granulomas of CD unlike tubercular granuloma. Presence of granuloma only in LN is not a feature of CD.

Table .2 . Histopathological features of Crohn's disease

Architectural abnormalities	Inflammatory features
• Crypt distortion • Crypt shortening • Crypt branching • Decreased crypt density • Irregular mucosal surface	• Focal and patchy inflammation • Granuloma • Basal plasmacytosis • Intraepithelial lymphocytosis • Transmural inflammation

Presence of above abnormailities if seen > 10% of crypt is considered significant	• Focal cryptitis • Aphthoid ulcers • Mucin preservation at the active regions • Nerve fibre hyperplasia

Imaging

It is an integral part of diagnostic workup which is helpful in evaluating areas not accessible to endoscopy. It includes barium and cross sectional imaging. Cross sectional imaging is useful in assessing transmural and extramural aspect of the disease. Imaging also helps in differentiating it from UC and TB, assess the disease activity and complications such as abscesses, perforation and fistulae. Barium studies may show evidence of long segment of terminal ileal involvement , with skip lesions and preservation of cecum and ileocecal valve. Other findings include long segment small bowel strictures and linear, curvilinear or speculated areas of ulceration along the mesenteric border with resultant retraction of the bowel wall leading to psuedodiverticlua and pseudosacculation of anti mesenteric wall. CT scan/MRI with enterography can show the location of the disease in the intestine, status of the lymph nodes, peritoneum and mesentery. Inflammatory activity can be assessed on the basis of wall thickness and the enhancement pattern. CT findings in CD include symmetrical bowel wall thickening, fat creeping, enlarged regional lymph node measuring 3 to 8 mm, and enlarged mesenteric vascular bundles in the diseased region (comb sign). CT and MRI has similar diagnostic accuracy. MRI scores over CT as repeated imaging with MRI avoid radiation exposure to the patients. Both enteroclysis or enterography have similar accuracy therefore either can be performed

Management

The goal of treatment of CD is induction and maintenance of remission, reduction in surgical interventions and hospitalisation and improvement of quality of life**.** Treatment depends upon the disease extent, location and behaviour, disease severity and presence of extra-intestinal complications.

Assessment of disease activity

There are many indices for measuring disease activity , but CD activity index (CDAI) is the most commonly used (Table 3) . CDAI score ranges from 0-600. Remission is defined as score < 150, Mild disease 150-219, Moderate 220-449 and severe > 450. This is further simplified clinically as remission when patient is asymptomatic with no evidence active disease, mild when patient is ambulatory and able to tolerate oral nutrition without any signs of dehydration, systemic symptoms or weight loss >10%, moderate when patient has systemic features such as fever, significant weight loss, intermittent nausea vomiting without obstruction, abdominal pain or significant anemia and severe or fulminant when patient has persistent symptoms like high grade fever, evidence of intestinal obstruction, peritonitis, abscess or cachexia.

Table 3. CDAI

Clinical or laboratory variable	**Weighting factor**
Number of liquid or soft stools each day for seven days	x 2
Abdominal pain (graded from 0-3 on severity) each day for seven days	X5
General well being, subjectively assessed from 0 (well) to 4 (terrible) each day for seven days	X7
Presence of complications	X20
Taking Lomotil or opiates for diarrhea	X30
Presence of an abdominal mass (0 as none, 2 as questionable, 5 as definite)	X10
Hematocrit of <0.47 in men and <0.42 in women	X6
Percentage deviation from standard weight	X1

Phenotypic classification

CD was phenotypically classified according to age of onset, disease location and disease behaviour by Vienna classification which has been modified later as Montreal Classification (Table 4).

	Montreal
Age at Diagnosis	A1: less than 16 years. A2: between 17 and 40 years. A3: over 40 years.
Location	L1: ileal. L2: colonic. L3: ileocolonic. L4: isolated upper digestive
Behavior	B1: non stricturing, non penetrating. B2: stricturing. B3: penetrating. P: perianal disease.

Table 4 . Montreal classification of CD

Before starting the treatment, other conditions such as intestinal infections, bacterial overgrowth, lactose intolerance, irritable bowel syndrome and tuberculosis should be ruled out. CD is diagnosed on basis of clinical features, endoscopic, radiological and histological findings.

General principles

Treatment should be continued until remission is achieved. There should be evidence of clinical improvement within 2 – 4 weeks. As 75 % relapse within 1 year of stopping therapy, maintenance therapy should be considered. Patient not responding to one therapy may be considered for alternative therapy. Surgery should be considered in obstructing lesions, suppurative complications, medically intractable disease or neoplastic lesions.

Mild to moderate disease

1. 5 Aminosalicylic acid – 2 RCTs have proven its superiority over placebo in treatment of colonic disease . They have no role in Ileal and ileo colic disease. They are less effective than steroids . About 50 % patients achieved clinical remission.
2. Mesalamine – 4g/day of mesalamine showed a statistically significant difference as compared with placebo (9).
3. Antibiotics – Metronidazole in a dose of 10-20 mg /kg/day may be useful in patients who failed to respond to 5-ASA.
4. Budesonide- controlled release formulation in a dose of 9 mg was found to be effective. It was more effective than mesalamine in patients with ileal and right colonic disease (10).
5. Prednisolone – used when patients do not respond to first line therapy and when systemic symptoms are presented.
6. Infliximab – should be reserved for patients with steroid resistant /steroid refractory disease.

Moderate to severe disease

Steroids are used to induce remission. Clinical remission is achieved in approx. 50 to 70 % in patients treated with predisolone 0.5 – 0.75 mg /kg /day over a period of 8 to 17 weeks. After obtaining clinical response , steroids are tapered , usually 5 to 10 mg every 2 weekly. DEXA scan and calcium & vitamin D supplementation is recommended in these patients. Remission can be achieved with Azathioprine and 6- Mercaptopurine for 16 weeks. Methotraxate at a dose of 25 mg subcutaneous once a week has also been found to be effective at inducing remission in refractory cases. Infliximab (antibody against TNF- α) is effective in attaining remission in these group when refractory to steroids. 40 % achieve clinical response after 4 weeks of single 5mg/kg infusion. Current recommendation is 3 infusions at 0,2 and 6 weeks followed by maintenance therapy. Other biological agents used include adalimumab, certolizumab and natalizumab.

Fulminant disease

These patients require hospitalization. In patients with high grade fever and or those with peritoneal signs, cross sectional imaging should be done to rule out any abscess which needs immediate drainage. If the patients are non responders to oral steroids, parenteral steroids are used (Hydrocortisone). Nutritional support through elemental feeding /parenteral nutrition should be provided. In patients with obstructive symptoms it is important to differentiate between inflammatory from fibrotic strictures.

Top –down Therapy

Earlier use of biologics and immunosuppressive agents improves clinical outcomes**.** Step up top down (SUTD) trial compared the effectiveness of early use of combined immunosuppression (infliximab + AZA) with conventional therapy (11). Although it showed 60% patients with top down group showed remission without steriods & surgery compared to 35.9% in step up (p=0.006) at 26 weeks. However It may be too early to universally treat all patients with top down approach. Therefore 3 risk factor including initial steriod requirement, presence of perianal disease and age <40 years were used to identify patients who are likely to develop disabling Crohns

Management of fistulising CD

Fistulising disease is seen in one third of patients with CD. Perianal fistula can be classified into simple or complex depending upon the number of opening and the associated lesions.

Simple fistulae: There is only one external opening and no associated abscess. They are usually associated with rectal disease.

Complex fistulae: These are high fistulae with multiple external opening and associated abscess.

Treatment for perianal fistulae depend upon presence or absence of infection and associated lesions such as abscesses. First line of medical therapy is the use of oral antibiotics in form of quinolones and metronidazole for 8 to 12 weeks. There have been benefits with short term treatment with cyclosporine and tacrolimus, however long term benefits are not proven. Most patients require maintenance therapy with azathioprine or 6-Mercaptopurine. The current gold standard of management off fistulising disease is the use of infliximab (12). The response rate is around 60%

Maintenance Therapy

75 % will have relapse within a year of induction with steroids, so maintenance therapy is recommended in majority of cases. The duration of therapy is difficult to predict because of variable individual response, complaince, treatment costs and long term drug safety.

Maintenance with immunomodulators
Azathioprine (2- 2.5 mg/kg) and 6 MP (1.5 mg/kg) have been shown to be effective at maintaining remission for 4 years. Parenteral MTX (15mg/ week) has also been shown to maintain remission. It is advisable to continue therapy for 4 -5 years. On relapse, immunomodulators should be restarted promptly.

Maintenance with Biologics
Scheduled Infliximab infusion (5mg/kg every 8 weeks) have been shown to maintain remission (13). Scheduled therapy has been shown to be more effective than episodic dosing. According to SONIC trial, the proportion of patients in steroid free clinical remission was significantly greater with the use of combination therapy of Infliximab with immunomodulators than biologic alone. The benefits of infliximab have shown to sustain over a period of more than 4 years. Infliximab can be stopped in some patients according to STORI trial (14). There is five fold increased risk of TB reactivation with infliximab. It usually occurs after a median of 12 weeks of therapy.

Role of surgery
Up to 75% of patients with CD will ultimately require surgery. Surgery in CD is meant for treating complications and improvement in quality of life. The indications for surgery are enlisted in Table 5.

Table 5 . Indications for Surgery in CD

Emergent	Urgent	Elective
Intestinal perforation	Fulminant colitis	Failure of medical therapy
Abscess rupture	Severe perianal sepsis	Stricturing /fistulising disease
Massive uncontrolled hemorrhage	Undrained intraabdominal abscess	Cancer

Emergency procedures

1) Intraabdominal abscess – Urgent surgery and drainage of abscess is done in undrained abscesses or failed to drain abscess. Definitive surgery with bowel resection will be done a few weeks later.
2) Fulminant Crohn's colitis – If there is no improvement in 7 days of medical management, urgent colectomy should be performed. In case of toxic megacolon the intensive regimen should not be continued for > 72 hours.
3) Severe perianal sepsis – needs aggressive intravenous antibiotics and parenteral nutrition along with drainage of abscess and ostomy.
4) Massive hemorrhage – It occurs in 1 % of cases. Bleed usually occurs from a single site where an ulcer has eroded into a large vessel. Angiography is advisable to localise the bleeding and for embolisation. Surgery is indicated only in uncontrolled bleeding.

Elective Procedures

1) **Small bowel CD**: Common indications are stricturing disease causing obstruction, internal fistulae and abscess and malignancy.

   Stricturing disease - It is important to find out the type of stricture (inflammatory ,fibrotic or anastomotic). Inflammatory stricture would respond to medical therapy and endoscopic dilatation may be useful in some cases. Endoscopic dilatation is recommended for anastomotic stricture. Fibrotic stricture needs surgical management. General indications are 2 or more episodes of partial recurrent bowel obstruction within a year, failure to discontinue steroid therapy after 12 – 16 weeks or doses of prednisolone more than 15 mg / day for more than 3 to 6 months.
   1) Stricturoplasty – It is indicated when there are multiple skip lesions or patients have had multiple resections in the past. Heineke – Miculickz stricturoplasty is considered in strictures less than 10 cm. For longer strictures , upto 25 cm , side to side Finney's Stricturoplasty is considered appropriate.
   2) Resection and anastomosis – It is indicated in single stricture or when there are multiple short segement strictures and when the remaining small bowel is sufficient.

2) **Colonic disease** : Most common indication is failure to medical therapy. There is no role for stricturoplasty in colonic disease. In case of rectal sparing, colectomy and ileorectal anastomosis is recommended. In patients with pancolitis and /or perianal disease, total proctocolectomy is considered.

3) **Perianal disease:** There is combined role of medical as well as surgical therapy in fistulising disease. The initial step in fistula therapy should be drainage of abscess and dilatation of anorectal strictures. The useful surgical procedures are (a) Seton placement : Seton is a silk or rubber abnd used to create a scar tissue around part of the sphincter muscle before cutting it with a knife , or allow it to slowly cut all the way through the muscle over the course of several weeks. (b) Fistulotomy : Surgeon cuts the

internal opening of fistula scrapes and flushes out the infected tissue. It is usually done in low fistulae, as for high fistulae there is possibility of incontinence. About 10 % requires proctectomy and permanent ileostomy.

Post operative Recurrence

Surgery in CD is not curative as disease recurs. Post operative clinical recurrence rates are 30 % at 1 years and 60 % at 3 year. Clinical recurrence is best predicted by endocopic recurrence. Factors predicting early post operative recurrence are listed in table 6 . Endoscopy of the anastomotic site is recommended within 6 months of surgery. Rutgeerts endoscopic score predicts postoperative recurrence (Table 7). Endoscopic score of 0-2 suggest a lower recurrence.

Table 6 . Factors predicting early post operative recurrence in CD

Factors predicting early post operative recurrence in CD
• Smoking • Extent > 100 cm • Fistulising disease • Shorter postoperative disease duration • Previous surgery

Table 7 . Endosopic scoring system for post operative recurrence in CD

Grade	Endoscopic finding
0	No lesions in distal ileum
1	< 5 aphthous lesions
2	5 aphthous lesions with normal mucosa between the lesions
3	Diffuse aphthous ileitis with diffusely inflamed mucosa
4	Diffuse inflammation with already larger ulcers, nodules /narrowing

Short term metronidazole at high doses (20mg /kg) and ornidazole (1g/ day) for a year have been sown to reduce recurrence for upto 1 year. Steroids are not effective in reducing the risk of postoperative recurrence. Recent trials have demonstrated benefits with Immunosuppresant (AZA/ 6MP) (15). Recently, infliximab has also shown efficacy in prevention of both clinical and endoscopic post operative recurrence (16).

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Retroperitoneal tumors

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Retroperitoneal tumors are masses that arise from tissues in the retroperitoneum other than the organs contained in it. Thus, tumors from kidneys, adrenals, ureters, pancreas, colon etc are not classified under this category. They are often referred as primitive retroperitoneal tumors (PRT) as they arise from tissues of non-organ differentiation and are thus considered histologically primitive. These include tissues contained in the retroperitoneal space like adipose, muscular, vessel and nerve tissue, embryonic remnants or heterotopies coming from one or more embryonic layers (ectoderm, mesoderm and endoderm) or from totipotent embryonic germs. Masses from systemic tumors (lymphomas) and metastases are also not considered part of PRT. Thus, primary retroperitoneal tumors (RPTs) represent a heterogeneous group of neoplasms comprising a majority of malignant mesenchymal cancers and a minority of benign lesions.

Epidemiology, Etiology, and Pathogenesis

RPTs represent a combination of sarcomas and other benign and malignant lesions, sarcomas being the most prevalent. Soft tissue sarcomas constitute roughly 1% and 15% of all adult and pediatric neoplasms, respectively. The anatomic site of origin of sarcomas is an important consideration in the management and expected treatment outcome of such tumors. It is reported that 60% of sarcomas originate from the extremities, 20% from the trunk, 15% from the retroperitoneum, and 5% to 10% from the head and neck. The prognosis of retroperitoneal sarcomas is generally poor. This is probably due to their location deep in the retroperitoneal cavity, where lesions do not readily lend themselves to detection by physical examination and the potential space of the abdomen allows for their growth to a considerable size and advanced stage before becoming clinically apparent. In fact, over 50% of tumors exceed 15 cm in diameter at the time of diagnosis and tumors weighing more than 30 kg have been reported. Combined liposarcoma, leiomyosarcoma, and malignant fibrous histiocytoma account for 80% of all retroperitoneal sarcomas. Although retroperitoneal sarcomas can occur in any age group, most are found in the sixth decade of life and men are affected slightly more often than women. Two thirds of the patients are diagnosed with high-grade disease and 10% with metastasis, mainly to the lungs and liver.

No specific causative factor has been identified for soft tissue sarcomas; however, radiation exposure has been implicated in the development of sarcoma within the radiated field in approximately 0.1% of the patients, typically 10 or more years after radiation exposure. The most characteristic post-radiation sarcoma is malignant fibrous histiocytoma. Other risk factors include genetic predisposition; exposure to certain carcinogens, particularly dioxin; viral infection; and immunodeficiency.
Occasionally, sarcoma may grow within a scar or site of previous injury and inflammation.

Although sarcomatous transformation of a neurofibroma into a neurofibrosarcoma has been described, benign mesenchymal tumors almost never transform into malignant counterparts, such as lipoma transforming into liposarcoma or hemangioma developing into hemangiosarcoma. Several hereditary syndromes and congenital conditions have been associated with the development of soft tissue tumors. Gardner syndrome -Low-grade fibrosarcoma has been associated with this syndrome, and mutations on locus 21 to 23 on chromosome 5 have been reported. Familial retinoblastoma has been associated with osteogenic sarcoma; and deletions in the retinoblastoma (Rb) gene have been associated with leiomyosarcoma. Other hamartomatous syndromes associated with increased soft tissue sarcoma risk include neurofibromatosis, tuberous sclerosis, von Hippel-Lindau syndrome, and Peutz-Jeghers syndrome

The origin of soft tissue sarcomas is believed to be dormant mesodermal embryonic stem cells residing within normal adult connective tissues. These cells might be affected by exogenous stimuli such as radiation exposure, inflammation, or genetic aberration induced by carcinogens or viruses, thereby initiating the process of tumor development and progression. Several observations support the stem cell origin of sarcoma which make reference to a process of tumorigenesis from a pluripotent progenitor cell—the mesenchymal stem cell.

Classification and Pathology

Benign Lesions
Benign RPTs are much less common than retroperitoneal sarcomas. The more frequent of these are lipoma, myelolipoma, leiomyoma, schwannoma, extra-adrenal pheochromocytoma, paraganglioma, and cystadenoma.

Although subcutaneous lipoma is the most common benign mesenchymal tumor, benign retroperitoneal lipoma is very rare. Similarly, uterine leiomyoma is very prevalent in adult women. Less frequently, leiomyomas have been reported in other organs, including the kidney, prostate, ureter, bladder, spermatic cord, and penis. However, retroperitoneal leiomyoma is very rare. These are relatively small tumors, and when larger than 6 cm in diameter they are considered malignant. On light microscopy, spindle-shaped cells with cytoplasmic vacuole and central

nuclei are typically present, although areas with clear cells may also be present. Although the distinction of benign lesions from malignant tumors is difficult, some features are more characteristic of benign lesions. Most benign RPTs are small, well-circumscribed lesions and are found incidentally in asymptomatic patients. Conversely, most malignant RPTs are large and may occasionally reach enormous size; they often have poorly defined boundaries and are frequently associated with symptoms, most of which are attributed to compression of nearby organs or inanition. In addition, calcifications in retroperitoneal lesions are more characteristic of malignancy and they are rarely found in benign tumors. In a multivariate analysis that included 194 patients with RPTs, the following features were independently associated with the presence of a malignancy: ill-defined margins, irregular surfaces, long diameter greater than 6.75 cm, short diameter greater than 6.25 cm, solid or mixed texture, and a sensitivity and specificity of 77% and 81%, respectively (Zheng et al, 2014). Benign retroperitoneal lipomas are typically homogenous, hypodense well-circumscribed or encapsulated lesions; however, distinction from low-grade liposarcoma, angiomyolipoma, or myelolipoma may be difficult. Microscopic examination reveals homogenous large cells with fat-laden cytoplasm leading to a flat eccentric nucleus. Excessive blood vessels or collagen may be found in variants termed as angiolipomas or fibrolipomas, respectively. Benign hibernoma (tumor of brown fat) has been reported mainly in adults. Schwannomas, ganglioneuromas, and paragangliomas are benign myxoid tumors often located in the paravertebral area. They may be oval, small, well-circumscribed masses but occasionally may be large. Anterior displacement of the pancreas or great vessels is typical. Whereas schwannomas are benign tumors arising from nerve sheath supporting cells typically with no associated symptoms, paragangliomas are composed of adrenergic nerve cells and are capable of releasing norepinephrine, provoking a syndrome akin to a pheochromocytoma, functionally producing catecholamines.

Malignant Lesions

Besides primary retroperitoneal sarcomas, other systemic cancers may manifest with retroperitoneal masses and need consideration in the differential diagnosis. Retroperitoneal lymphoma may manifest with retroperitoneal diffuse lymph node enlargement.

Occasionally the involved lymph nodes will coalesce to form irregular masses that are indistinguishable from other primary RPTs. Lymphoma may even mimic retroperitoneal fibrosis with a homogenous dense midline mass that resembles fibrosis. Metastatic germ cell tumors may lead to retroperitoneal lymphadenopathy that may be bulky. Typically such masses deflect the ureters laterally, but may occur in between or anterior to the great vessels. The diagnosis of germ cell tumor can be established easily by finding testicular mass and elevated relevant serum markers. Lymphoma may be associated with splenomegaly, elevated lactate dehydrogenase, and other symptoms. Primary mesenchymal tumors can be classified according to the mesenchymal tissue component of origin (Table 1).

Table 1. Classification of Mesenchymal Tumors

TISSUE OF ORIGIN	BENIGN TUMOR	MALIGNANT TUMOR
Adipose	Lipoma Angiolipoma/angiomyolipoma Lipoblastoma Hibernoma Lipomatosis	Well-differentiated liposarcoma De-differentiated liposarcoma Myxoid liposarcoma Round cell (poorly differentiated) Pleomorphic type
Fibrous	Fibroma Angiofibroma Myositis ossificans Elastofibroma Aggressive fibromatosis	Fibrosarcoma
Fibrous histiocytic	Fibrous histiocytoma Juvenile xanthogranuloma Xanthoma Others	Malignant fibrous histiocytoma Storiform, myxoid, giant cell, xanthomatous variants
Muscle tissue Smooth muscle Striated muscle	Leiomyoma Epithelioid leiomyoma Angiomyoma Leiomyomatosis Rhabdomyoma	Leiomyosarcoma Epithelioid leiomyosarcoma Rhabdomyosarcoma
Neural tissue Sympathochromaffin tumors	Schwannoma Neurofibroma Neurofibromatosis Ganglioneuroma Pheochromocytoma	Malignant schwannoma Malignant peripheral nerve sheath tumor Malignant granular cell tumor Malignant melanoma Neuroepithelioma Ewing sarcoma Ganglioneuroblastoma Neuroblastoma Malignant pheochromocytoma
Synovial tissue	Synovioma Giant cell tumors of the tendon sheath	Synovial sarcoma
Vascular tissue	Hemangioma	Angiosarcoma Kaposi sarcoma
Lymphatic tissue	Lymphangioma	Lymphangiosarcoma

Liposarcoma is by far the most common type of retroperitoneal sarcoma. Enzinger and Winslow (1962) modified a previous classification by Stout and proposed five categories: (1) myxoid, (2) well-differentiated, (3) round cell, (4) de-differentiated, and (5) pleomorphic.

The first two are considered low-grade and the last three high-grade sarcomas. Myxoid liposarcomas are composed of primitive lipoblasts that do not have the typical fat-laden cytoplasm but rather resemble primitive mesenchymal cells. Abundant capillary network and myxoid matrix are other typical components. The histologic appearance of well-differentiated liposarcoma closely resembles that of a benign lipoma, and the distinction between the two by imaging and even under the microscope is a challenge. In fact, many well-differentiated liposarcomas are misdiagnosed as deeply seated lipomas. Distinction criteria included nodularity, stranding, and tumor borders (O'Donnell et al, 2013). Although well-differentiated liposarcomas seldom metastasize, local recurrence is common and long-term prognosis is influenced by the morbidity caused by such recurrences involving other organs and the morbidity of the necessary surgeries. Round cell liposarcoma is composed of small round cells uniform in size and closely packed together. There is no specific pattern of cellular arrangement and intracellular lipid content is scarce. Dedifferentiated liposarcoma is characterized by the coexistence of well-differentiated and poorly differentiated areas within the same tumor. Occasionally, at the time of local recurrence other phenotypes may be present, including malignant fibrous histiocytoma, rhabdomyosarcoma, or leiomyosarcoma. Characteristic features of pleomorphic liposarcoma include a disorderly growth pattern with cellular pleomorphism, giant cells, and anaplastic pyknotic nuclei. Because this anaplastic tumor resembles other undifferentiated sarcomas, some lipoblastic presence must be documented to confirm this diagnosis. All lipocytes and lipoblasts stain positive with the immunostaining agent S-100, rendering this a useful tool in establishing this diagnosis. Genetic aberrations, including a balanced translocation of chromosomes 12 and 16 t(12:16) (q13:p11), appear in 90% of myxoid liposarcoma cases and are pathognomonic of this sarcoma (Eneroth et al, 1990). Ring chromosome 12 is typical of well-differentiated liposarcomas but also has been demonstrated in benign lipomas (Dal Cin et al, 1993).

Malignant fibrous histiocytoma. Although its name implies that histiocytes are the building block and cell of origin, truly this is a fibroblast neoplasm. Microscopic findings include round histiocyte-like cells, spindleshaped fibroblasts, foamy cells, giant cells, and lymphocytes. Several subtypes have been reported;whereas the myxoid subtype is associated with a somewhat more favorable prognosis, the other subtypes are aggressive and show a high tendency to metastasize. In addition, some studies have shown an association between the presence of lymphoproliferative disorders, including leukemia, and both Hodgkin and non-Hodgkin lymphoma, and the development of malignant fibrous histiocytoma. The cause of this apparent relationship between malignant fibrous histiocytoma and hematologic malignancies remains unclear.

Retroperitoneal leiomyosarcomas usually occur in women in their 7th decade. The tumors attain very large size and include cystic degeneration and necrosis. Microscopic findings include spindle-shaped cells with abundant cytoplasm and cigar-shaped nuclei. As is the case with well-differentiated liposarcoma, distinction of a leiomyoma from a leiomyosarcoma is difficult even under rigorous microscopic review. Parameters suggestive of malignancy include tumor size, pleomorphism, cellularity, necrosis, atypia, and mitosis. Of these, mitosis is the most highly predictive feature and in RPTs 1 mitosis per 10 high-power fields (HPFs) is characteristic of malignancy, whereas more mitotic figures are tolerated in smooth muscle tumors in other anatomic locations. Tumor grade is an important prognostic factor because high-grade tumors are associated with a less favorable outcome.

Staging of Retroperitoneal Sarcomas

Hematogenous spread is the principal route of metastasis for sarcomas, and the lungs are the most common metastatic site for such tumors, followed by the liver. As cross-sectional imaging is necessary as the initial diagnostic workup, liver involvement will be picked up in the initial imaging procedure. Chest computed tomography (CT) is required for all retroperitoneal sarcomas to detect pulmonary metastasis. Other sites such as bones and brain are infrequently involved, and routine imaging of these sites using brain MRI and bone scintigraphy is not required in the absence of relevant symptoms. The exceptions may be lymphangiosarcoma, osteogenic sarcoma, and Ewing sarcoma—all of which also may involve the skeleton, and bone scans should be obtained in such patients.

(TNM) staging system

T0	No demonstrable tumor
T1	Tumor measuring <5 cm in maximal diameter
T2	Tumor measuring ≥5 cm in maximal diameter
T3	Evidence of macroscopic invasion of nearby structures by the tumor
N0	No histologic evidence of regional lymph node involvement
N1	Histologically proved regional lymph node involvement
M0	No distant metastasis
M1	Distant metastasis present

In addition, the extent of surgical resection of the primary tumor is also reported, because this has been shown to portend prognostic implication, as follows:

R0	Tumor was entirely resected with no residual tumor and negative surgical margins
R1	Microscopic residual tumor = positive surgical margins
R2	Macroscopic residual tumor
R3	Tumor spillage and dissemination during resection

In addition to TNM clinical staging, other prognostic factors for retroperitoneal sarcomas include tumor grade, mitotic index, necrosis, and molecular markers.

Clinical Presentation and Workup

Due to their location deep in the retroperitoneum, which is not a confined space, many RPTs can grow to a vast size before prompting the patient's attention. Thus very large tumors (>15 cm or weighing several kilograms) may occasionally be found. In the absence of distant metastasis and local involvement of nearby organs, most tumors can remain asymptomatic for an extended duration. Eventually, however, a sensation of an abdominal mass or abdominal pain (in 80% of patients) and constitutional symptoms, such as weight loss (30% of patients), fatigue, early satiety, and inanition may ensue, as the metabolic requirements of the growing tumor deplete the host of needed resources. Neurologic symptoms also occasionally may occur. A typical complaint is of weight loss in conjunction with abdominal girth enlargement as a result of the presence of a large abdominal tumor. Compression of nearby organs may elicit additional symptoms, including abdominal discomfort, nausea, flank or pelvic pain, and hematuria.

Physical examination may be unrevealing, or a large abdominal mass may be palpated and sometimes even be visible. Leg edema and symptoms of inferior vena cava syndrome may be found. Abdominal ultrasound is often used as a screening tool to evaluate physical findings of an abdominal mass or suspicious symptoms. However, cross-sectional imaging with CT or MRI provides a more accurate diagnosis of the primary tumor and provides local staging.

Cross-sectional imaging by CT or MRI provides accurate data on tumor size, location, relations to nearby structures, and other features, including heterogeneity, boundaries, vasculature, necrosis, and calcification. CT depicts a solid (>15 Hounsfield units) texture to the suspect lesions, but may demonstrate necrosis, calcifications, and anatomic relations to nearby blood vessels and organs. Adipose tissue tumors may show the typical hypodense attenuation; however, the distinction of various types of benign and malignant fat-containing tumors is not possible by CT. The presence of dense areas within a fatty tumor may allude to de-differentiated liposarcoma. Further staging with a chest CT is routine. MRI has been very sensitive in demonstrating fat-containing tumors. The role of positron emission tomography (PET-CT) for initial diagnosis and staging is less well established, and probably it is most useful to delineate retroperitoneal lymphoma, which is PET positive in many cases, and distinguish it from other tumors. In the post-surgery follow-up phase there may be a role for PET-CT, because it showed superior specificity compared with contrast-enhanced CT for well differentiated liposarcoma, lymph node metastasis, and pulmonary metastasis. The specificity of PET-CT remained poor for leiomyosarcoma and liver metastasis (Niccoli-Asabella et al, 2013). At the present time, the role of PET-CT in the management of RPTs remains unclear.

The differential diagnosis of retroperitoneal masses includes lymphoma, retroperitoneal sarcoma, metastasis, and, rarely, benign RPTs. Nonsolid lesions such as congenital and acquired cysts, arterial aneurysms, and inflammatory lesions (i.e., psoas abscess) usually can be suspected based on previous patient history and the liquid content that is readily discerned by cross-sectional imaging.

Role of Pretreatment Biopsy

A pretreatment biopsy is important in cases in which lymphoma is suspected. In addition, a biopsy may be indispensable in patients in whom metastasis from a preexisting cancer is suspected, patients with a mass that appears surgically unresectable, or patients with a suspected sarcoma in whom metastatic disease is noted on imaging and a biopsy may guide subsequent systemic therapy. It is also highly recommended to perform a pretreatment biopsy to establish the diagnosis and grade in select patients suspected of having a surgically resectable retroperitoneal/intra-abdominal sarcoma.

If a pretreatment biopsy is felt to be beneficial, it can be obtained by an interventional radiologist or surgeon using either an image (CT, MRI, or ultrasound)-guided core (14- or 16-gauge coaxial needle) or, rarely, an open/minimally invasive surgical incisional-guided technique depending on the location of the retroperitoneal mass and amenability to a minimally invasive approach.

Treatment

Principles of Sarcoma Surgery

Definitive surgical resection remains the standard primary treatment of retroperitoneal sarcomas; however, if it is deemed a tumor cannot be surgically resected while ensuring negative surgical margins, preoperative (neoadjuvant) radiotherapy and/or systemic therapy should be considered. In retroperitoneal sarcomas deemed

resectable with anticipated negative final surgical margins, it cannot be emphasized enough that the quality and adequacy of the surgical resection is imperative in determining the likelihood of potential cure (Bonvalot et al, 2012).

Retroperitoneal sarcomas typically extend, with direct contact to a number of abdominal/ retroperitoneal structures without necessarily invading them based on preoperative imaging. In consequence, local control remains a significant problem and furthermore is the leading cause of death, particularly for the low- to intermediate-grade tumors, which are estimated to constitute approximately 75% of all retroperitoneal sarcomas. Earlier retroperitoneal sarcoma surgical series had reported disappointing local recurrence-free survival (RFS) rates of 50% at 5 years (Lewis et al, 1998); however, more recent surgical series have reported significantly improved RFS rates of up to 75% to 80% at 5 years (Bonvalot et al, 2010; Gronchi et al, 2012). The better surgical outcomes (Table 2)reported in recent years can be
attributed in large part to a more aggressive approach in which all concerning organs suspected to be involved are resected en bloc with the specimen whenever feasible. This minimizes the risk for microscopically positive surgical margins.

Table 2.

Historical Series on Surgical Outcomes of Retroperitoneal Sarcoma Resection

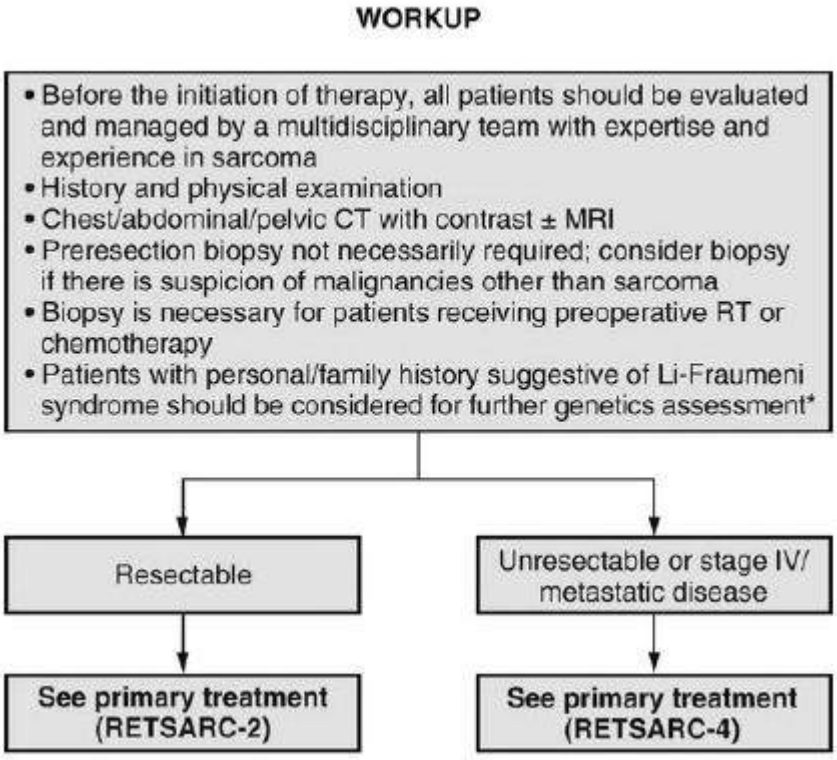
SURGICAL SERIES	STUDY PERIOD	STUDY POPULATION	COMPLETE RESECTION (%)	OVERALL SURVIVAL (% AT 5 YR)	LOCAL RFS (% AT 5 YR)	MEDIAN FOLLOW-UP (MO)
Lewis et al (1998)	1982-1997	231	80	54	59	28
Stoeckle et al (2001)	1980-1994	145	65	49	42	47
Gronchi et al (2004)	1982-2001	167	88	54	63	66
van Dalen et al (2007)	1989-1994	143	70	39	NR	122
Strauss et al (2010)	1990-2009	200	90	68	55	29
Bonvalot et al (2010)	2000-2008	249	93	65	78	37
Gronchi et al (2012)	2002-2008	136	94	68	79	48

NR, not reported; RFS, recurrence-free survival.

It must be emphasized, however, that the liberal resection of adjacent uninvolved viscera may allow a subset of patients to more consistently achieve microscopically negative resection margins, but it remains unclear whether this additional resection translates into an improvement in cancer-specific survival.

A principle to adopt is that any large lipomatous tumor originating from the retroperitoneal space be considered a well differentiated retroperitoneal liposarcoma until proved otherwise.

Although many surgical approaches can be employed in tackling what often can be large retroperitoneal liposarcomas, the most common incisions are typically a midline or subcostal/chevron approach. Both incision types allow for excellent exposure to abdominal/ pelvic organs, which can be reflected superiorly to allow access to retroperitoneal organs and major vascular structures (van Vreeland et al, 1995). For large RPTs situated in the right upper quadrant, some surgeons prefer a thoraco-abdominal incision allowing great visibility and enabling extensive mobilization of the liver, with great exposure of the intrathoracic and intra-abdominal components of the inferior vena cava as well as the right kidney and adrenal gland. The pivotal therapeutic consideration in the management of retroperitoneal/intra-abdominal sarcomas pertains to a determination of whether it is felt the retroperitoneal sarcoma is resectable versus unresectable (or stage IV). It is imperative for surgeons conducting retroperitoneal sarcoma surgery to strictly adhere to the principle of surgical resection with negative margins with the removal of all involved organs. Surgical margins should be documented by both the surgeon and pathologist in evaluating the status of the resection margins. If a surgical margin is deemed positive on final pathologic review, surgical repeat resection should be strongly considered provided this is not deemed either excessively morbid and/or adversely affecting the subsequent quality of life these patients (Von Mehren et al, 2015). Adjuvant radiotherapy is not generally advocated for low-grade retroperitoneal/intra-abdominal soft tissue sarcomas, some have advocated postoperative adjuvant radiotherapy for intermediate- to high grade tumors, but it is widely believed that such therapy has a limited role because the required radiation dose for local cancer control in the adjuvant setting exceeds that tolerable by the bowel. In this regard, most experts believe adjuvant radiotherapy should be reserved to imperative indications such as grossly positive surgical margins after surgical resection in patients not amenable to repeat resection with negative gross and final surgical margins.



Algorithm illustrating the workup of a retroperitoneal sarcoma. CT, computed tomography; MRI, magnetic resonance imaging; RT, radiotherapy

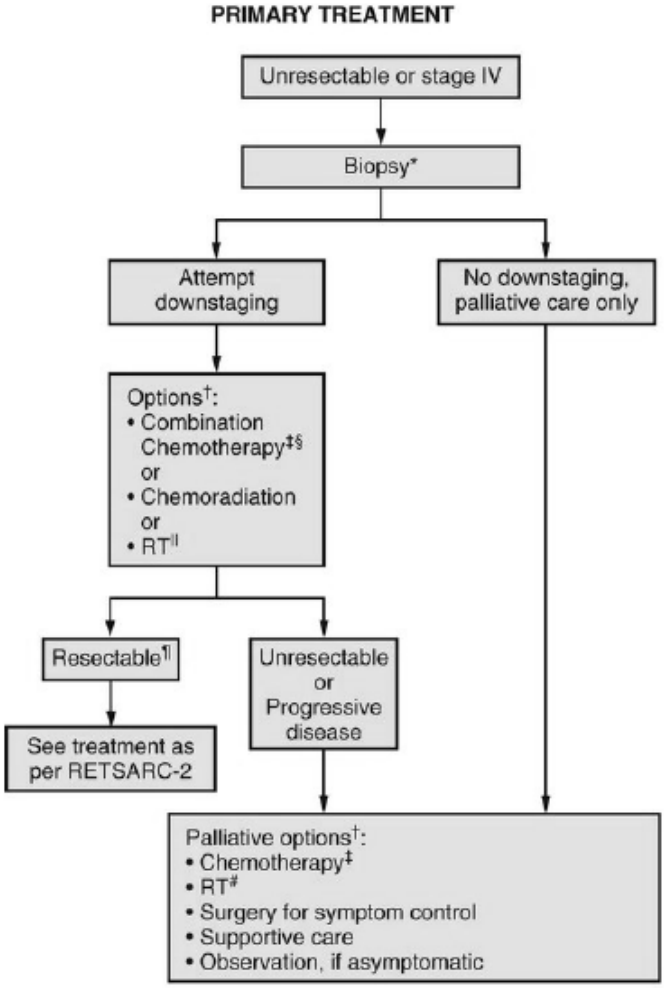
In retroperitoneal/intra-abdominal sarcomas deemed unresectable (or stage IV), a biopsy (preferably percutaneous image guided) to establish the diagnosis should be considered to help confirm first the diagnosis of a soft tissue sarcoma as well as the grade and histopathologic features of the underlying tumor, because these may help dictate which systemic therapies may be best suited for such patients. In patients with unresectable (or stage IV) retroperitoneal/intra-abdominal sarcomas being treated with a combination of radiotherapy and systemic therapy, external beam radiotherapy typically is employed in an attempt to obtain local control, often concomitantly with systemic therapy (i.e., chemotherapy and/or small molecule targeted therapy). If the tumor is deemed to have a favorable response with downstaging such that it becomes resectable, subsequent consolidative surgery is recommended. Patients with unresectable (or stage IV) retroperitoneal/intra-abdominal sarcomas exhibiting either no evidence of downstaging after systemic therapy (± radiotherapy) or deemed unresectable at time of attempted consolidative surgery, should be treated with palliative therapeutic options (radiotherapy, chemotherapy, surgery), with the end point of such therapy being symptomatic control. Additional therapeutic options for such patients include resection of metastatic sites of disease if the primary tumor can be controlled as well as observation if they remain asymptomatic. If these patients are symptomatic, it is reasonable to consider a palliative surgical resection, which can provide some degree of (short-term) local cancer control with a resulting improved quality of life. Clinical trial participation should be considered for such patients, with best supportive care measures being initiated in patients with symptomatic disease progression. Similarly, in some select reports, incomplete surgical resection of retroperitoneal liposarcomas has in fact been shown to improve survival in addition to successful symptom palliation (Shibata et al, 2001).

Role of Perioperative Radiotherapy

Radiotherapy is an integral therapeutic tool in the management of retroperitoneal soft tissue sarcomas, with its potential role as a primary treatment modality or as part of a multimodal treatment in which it is typically delivered in the neoadjuvant (preoperative) or adjuvant (postoperative) setting.

The readily available choices for delivery of radiotherapy are brachytherapy, intensity-modulated radiation therapy (IMRT), and intraoperative radiation therapy (IORT), offering patients potential superior treatment outcomes (DeLaney et al, 2005). Preoperative radiotherapy is frequently used in the management of large or poorly differentiated retroperitoneal sarcomas because, first, the treatment volume is typically a smaller field, being that the entire operative field does not need to be covered, and as well the risk for tumor seeding at time of surgical resection is reduced as a consequence of the preoperative radiotherapy. The sarcoma may or may not

shrink, but the pseudocapsule surrounding the tumor often will thicken and be rendered avascular, which can facilitate the subsequent surgical resection.



Treatment algorithm for an unresectable or stage IV retroperitoneal sarcoma. RT,radiotherapy

The main drawback to preoperative radiotherapy is that it can impair wound healing, typically with an interval of 3 to 6 weeks between the completion of radiotherapy and the definitive proceeding surgical resection, which may result in significant local effects of acute radiation delivery (inflammation, tissue edema, and poor tissue and wound vascularity). It is important to note, however, that some reports would suggest that preoperative radiotherapy followed by aggressive surgical resection, although well tolerated, did not result in a significant clinical improvement in treatment specific outcomes versus surgery alone (Ballo et al, 2007).

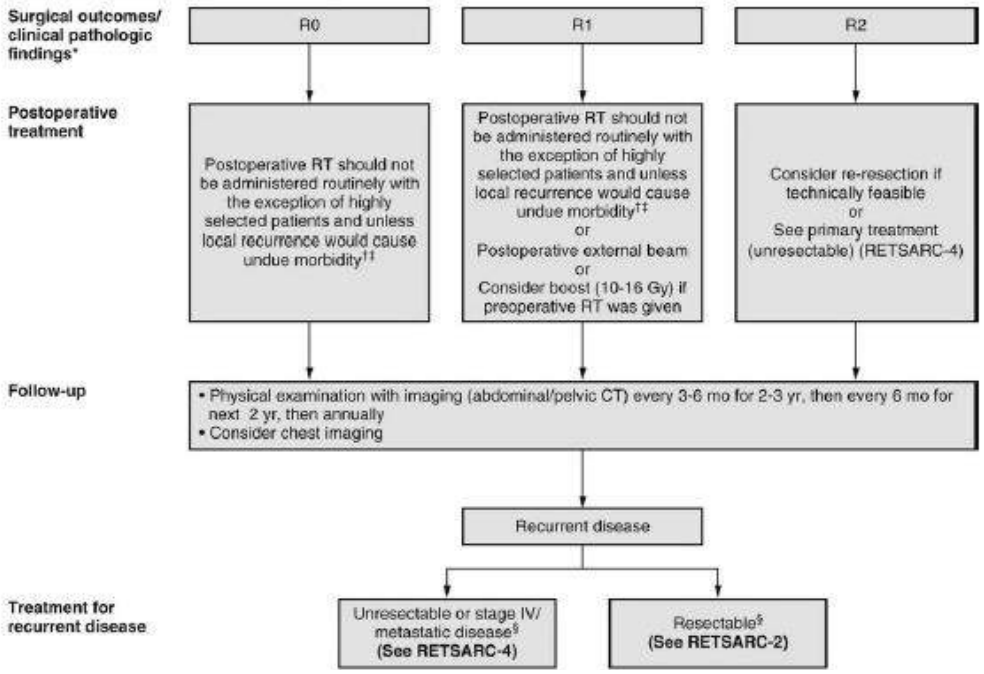
A typical preoperative dose of radiotherapy of 50 Gy is employed, and if wide negative surgical margins are obtained at the time of resection, no further radiotherapy is often recommended, because reported local control rates of up to 95% have been reported when preoperative radiation at a treatment dose of 50 Gy is employed and negative surgical margins are obtained on the subsequent surgical resection. However, in cases in which a positive or close positive margin is demonstrated, a radiation boost delivered by external beam radiotherapy or IORT is often recommended. An IORT dose of 10 to 12.5 Gy is recommended for microscopically positive margins, and an IORT dose of 15 Gy is recommended for gross residual disease.

Postoperative radiotherapy has been demonstrated to improve local cancer control for high-grade soft tissue sarcomas in patients with positive surgical margins (Alektiar et al, 2000; DeLaney et al, 2007). Recommendations pertaining to adjuvant radiotherapy, however, should be individualized and not entirely based on margin status at time of the original or subsequent repeat resection. Postoperative radiotherapy can be delivered in one of several ways, including external beam radiotherapy, brachytherapy, or IORT. It is important to emphasize that adjuvant radiotherapy should not be considered in any way as a compensation for incomplete or poorly conducted surgical resection because the primary end point of retroperitoneal sarcoma surgery should be complete resection with negative gross and microscopic surgical margins while attempting to preserve all nonaffected organs. A therapeutic principle often adhered to is that adjuvant radiotherapy would be the treatment of choice to control

microscopic residual disease if repeat resection is not feasible or is refused by patients. When administered to patients with positive surgical margins, IORT is delivered at 10 to 16 Gy followed by consolidative external beam radiotherapy at a dose of 50 Gy (Von Mehren et al, 2015).

Role of Perioperative Systemic Therapy

Neoadjuvant/adjuvant chemotherapy for the majority of histological subtypes has not shown consistent evidence of a disease-free survival benefit although there may be certain situations where it is advantageous. For subtypes such as the Ewing family of tumours, for which chemotherapy is an essential part of primary management, chemotherapy has definitely improved survival. There is a role for agents such as doxorubicin and ifosfamide in the palliation of symptomatic advanced sarcoma. There is increasing specialisation of chemotherapy according to histological subtype, such as the use of taxanes for angiosarcoma, gemcitabine and docetaxel for leiomyosarcoma, and trabectedin for leiomyosarcoma and myxoid/round cell liposarcoma. Targeted agents like tyrosine kinase inhibitor pazopanib have shown great promise in the management of advanced and/or unresectable soft tissue sarcomas of various subtypes. (Sleijfer et al, 2009).



Algorithm detailing the indications for postoperative and proposed surveillance strategy of retroperitoneal sarcoma after primary treatment.

Conclusion

The retroperitoneum can host a wide spectrum of rare pathologies, including benign and malignant tumours. Tumours usually present late and cause symptoms or become palpable once they have reached a significant size. Retroperitoneal tumours are best evaluated with good quality cross-sectional imaging and preoperative histology by core needle biopsy is required when imaging is non-diagnostic. Complete surgical resection is the only potential curative treatment modality for retroperitoneal sarcomas and is best performed in high-volume centres by a multidisciplinary sarcoma team. Local recurrence occurs in a large proportion of patients. The ability to completely resect a retroperitoneal sarcoma and tumour grade remain the most important predictors of local recurrence and disease-specific survival. Further research is required to define the role of radiotherapy and develop novel biological therapies to target the various molecular pathways.

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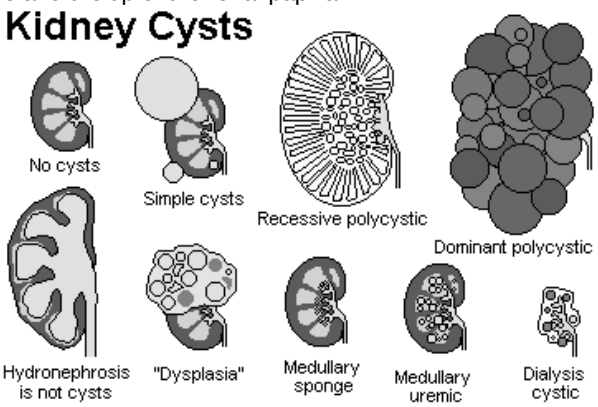
Cystic Diseases of the Kidney

Kim Mammen, Abhinav Jaiswal

Renal Cysts

"Cavities derived primarily from renal tubules and are composed of a layer of partially dedifferentiated epithelial cells enclosing a cavity filled with urine-like liquid or semisolid material." They originate from any tubular segment between the Bowman capsule and the tip of the renal papilla.



Classification

Many classification systems were proposed (9 proposed schema over past 120 years). Initially they were based on structural features but gradually they evolved to include advances in genetics. Ideal classification system is one which takes into account morphological features, pathogenesis, and therapeutic potential

Classification of Renal cysts (AAP 1987)

Inheritable

Autosomal recessive (infantile) polycystic kidney disease
Autosomal dominant (adult) polycystic kidney disease
  Juvenile nephronophthisis/medullary cystic disease complex
  Juvenile nephronophthisis (autosomal recessive)
Medullary cystic disease (autosomal dominant)
Congenital nephrosis (familial nephrotic syndrome) (autosomal recessive)
Familial hypoplastic glomerulocystic disease (autosomal dominant)
Multiple malformation syndromes with renal cysts (e.g., tuberous sclerosis, von Hippel-Lindau disease)

Noninheritable

Multicystic kidney (multicystic dysplastic kidney)
Benign multilocular cyst (cystic nephroma)
Simple cysts
Medullary sponge kidney
Sporadic glomerulocystic kidney disease
Acquired renal cystic disease
Calyceal diverticulum (pyelogenic cyst)

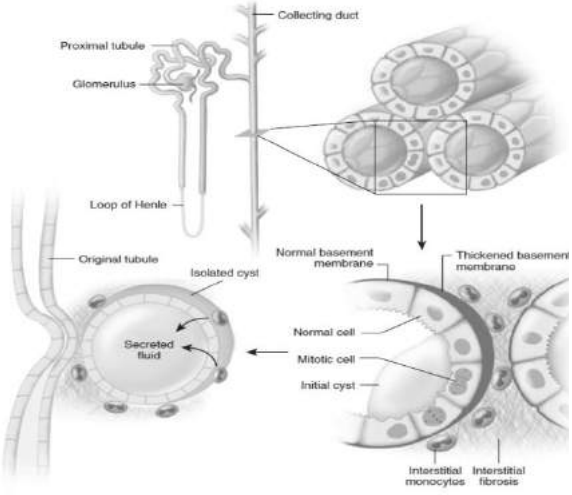
Other Classification

- **Developmental** - Multicystic dysplastic kidney (MCDK)
- **Genetic** - Autosomal recessive polycystic kidney disease (ARPKD), autosomal dominant polycystic kidney disease (ADPKD), juvenile nephronophthisis (JNPHP), medullary cystic kidney disease (MCKD), glomerulocystic kidney disease (GCKD)
- **Cysts associated with systemic disease** - Von Hippel-Lindau syndrome (VHLS), tuberous sclerosis (TS)
- **Acquired** - Simple cysts, acquired cystic renal disease, medullary sponge kidney (MSK)
- **Malignancy** - Cystic renal cell carcinoma (RCC)

Pathogenesis of cystic diseases

Include three fundamental processes:

1. Proliferation of epithelial cells in segments of renal tubule
2. Accumulation of fluid within the expanding tubule segment
3. Disturbed organization and metabolism of the extracellular matrix



Evolution of cysts from renal tubules

- Abnormal proliferation of tubule epithelium begins in a single cell after a “second-hit” process disables the function of the normal allele.
- Repeated cycles of cell proliferation lead to expansion of the tubule wall into a cyst.
- The cystic epithelium is associated with thickening of the adjacent tubule basement membrane and with an influx of inflammatory cells into the interstitium.
- The cystic segment eventually separates from the original tubule, and net epithelial fluid secretion contributes to the accumulation of liquid within the cyst cavity

Tal nsib (2009) Classification of Renal Cystic Diseases and Congenital Anomalies of the Kidney and Urinary Tract

I. Polycystic renal diseases
  A. Autosomal-recessive polycystic kidney disease
    Classic in neonates and infants
    Childhood with hepatic fibrosis
  B. Autosomal-dominant polycystic kidney disease
    Classic adult form
    Early onset childhood form
  C. Acquired renal cystic disease
  D. Glomerulocystic kidney diseases
  A. Familial GCKD
    Renal hypoplasia and *UROM* mutation
    Associated with *HNFB1* mutations
  B. Hereditary GCKD
    Associated with ADPKD/ARPKD/TSC
  C. Syndromic nonhereditary GCKD
  D. Sporadic GCKD
  E. Acquired GCKD

II. Congenital anomalies of the kidney and urinary tract
  A. Renal agenesis and dysplasia
    Agenesis
    Sporadic: unilateral or bilateral
    Syndromic
    Nonsyndromic, multiple malformation syndromes
    Renal dysplasias
    Sporadic: unilateral or bilateral
    Syndromic
    Nonsyndromic, multiple malformation syndromes
    Hereditary adysplasia
  B. Renal hypoplasias
    Simple hypoplasia: unilateral or bilateral
    Oligomeganephronic hypoplasia
    Reduced nephron generations ("cortical hypoplasia")
    Reduced nephron numbers (premature and low birth weight risk of hypertension)
  C. Abnormalities in form, position, and number
    Rotation anomaly
    Renal ectopias
    Renal fusions
    Supernumerary kidney
    In combination with A, B, or D
  D. Ureteral and urethral abnormalities
    Ureteropelvic junction obstruction
    Ureteral duplication/bifid ureter
    Vesicoureteral reflux
    Primary megaureter
    Ureteral ectopia
    Posterior urethral valves
    In combination with A, B, or C

III. Tubulointerstitial syndromes ±cysts
  A. Renal tubular dysgenesis
    Autosomal recessive
    Secondary twin-twin transfusion
    ACE inhibitor
  B. Nephronophthisis: types 1–6
  C. Medullary cystic diseases:
    Type 1
    Type 2/familial juvenile hyperuricemic nephropathy
  D. Bardet-Biedel syndromes, types 1–12

IV. Cystic neoplasms and neoplastic cysts
  A. Cystic nephroma
  B. Cystic partially differentiated nephroblastoma
  C. Mixed epithelial and stromal tumor
  D. Multilocular cystic renal cell carcinoma
  E. Tubulocystic renal cell carcinoma
  F. Von Hippel–Lindau disease
  G. Lymphangioma/hygroma renalis

V. Miscellaneous cysts
  A. Simple cortical cysts
  B. Medullary sponge kidney
  C. Localized renal cystic disease

ARPKD [Autosomal Recessive (Infantile) Polycystic Kidney Disease]

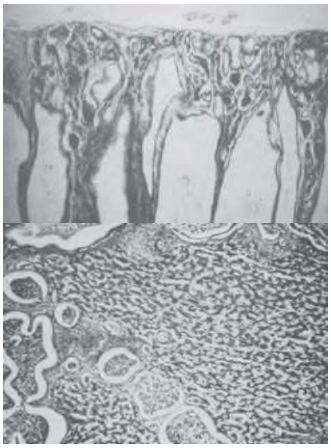
- Incidence - 1 in 10,000 to 50,000 live births
- 50% of affected newborns die in the first few days of life
- Those who survive - Approximately 50% are alive at 10 years of age
- Spectrum of severity - Most severe forms appear early
- If it is not apparent at birth, the disease will become apparent later in childhood (up to age 13 years or, rarely, up to age 20 years).
- Rapid, symmetrical, and bilateral enlargement of the kidneys are seen in infants
- Often associated with congenital hepatic fibrosis

Genetics

- Detailed history to be taken - At least three generations.
- Disease transmission is by Autosomal recessive trait
- Siblings of either sex has 1 in 4 chance of having the disease
- Mutations of gene – *PKHD1* (Protein Fibrocystin (aka polyductin)) implicated
- On Chromosome 6 (6p12)

Clinical Features

- In utero - Enlarged, echogenic kidneys can be seen.
- Associated with Oligohydramnios - lack of normal urine production by the foetus.
- Potter facies and deformities of the limbs can be seen.
- Respiratory distress - pulmonary hypoplasia can occur.
- Enormous, kidney-shaped, non bosselated flank masses can be felt which are hard and non transilluminant.
- In some cases the enlarged kidneys may impede delivery.
- Infant's serum creatinine and BUN gradually rise.
- Mortality is about 30-50% which occurs shortly after birth due to Uremia or respiratory failure
- The earlier the diagnosis – More severe the disease.
- If diagnosed in young children/ Time of birth: child has severe renal disease
- In Older children: there are chances of less severe renal disease and more significant liver damage.
- Hypertension and renal insufficiency are the major manifestations in surviving children, with liver disease becoming more prevalent in older patients.
- In all patients there is liver involvement - CHF, biliary ectasia, periportal fibrosis
- Hepatic fibrosis - Portal hypertension, oesophageal varices, and hepatosplenomegaly.
- It has got no association with renal neoplasms

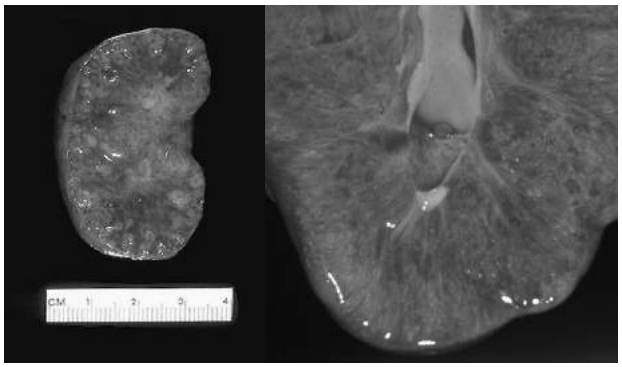


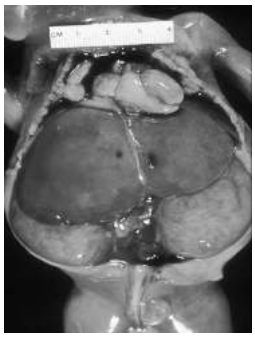
Histopathology

A, Renal histology demonstrates dilated ducts radiating out to the periphery of the kidney. B, On liver histology, ectatic biliary ducts are seen in the left half of the figure, and periportal fibrosis is seen at the upper edge.

On histopathology the kidneys are symmetrically enlarged (x 20 times). They retain a reniform configuration. Parenchyma contains small subcapsular cysts; there are generalized fusiform dilations of the collecting tubules radiating from the medulla to the cortex. Long axis is perpendicular to the renal surface and the renal pedicle, renal pelvis and ureter are normal.

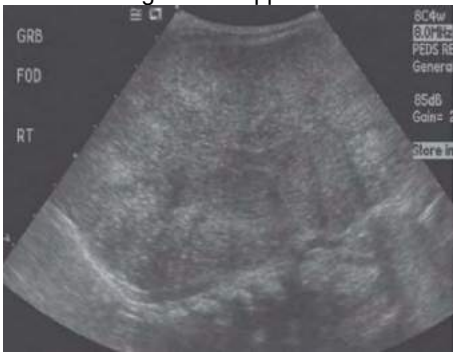
Newborn with abdominal mass and pulmonary hypoplasia

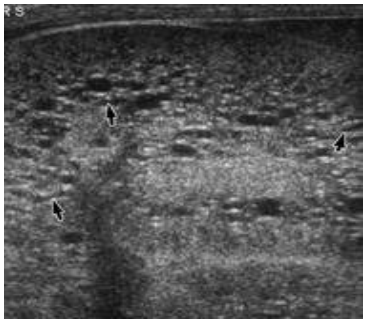




Evaluation

- In Utero USG can pick up Oligohydramnios and/or bilateral, very enlarged, diffusely echogenic kidneys
- Increased echogenicity is due to presence of numerous microcysts (created by tightly compacted, dilated collecting ducts).
- Renal pyramids are hyperechogenic - They blend in with the rest of the kidney, and the kidneys typically have a homogeneous appearance.

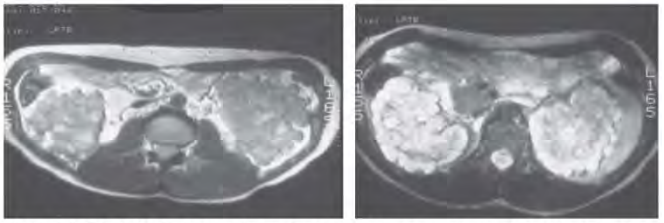




- ***Differential diagnosis:***
    - Severe bilateral hydronephrosis (the kidneys are enlarged with hypoechogenic calyces),
    - Multicystic kidney (hypoechogenic cysts lie within a nonreniform mass that has very little parenchyma),

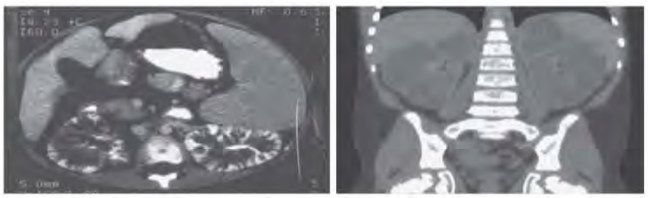
- When in doubt: MRI / CT scan

MRI



A1 and **A2**, MR images of an 8-month-old child with autosomal recessive polycystic kidney disease (ARPKD) demonstrating multiple renal cysts.
A1, On T1-weighted image, fluid content of cysts appears dark.
A2, On T2-weighted image, the fluid content appears white.

CT



A, CT scan of a child with ARPKD. Horizontal cuts showing contrast puddling in collecting ducts.
B, Coronal cut. The kidneys are enlarged, and the enhancing renal parenchyma is effaced by nonenhancing cysts and represents the progression/normal history of the disorder.

Treatment

- Usually there is no cure.
- Respiratory care can only ease or extend the child's life.
- Severely affected neonates may need unilateral or bilateral nephrectomy – Primarily to relieve respiratory and nutritional compromise.
- Survivors - Treatment for hypertension, congestive heart failure, and renal and hepatic failure.
- In cases of portal hypertension - Decompressive procedures can be done such as splenorenal shunt.
- Oesophageal varices need gastric section and reanastomosis.
- Endoscopic sclerotherapy can do done for bleeding varices.
- Ultimately they need haemodialysis and renal transplantation

ADPKD [Autosomal Dominant (Adult) Polycystic Kidney Disease]

- This is the most common inheritable form of renal cystic disease
- Incidence- 1 in 400 to 1000 live births
- Autosomal dominant (10% sporadic)
- Age group - 4th-5th decade
- An important cause of renal failure, accounting for 7% to 15% of patients who receive hemodialysis

Genetic causes implicated

1. PKD Gene products
2. Focal disease and the Knudson's second hit hypothesis
3. Contiguous gene syndrome

PKD Gene products

- **Two major genetic forms of ADPKD caused by mutation in the genes *PKD1 and PKD2***
- **PKD1 gene-** Found on chromosome 16p, protein **polycystin-1**
    - Seen in 85% OF ADPKD cases
    - Associated with more rapidly progressive form of the disease

- Cysts usually start developing by the age of 20 years
- Patient lands up in ESRD in 50s

- **PKD2 gene-** Found on chromosome 4q, protein **polycystin 2.**
  - Seen in 15% of ADPKD cases
  - Associated with slow progression
  - Manifest as ESRD in 70s
- **PKD3 gene**: The presence of a third locus **(PKD3)** is now accepted as the cause of disease in a very small percentage of patients who have been found to have neither a *PKD1 nor a PKD2 gene defect*

Knudson's two hit hypothesis

- Every cell of the nephron and collecting duct has the *PDK1 or PDK2 mutation; however, only **1% to 2% of these glomerular units*** are affected by cyst formation.
- Only those nephrons that undergo a disruption of a second allele undergo cystic enlargement.
- This is the "second hit" of the Knudson theory, which has been proposed to explain the focal nature of the cysts.

Contiguous gene syndrome

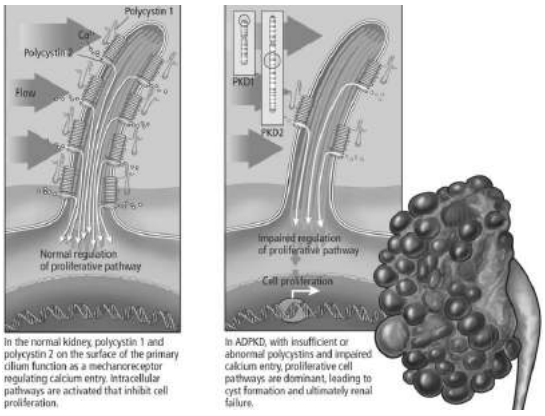
- Characterized by multiple, apparently unrelated, clinical features caused by deletion of the multiple adjacent genes loci that are adjacent to one another.
- *Eg. PDK1 gene* is immediately adjacent to the *TSC2 gene* on chromosome 16

Pathogenesis: Mechanism of cyst formation and growth

Due to

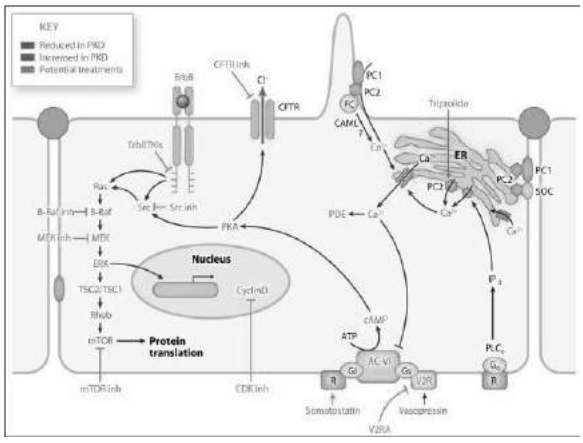
- Abnormal targeting of cell proteins- **Polycystin1 and 2**
- Abnormal cilia function (**Primary ciliopathy)**
- Role of cAMP and intracellular calcium
- Role of mTOR
- Role of Vasopressin
- Cyst growth – Cellular + ECM + more fluid secretion than absorption

- **Polycystin1** is involved in cell-cell interactions; activates JAK-STAT pathway (Janus kinase (JAK) and Signal Transducer and Activator of Transcription (STAT), causing cell cycle arrest.
- **Polycystin2** involves calcium signaling via G-proteins
- They are expressed in renal tubular epithelium, hepatic bile ducts, and pancreatic ducts.
- In ADPKD, the polycystins do not function properly, and the proliferative pathways are unopposed and cyst formation occurs to varying degree.
- PC1 & PC2 complex regulates the proliferative state of the renal tubular cells through a variety of signalling pathways (cAMP, extracellularly regulated kinase [ERK], mammalian target of rapamycin [mTOR], etc.).
- Cilia serve as organization centres for this signal transduction.
- There are increased levels of cAMP - ADPKD.
- There is upregulation of the vasopressin V2 receptor - increase cAMP levels.
- Vasopressin receptor antagonists – They decrease cAMP and ERK, prevent or reduce renal cysts, and preserve renal function.



In the normal kidney, polycystin 1 and polycystin 2 on the surface of the primary cilium function as a mechanoreceptor regulating calcium entry. Intracellular pathways are activated that inhibit cell proliferation.

In ADPKD, with insufficient or abnormal polycystins and impaired calcium entry, proliferative cell pathways are dominant, leading to cyst formation and ultimately renal failure.



Manifestation

– Renal Cysts
  - Start small but enlarge over time
  - They enlarge the kidney

- Often complicated with Calcification, hemorrhage
- Usually bilateral, symmetric involvement

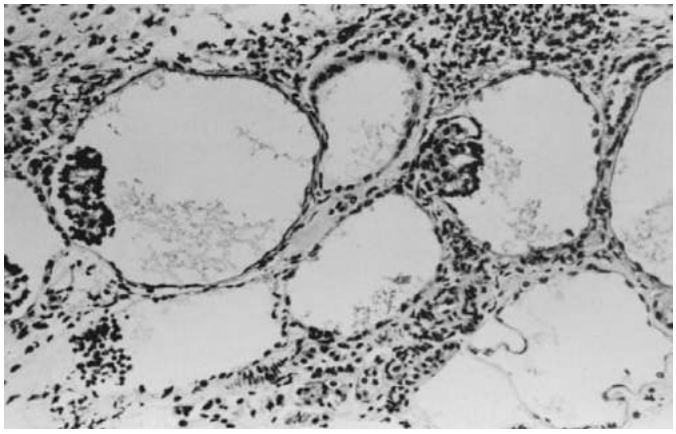
– Extrarenal cysts – Seen in
  - Liver (40-90%)
  - Pancreas (10%)
  - Spleen (5%)
– Cerebral aneurysms (15-40%)
– There is no increased risk of RCC.

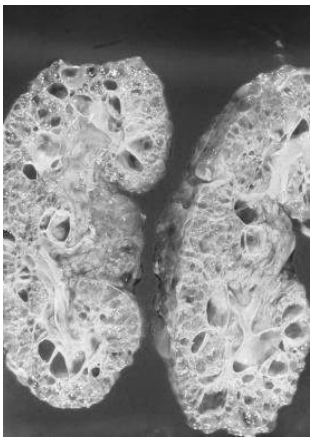
Clinical Features

Renal	**Extra Renal**
1.Hematuria	1.Polycystic liver disease
2.Infection	2.Intracranial Aneurysms
3.Nephrolithiasis	3.Valvular heart disease
4.Hypertension	
5.Renal failure	
6.Pain	
7.Cyst rupture and torsion	
8.Functional renal disease	

Histopathology

- Kidneys maintain reniform shape
- Size could be variable
- Both kidneys are equally affected
- Cysts can range from few millimetres to a few centimetres in diameter
- They appear diffusely throughout the cortex and medulla with communications at various points along the nephron.
- Epithelial hyperplasia or adenoma formation in the cyst wall is common
- Basement membrane of the wall is thickened.
- Arteriosclerosis is seen in more than 70% of patients.
- Interstitial fibrosis, with or without infiltrates is common.





ADPKD Work up: Pre requisite

- At least three generations of the patient's family history should be taken.
- Questions should be asked about renal disease, hypertension and stroke.
- Patients and families should be counseled before any imaging or other testing is undertaken.

Imaging

1. Abdominal Ultrasonography / IVP
2. CECT Abdomen
3. MRI Abdomen

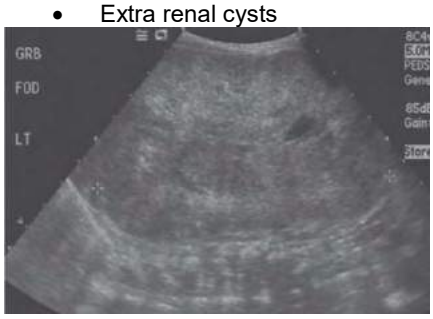
IVP

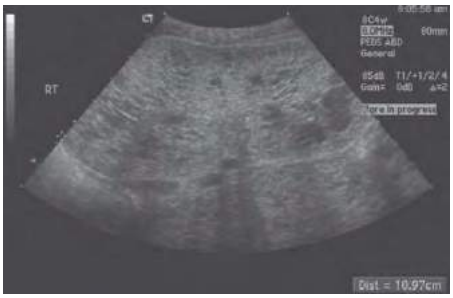
- Bilateral enlarged lobulated kidneys
- Swiss cheese nephrogram (multiple lucencies on nephrogram)
- Arachnoid calyces (elongated, stretched calyces)

USG

- Bilateral large kidneys with cysts

- Often with Calcification, hyperdense
- Extra renal cysts





Newborn with ADPKD. Note the abnormal renal architecture and the hyperechogenic appearance of the kidneys. The parenchyma consists of multiple tiny cysts, with some being slightly larger than others.

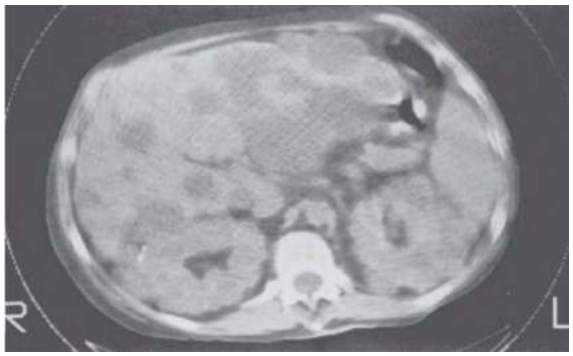
Ravine ultrasonographic criteria for diagnosing ADPKD

AGE	POSITIVE FAMILY HISTORY	NEGATIVE FAMILY HISTORY
< 30 years	2 cysts bilaterally (or unilaterally)	5 cysts bilaterally
30–60 years	4 cysts bilaterally	5 cysts bilaterally
> 60 years	8 cysts bilaterally	8 cysts bilaterally

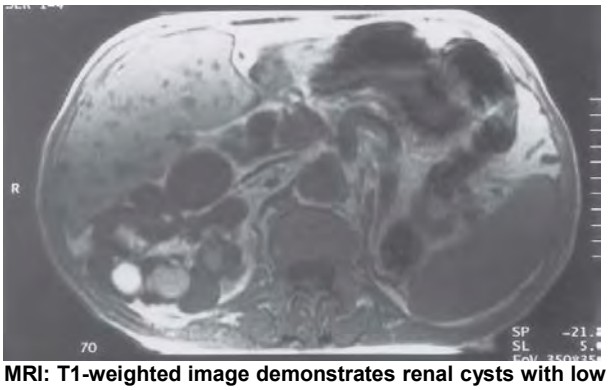
BASED ON RAVINE D, GIBSON RN, WALKER RG, SHEFFIELD LJ, KINDCAID-SMITH P, DANKS DM. EVALUATION OF ULTRASONOGRAPHIC DIAGNOSTIC CRITERIA FOR AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE 1. LANCET 1994; 343:824–827.

Sensitivity of Ravine criteria
The sensitivity of these criteria is nearly 100% for individuals 30 years or older and for younger individuals with PKD1 mutations but only 67% for individuals with PKD2 mutations younger than 30 years

Imaging: CT/MRI
- It is superior to ultrasonography for detecting cysts in organs other than the kidney
- Helpful in making the diagnosis of hemorrhage within a cyst.
- More acute hemorrhage has a higher density (50 to 90 HU) than old hemorrhage
- MRI also may be helpful, particularly in patients with compromised renal function, because no contrast agent is needed.



CT scan of an adult male patient with autosomal dominant polycystic kidney disease (ADPKD). Bilateral renal cysts are seen in enlarged kidneys with calcification. Large asymptomatic cysts are seen throughout the liver as well



MRI: T1-weighted image demonstrates renal cysts with low and high (white) signals. High-signal cysts correlate with intracystic hemorrhage.

- When there is no family history to support a diagnosis of ADPKD, a **presumptive diagnosis** can be made if bilateral renal cysts are present and two or more of the following symptoms are present as well:
- bilateral renal enlargement,
- three or more hepatic cysts,
- Cerebral artery aneurysm, and a solitary cyst of the arachnoid, pineal gland, pancreas, or spleen

ADPKD Work up: Genetic testing

Indications

- When the imaging results are equivocal
- When a definite diagnosis is required.

Benefits of testing

- Making a diagnosis that may affect family planning,
- Early detection and treatment of disease complications, and
- Selection of genetically unaffected family members for living donor–related renal transplantation.

Differential diagnosis

- ARPKD in children
- Tuberous sclerosis
- Multiple simple cysts
- Multicystic dysplastic kidney
- Von Hippel-Lindau syndrome
- Acquired cystic kidney disease

Treatment

- **No treatment** has been proven to delay progression of disease
- Management focus on
  - Control of hypertension
  - Pain Management
  - Prevention of ESRD
  - Renal replacement therapy
  - **Novel therapies**

Treatment: Control of Hypertension

- **Complications of ADPKD are reduced significantly by controlling the blood pressure.**
- **For control of hypertension – (First choice)** ACE-I (ACE inhibitors) due to increased RAS activity from focal ischemia due to cyst expansion.
- Alternatively Angiotensin receptor blockers (ARB) can be used.
- Others drugs– CCBs, Beta blockers
- **Target BP should be less than 130/80 mm Hg**

Treatment: Control of Pain

- **Causes of pain:** Cyst expansion, Hemorrhage, infection, stone, and tumor
- **Treatment – NSAIDs –** but patients should avoid chronic use
- **Use of Opioids** is limited to acute pain episodes
- **Surgical treatment** to be done if conservative measures fail

Management of ESRD

- Patients with ADPKD do better on **dialysis** than do patients with other causes of ESRD due to higher concentrations of erythropoietin and hemoglobin or due to lower co morbidity.
- **Management options are either HD or PD**
- **Peritoneal dialysis** – is done when the kidneys are not too large, they carry increased risk of hernias.
- **Transplantation** - the treatment of choice for ESRD in ADPKD
- There is no difference in patient or graft survival between patients with this disease and other ESRD populations.
- Complications after transplantation are no greater than in the general population.
- Pretransplant nephrectomy is done in patients with a history of infected cysts or frequent bleeding or large kidney below iliac crest – Can be hand-assisted laparoscopic nephrectomy

Novel therapies

- No specific treatment – Can only prevent or delay progression.
- Therapies under evaluation are:
  – Rigorous blood pressure control
  – Maximal inhibition of the renin-angiotensin-aldosterone system
  – Increased fluid intake
  – Vasopressin receptor antagonists
  – mTOR inhibitors

Ideas for the future?

- MTOR inhibitors: show some benefit in limiting the increase in kidney size, but do not limit the decrease in GFR (over 2 yrs) and cause more proteinuria

- Vasopressin receptor antagonists have shown promising results in mice/rat models (via intracellular cAMP), phase 3 trials in progress

Prognosis

- **50% of ADPKD patients eventually land up in ESRD**
- They require either renal transplant or dialysis by age **60 years.**
- Prognosis depends on the form of gene mutation.
- ADPKD2 - Milder disease, based on the age of onset of ESRD. Median age of renal survival is 68 years.
- ADPKD1 - Median age of renal survival is 53 years.

ARPKD vs. ADPKD

Comparison of Autosomal Recessive and Autosomal Dominant Polycystic Kidney Disease

	AUTOSOMAL RECESSIVE POLYCYSTIC KIDNEY DISEASE	AUTOSOMAL DOMINANT POLYCYSTIC KIDNEY DISEASE
Gene defect	Chromosome 6	Chromosome 4 and 16
Incidence	1: 5000-40,000	1: 500-1100
Usual age at clinical presentation	Perinatal	Third to fifth decades
Typical ultrasonographic appearance of kidneys	Symmetrically enlarged, homogeneous, hyperechogenic	Large, cystic kidneys, sometimes asymmetrical
Histology	Collecting duct ectasia; cysts derived principally from collecting duct	Microcysts and macrocysts derived from the entire nephron
Liver	Always with congenital hepatic fibrosis but of varying severity	Cysts, mostly in adults
Other organ system(s) involvement	None	Intracranial (berry) aneurysms, colonic diverticuli; mitral valve prolapse; cysts of other organs (seminal vesicle, arachnoid membrane, pancreas)

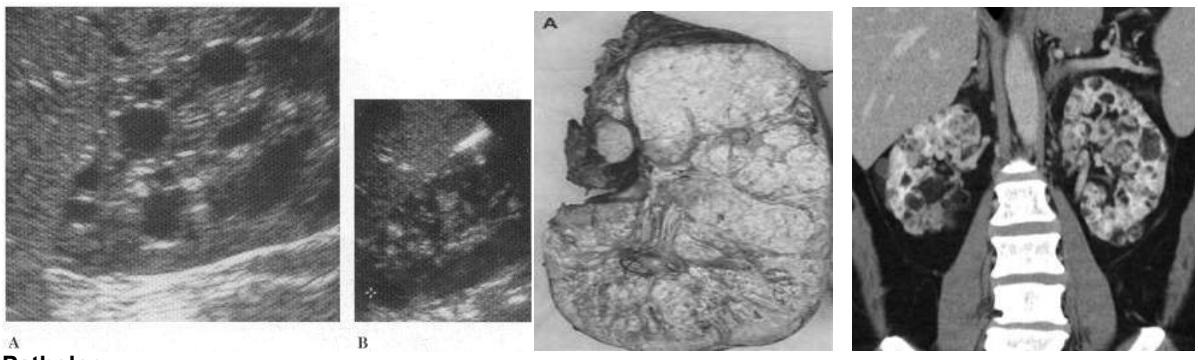
TUBEROUS SCLEROSIS COMPLEX

- Inheritance is Autosomal dominant
- 1/3 cases are familial
- Prevalence is 1:10,000
- **Genetic loci:**
  TSC1 - Chromosome 9q
  TSC2 - Chromosome 16p adjacent to PKD1 locus
- 2 genes implicated - TSC1 (hamartin) and TSC2 (tuberin)

Clinical features

- Renal cysts and angiomyolipomas
- Renal cell carcinoma (bilateral)
- Cortical tuber
- Retinal hamartoma
- Glioma
- Astrocytoma
- Facial angiofibroma
- Ungual fibroma
- Shagreen patch
- Cardiac rhabdomyoma
- Pulmonary lymphangioleiomyoma
- Thyroid adenoma

- Renal manifestations occur in majority
  - Cysts – 15-50%
    - When occur tend to be in young children
  - AML's – 80%
  - Neoplasm (RCC)
    - Controversial whether increased incidence
    - Predisposition to RCC is suggested by younger age and bilateral nature
  - No extra renal cysts are seen.



Pathology

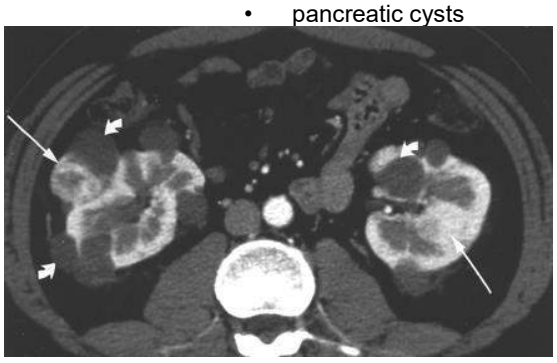
- Commonest lesion seen is Angiomyolipoma (50-70%), benign cysts (30-50%)
- Symptoms - Flank pain, hematuria from mass effect of angiomyolipoma; cysts are usually asymptomatic
- Renin-dependent HTN from ischemia
- Since TSC2 gene is adjacent to PKD1, some have both diseases

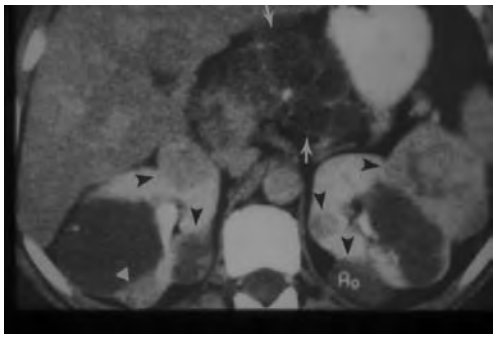
Management

- ESRD – Due to mass effect
- RCC can be seen in 1-2% - USG follow up to be done every 1-3 years
- Intervention for pain, bleeding, malignancy – 1st line arterial embolization, second line partial or total nephrectomy.
- **Transplantation accompanied by bilateral nephrectomy** – due to increased risk of RCC by immunosuppression.

VON HIPPEL LINDAU DISEASE

- Prevalence is 1:30,000
- 2 types:
    - **VHL1 :**
        1. Retinal Angioma
        2. Spinal/ cerebellar hemangioblastoma
        3. Pancreatic and renal cysts
        4. Renal cell cancer
    - **VHL2 : as in VHL1 + Pheochromocytoma**
- It is an autosomal dominant syndrome with a variety of benign and malignant tumors
- Commonest systemic lesion are hemangioblastoma of eye/brain; pheochromocytoma in 10-20%
- Renal involvement includes multiple cysts and RCC (2/3 of patients)
- Renal manifestations are also common
- Findings
    - Cysts – 50-75%
        - BL; Multiple
    - RCC - 35%
        - B/l and multiple
        - Aggressive behavior
    - pancreatic cysts





Treatment

- New tumors arise every 5 years in 30% of patients; every 10 years in 85%
- Small lesions can be kept under observation (<3cm), or can undergo radiation ablation, cryotherapy, or partial nephrectomy

- Transplantation is feasible in setting of bilateral nephrectomy; minimal data available regarding RCC recurrence.

MEDULLARY SPONGE KIDNEY

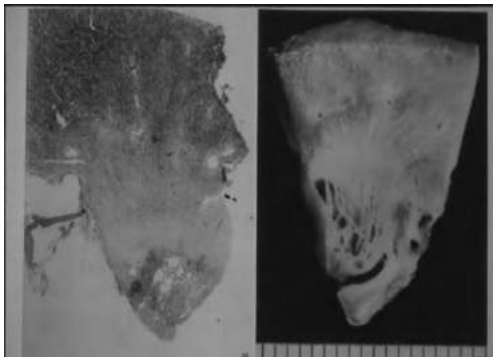
- Idiopathic
- Very common (1 in 200 people)
- Sometimes autosomal dominant, but usually due to sporadic mutations
- Malformation of terminal collecting ducts in pericalyceal region of pyramids
- Dilated distal portions of collecting ducts superficially resemble cysts:
  - Urinary stones within the "cysts“
  - Superimposed infection (pyelonephritis)

Clinical Characteristics

- Usually asymptomatic except stones - incidental
- Found in Young adults
- Non-hereditary; non-progressive in nature
- Associated with Caroli’s, ARPCKD; hemihypertrophy
- Recurrent calcium phosphate or calcium oxalate stones are found – Due to concretions within cysts which act as nidus for stone formation
- UTI (secondary to stones, stasis)
- Hematuria

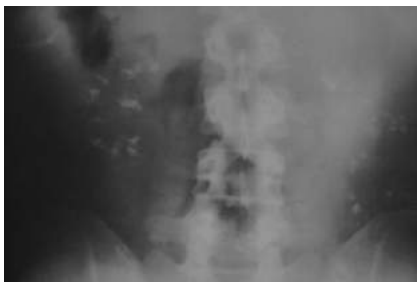
Pathology

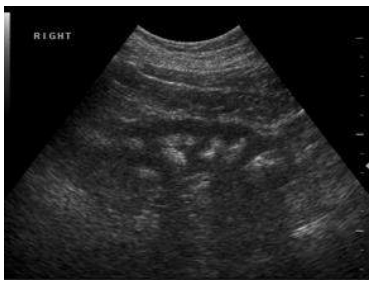
- Saccular 1-8mm dilatation of the distal collecting ducts seen with sluggish flow and predisposition to stone formation

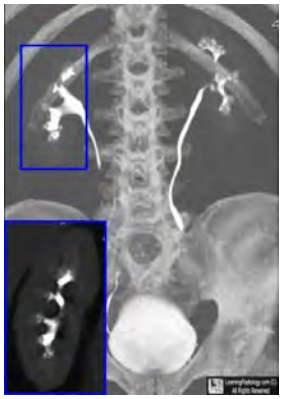


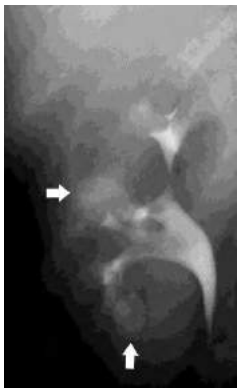
Diagnosis

- Normal renal function
- Patients present with chronic back pain
- Diagnosis is usually incidental - Made by IVP, with dilation of cystic ducts showing “brush” appearance radiating outward from calyces
- U/S and CT are less specific – Show nephrocalcinosis
- Imaging (Plain Xray, US and CT)
  - Show Medullary nephrocalcinosis
    - Can be bilateral, unilateral or focal
    - “growing calculus sign”
  - Urolithiasis
  - Discrete linear collections in papilla on IVP
    - Should be distinguished papillary blush - a nondiscrete blush of contrast within the papillary which can be normal









Treatment

- Patients with stone risk factors (hypercalciuria, hyperuricosuria, hyperoxaluria, hypocitraturia) may benefit from potassium citrate
- Initial dose 20meq/day titrated to urinary citrate level of 450mg/day

NEPHRONOPHTHISIS AND MCKD

Nephronophthisis

- It is an Autosomal recessive, heterogenous disorder affecting proteins in cilia
- Most common cause of ESRD in children and young adults
- Pathology:
  - Cysts in the medulla
  - Cortical tubular atrophy
  - Interstitial fibrosis

Manifestations

- Polyuria/polydipsia due to impaired concentration of urine
- Hepatic Fibrosis
- Situs Inversus
- Characteristic findings are reduced urinary concentrating ability; chronic tubulointerstitial nephritis resulting in ESRD by age of 20
- Commonest extrarenal manifestation - Retinitis pigmentosa (20%)

Diagnosis

-Polyuria with bland urinalysis
-Progressive CKD without HTN
-Normal Size Kidneys

- If above 3 are present - genetic testing is warranted.
- If genetic test negative - biopsy can be suggestive of tubulointerstitial nephritis with thickened basement membrane.

Medullary Cystic Kidney Disease

- Rare (~50 cases per year in USA) autosomal dominant disease
- Two types, with variable clinical courses - ESRD at age 20-70

MCKD1

- Gene within chromosome 1q21 - not been identified
- Pathophysiology is unknown
- Manifests as hypertension and hyperuricemia - More prevalent as renal function declines, therefore late features (contrast to MCKD2)
- Course within families is extremely variable (ESRD ranging from age 30-75)
- Biopsy reveals Tubular atrophy, interstitial fibrosis, splitting of basement membrane (which is thick and irregular)
- No specific treatment
- Transplant is the preferred therapy – disease will not recur

MCKD2

- Also called Familial Juvenile Hyperuricemia
- Describes families with mutations in the uromodulin gene – a Tamm-Horsfall mucoprotein

Pathophysiology

- Uromodulin is produced exclusively in thick ascending limb of Loop of Henle
- It is a sticky insoluble protein - Assist with water-tight integrity
- Mutant proteins cannot exit cell, and cause tubular atrophy/death

Clinical Characteristics

- Hyperuricemia/Gout results from reduced urate excretion (mechanism not well understood)
- Progressive decline in renal function occurs secondary to tubular death

Diagnosis

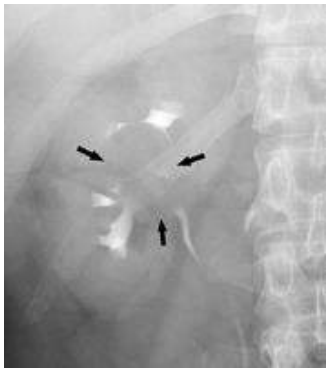
- 3 criteria:
  -Family history of renal disease in autosomal dominant pattern
  -Family History of Gout
  -Bland Urinary sediment without little or no proteinuria
- Definitive Diagnosis is through genetic test, which is cheaper and more specific than biopsy (IF with antibody to uromodulin shows deposition in tubules)

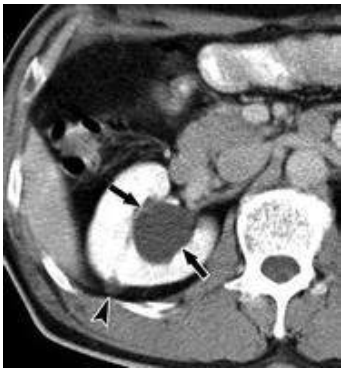
Treatment

- Gout to be treated with Allopurinol; it is uncertain whether this slows progression of kidney disease.

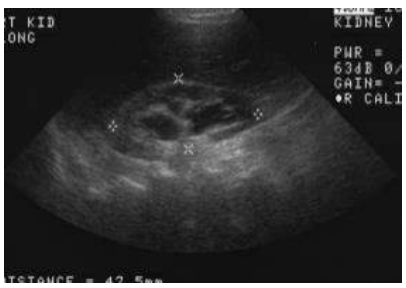
RENAL SINUS CYSTS

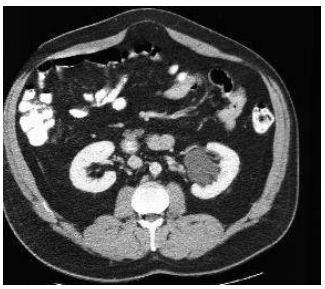
- They are of 2 types
  - **Parapelvic cyst**
    - Which originate from parenchyma which projects into the sinus
  - **Peripelvic cyst**
    - It is an extraparenchymal cyst arising in sinus (?origin; ? congenital and lymphatic etiology)
- **Imaging (Peripelvic cyst)**
  - May be multiple and bilateral, unilocular or multilocular; usually small and insinuating
  - There is smooth splaying of collecting system
  - It rarely results in obstruction and hydronephrosis

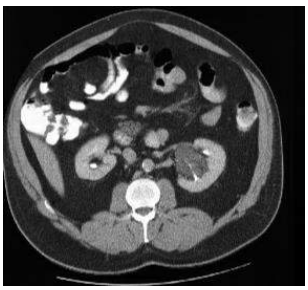




- ***<u>Imaging</u>***
  - US- Shows cyst in renal sinus
  - CT- Suggestive of sinus cyst (delayed films needed to exclude hydronephrosis)
  - **D/D – hydronephrosis**







MULTI CYSTIC DYSPLASTIC KIDNEY

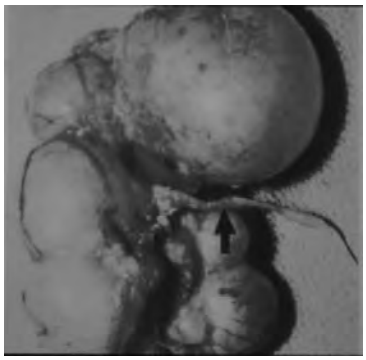
- It is a congenital, non-hereditary dysplasia characterized by renal parenchyma replaced by multiple cysts
- Which are due to dysplastic ureteral bud

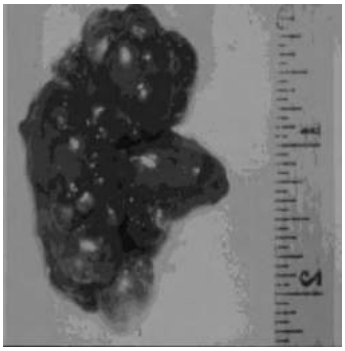
Clinical presentation

- It may present as abdominal mass in child or incidental in adult
- There is 10-30% incidence of contralateral anomaly, especially UPJ obstruction and reflux

Types

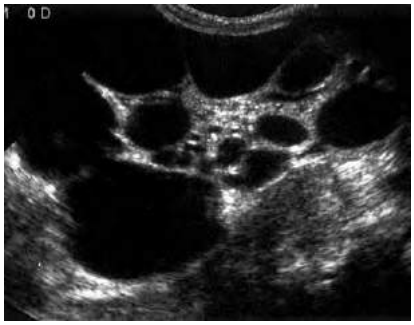
- **Pelvoinfundibular atresia (most common)** - atretic renal pelvis and ureter; cystic renal mass
- **Hydronephrotic type (rare) -** ureteral atresia but dilated pelvis
- **Segmental (rare) –** Seen in duplicated system

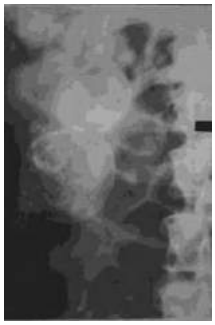


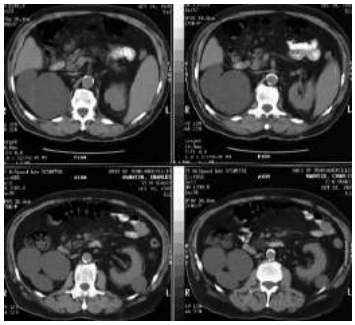


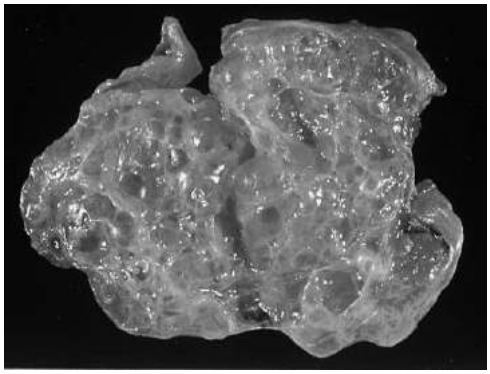
Findings

- No renal function
- Multiple noncommunicating cysts replacing kidney
- Usually no large central cystic area (UPJ)
- Usually unilateral, with compensatory hypertrophy of contralateral side
- Often detected on prenatal sonography, or palpable flank mass
- MUST evaluate contra-lateral side









Management

- Evaluation of contralateral kidney, including ultrasound and voiding cystourethrography to rule out vesicoureteral reflux (25%)
- There is no indication for nephrectomy (as no increased risk of Wilms' tumor)

ACQUIRED CYSTIC KIDNEY DISEASE

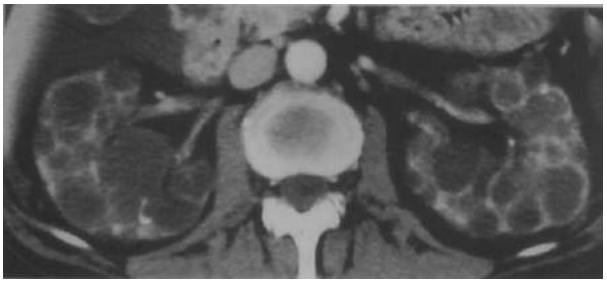
- Hemodialysis and peritoneal dialysis is associated with development of multiple bilateral small cysts; usually less than 0.5cm but up to 3 cm
- Criteria: 4 or more total cysts in both kidneys
- Differentiated from ADPKD by lack of family history, small/normal size kidneys, smooth contoured kidneys
- Can occur without dialysis (10%) but very common in patients with dialysis (either hemo or peritoneal)
    - ??Dialysis prolongs lifespan so cysts develop
    - Incidence is 50% at 5 yrs, 90% at 10 years
- Incidence increases with increased time on dialysis; also occurs in children

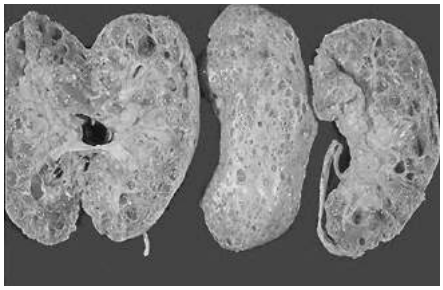
Pathology

- Fibrosis and a few chronic inflammatory cells
- Oxalate crystals in the tubules
- Fibromuscular masses in the blood vessels
- Cortical adenomas and renal cell carcinomas

Findings

- Cysts
    - Early small in size; enlarge and multiply in time; can mimic ADPCKD
    - Commonly Calcification, hemorrhage
- Neoplasms
    - Definite increased risk with CRF, again esp. dialysis
    - Often indolent in nature (papillary RCC)
- kidneys small; atrophic; hyperechoic; no other cysts





Complications

- Commonest symptoms: hematuria, lumbar pain, UTI
- RCC has varied incidence, ~5%; malignancy develops after 8-10 years on dialysis; risk factors are male and large cysts
- No guidelines for screening; some suggest radiological studies only for new symptoms (hematuria/flank pain), or young patients (long duration of HD)

Treatment

- Nephrectomy
- Transplant
- Impact of transplant
    - Controversial
    - Cysts - some regress, some don't
    - Neoplasms - again controversial

SIMPLE RENAL CYSTS

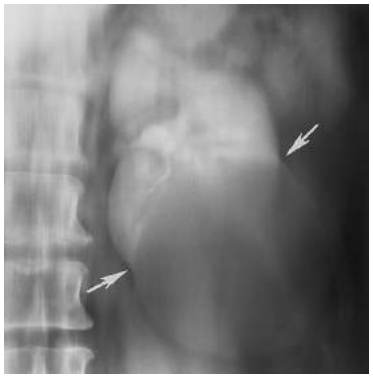
- They are extremely common in old age
- Incompletely understood pathogenesis
- They are commonly associated with scarred kidneys
    - Develop after small kidney infarcts ("arterial nephrosclerosis")
- Generally asymptomatic, may produce pain or hemorrhage.
- Patients have normal renal function
- They may be solitary/multiple/unilateral/bilateral
- They are generally unilocular, round to oval of varying sizes
- Commonly - 1-5 cm in diameter.
- They arise as dilated tubules or collecting ducts
- Have thin, translucent fibrous wall containing clear or amber colored serous fluid

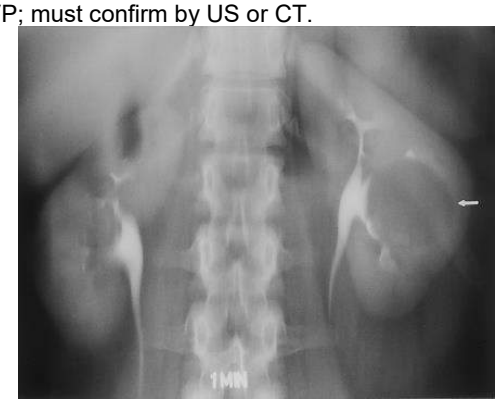
Microscopically

- They have a membrane composed of single layer of flattened or atrophic epithelium.
- They are often confined to the cortex.
- Differentiated from renal tumor in three aspects:
    1. Renal cyst has smooth contour.
    2. They are almost Avascular
    3. They give fluid rather than solid signal on ultrasonography

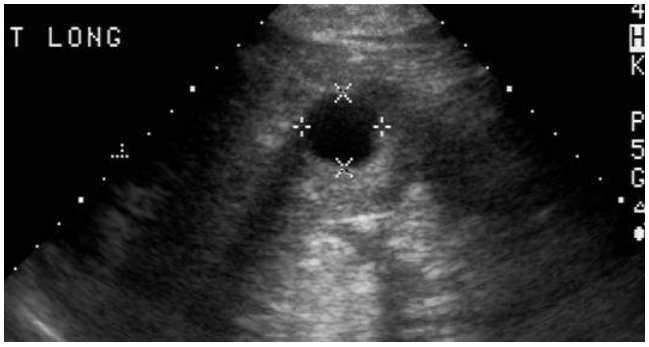
Imaging

- **IVP (historical)**
    - Homogeneous, lucent
    - Thin walls, smooth interface
    - "Beak sign"
    - Cannot dx on IVP; must confirm by US or CT.

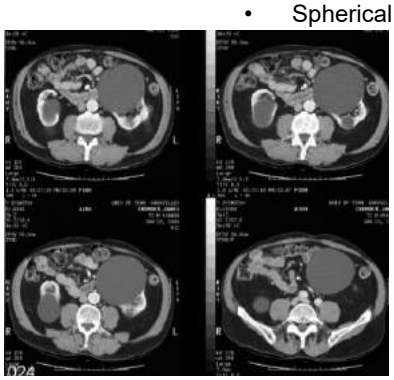


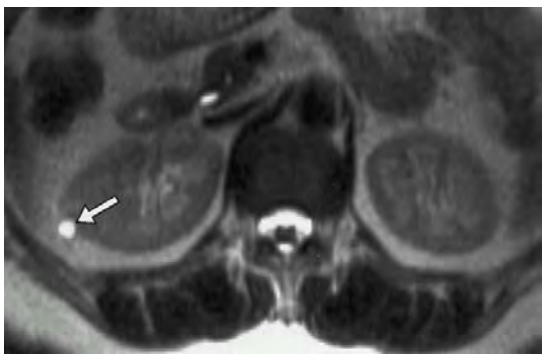


- **Ultrasound**
    - Anechoic
    - Thin, smooth wall
    - Increased thru transmission



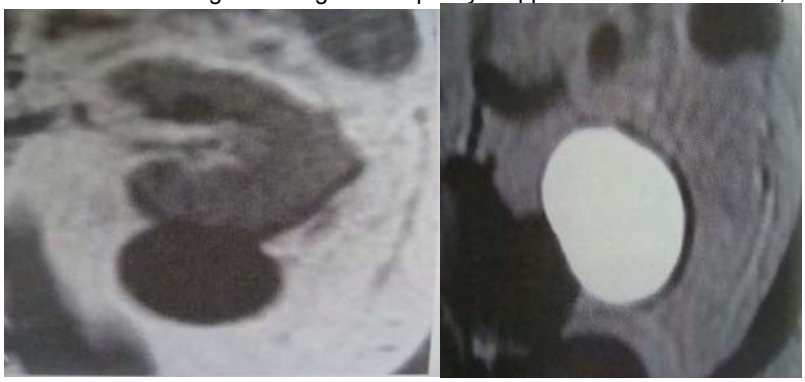
- **CT -**
    - They have near water density (- 10 to +20 HU)
    - Thin, smooth wall
    - Homogeneous
    - No enhancement
    - Spherical or ovoid





- **Magnetic resonance imaging**

On T1 weighted images - Simple cyst appears as Round or oval, homogenous, low intensity mass

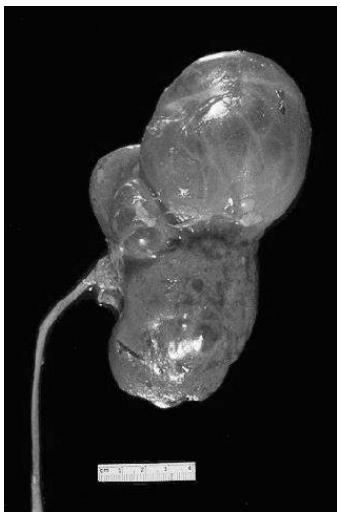


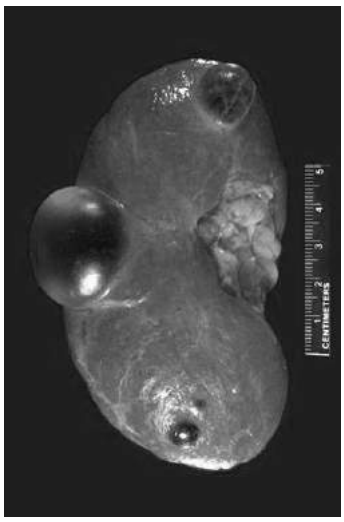
On T2 weighted images

- Cyst will remain homogenous
- Its intensity increases
- Cyst wall is barely perceptible
- Inner margin of cyst is smooth and distinct
- Sharp interface separates the cyst from rest of the kidney

- MRI is indicated in
  - Patients with renal insufficiency
  - Patients with prior history of allergic reaction to iodinated contrast material
  - Patient who had abnormal imaging study results (USG, IVU, CT)

MRI with gadolinium labeled DTPA on T1 weighted scan before and after administration of contrast may be useful in diagnosing malignant lesions.



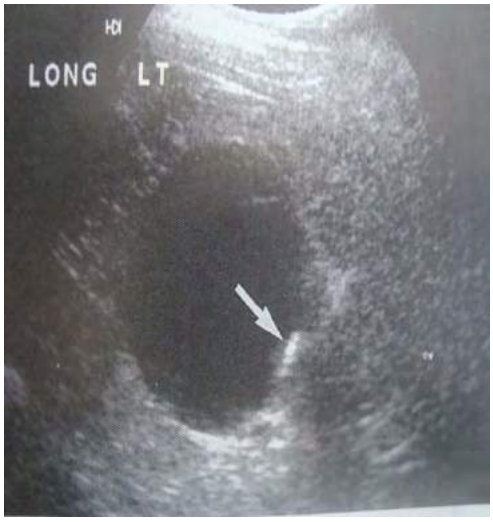


Complicated Renal Cyst

- Simple cysts may become infected or hemorrhage/trauma
- US/CT/MRI
  - Thick walls; calcifications, septations, debris or increased attenuation
  - And so, overlaps the appearance of cystic RCC
    - And therefore Bosniak Classification

In evaluating complicated renal cysts important sonographic features to be looked for are:

- Thickness and contour of cyst wall
- Presence, number and thickness of any septa
- Presence of calcification
- Density of renal cyst fluid
- Presence of solid component



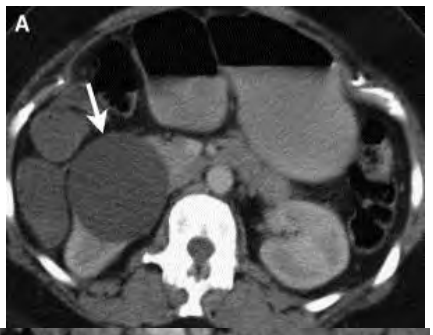
Bosniak Classification

- Bosniak created a classification scheme to guide proper management – CT based
- **Classification (1986)**
  - I - Simple cyst
  - II - Minimally complicated (1 or 2 thin, "nonenhancing"septi, delicate Calcification in septi or wall; hyperdense)
  - III - Thick walls or Calcification, thick septi, nodules
  - IV - Definitely malignant (necrotic masses, etc.)

A high quality CT examination should be done-

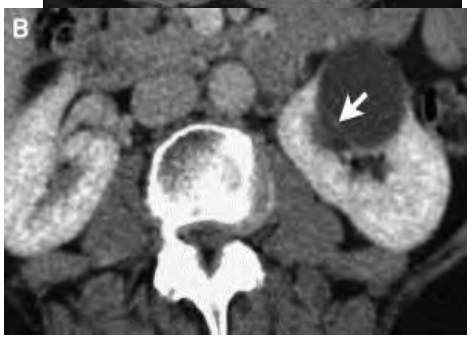
- Films to be taken before and after intravenous contrast injection – So that enhancement can be made out and measured
- An adequate amount of contrast medium is injected (30 to 40gm of iodine)
- Thin section taken through the kidney generally 5mm.

- **Benign or Malignant nature of a complicated renal cyst is based on:**
  - Evaluation of wall of the lesion - its thickness and contour
  - Number, contour and thickness of septa
  - Amount, character and location of any calcification
  - Density of fluid in the lesion
  - Presence of solid components
  - ***Enhancement after contrast administration***



Bosniak I

- Well defined cysts
- Round or oval in shape
- Homogenous
- Water density mass (HU less than 20)
- Thin imperceptible wall
- Does not enhance after administration of contrast injection



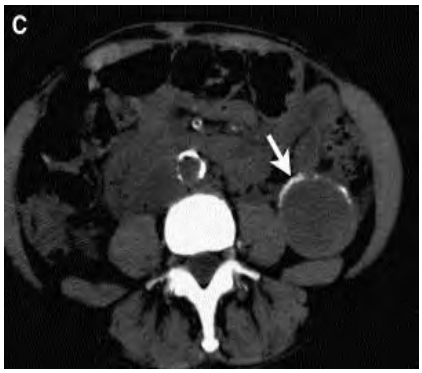
Bosniak II

- Septated cyst
- Minimally calcified cysts (thin and curvilinear)
- Infected cysts
- Hyperdense cysts
- Minimally irregular cysts
- Cluster of cysts
- Perceivable enhancement of septae or wall

- Bosniak (1993) - Revised his original classification system to include a subset of category II lesions to a separate category IIF
- These lesions do not fall into category II because
  - They are more complex

– Do not require surgical exploration because they are thought to be benign - Hence they do not fall in category III

But they do require follow up examination to prove their benignity

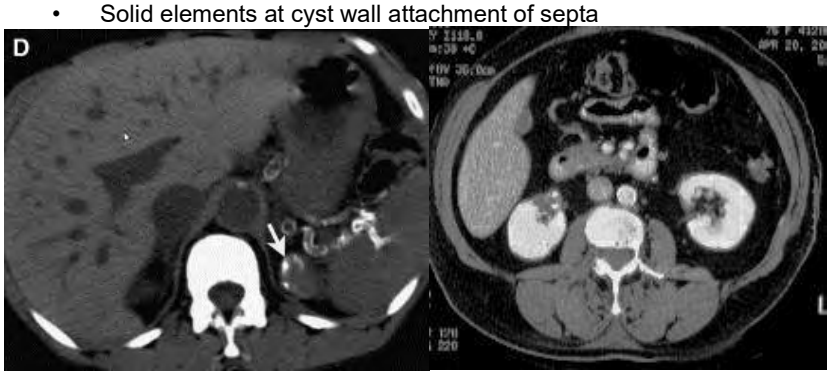


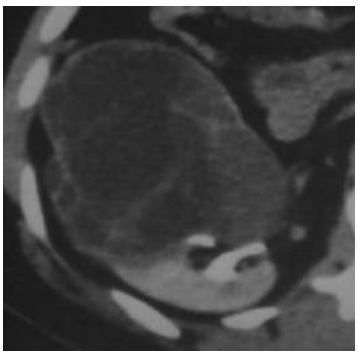
Bosniak II-F

- Increased number of thin (hairline) septa
- Minimal thickening of hairline septa wall
- Mildly thickened or nodular calcification
- Perceptible enhancement of wall or septum
- Non enhancing high attenuation lesions that are 3 cm or larger
- Completely intrarenal cyst

Bosniak III

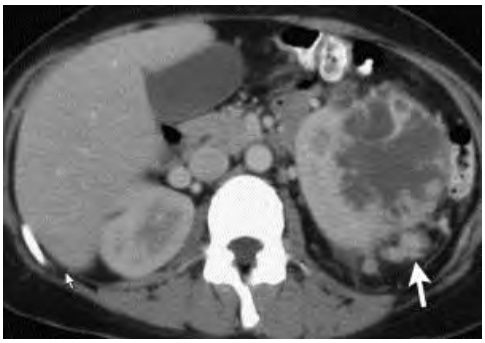
- Multilocular cystic mass
- Irregular, thickened, multiple enhancing septae
- Uniform wall thickening
- Nodular thick or irregular calcification
- Irregular margins
- Small nonenhancing nodular mass
- Solid elements at cyst wall attachment of septa





Bosniak IV

- Irregular wall thickening
- Contains enhancing large nodules or clearly solid components



Risks of malignancy

- Bosniak Category -
  - Category I – 0-2%
  - Category II – 0-5%
  - Category IIF – 5-14%
  - Category III – 45-50%
  - Category IV - >90%

Management

- Principles of management -
  Try to remove least possible number of benign lesions, at the same time remove all malignancies
- Asymptomatic Simple cysts (I) do not require follow-up or treatment
- Complex cysts require either
  - Follow-up (category IIF)
  - Exploration (category III)
  - Excision (category IV)

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Suggested Readings

1. Campbell-Walsh Urology, 10th Edition by Alan J. Wein, Louis R. Kavoussi, Andrew C. Novick, Alan W. Partin, and Craig A. Peters.
2. Campbell-Walsh Urology, 11th Edition by Alan J. Wein, Louis R. Kavoussi, Alan W. Partin, and Craig A. Peters.
3. Smith and Tanagho's General Urology, Eighteenth Edition (Smith's General Urology) by Jack W. Mcaninch, Tom F. Lue

Genitourinary tuberculosis

Madhu Sudan Agrawal, Manoj Sharma

Introduction

Globally, tuberculosis (TB) is a leading cause of death from infectious disease, second only to AIDS. Its impact on the society is huge; also because it affects mainly young adults in their most productive years, with two-thirds of cases estimated to occur among people aged 15-59.

In 2011 there were 8.7 million new cases of TB and 1.4 million deaths (this includes 430,000 deaths among people who were HIV-positive). Incidence of tuberculosis in developing countries is 440 per 10000 population, in developed world the incidence is 13/10000 population. The vast majority of deaths from TB, over 95 percent, are in the developing world.

The genitourinary system is a common site of extra-pulmonary tuberculosis (TB), accounting for 15-20% cases of total extra pulmonary TB.[i] GUTB in developing countries comprises approximately 15-20% of extra-pulmonary cases of TB while in developed world this figure is 8-10%. Approximately 4%–8% of patients with pulm**on**ary **tuberculosis** will develop clinically significant **genitourinary** infecti**on.**

Genitourinary tuberculosis (GUTB) may involve the kidneys, ureter, bladder, or genital organs. Clinical symptoms usually develop 10-15 years after the primary infection. Only about a quarter of patients with GUTB have a known history of pulmonary TB; about half of these patients have normal chest radiography findings. [ii]

Etiology

The most common pathogen associated with TB is *Mycobacterium tuberculosis*.

Uncommonly implicated pathogens include the following:

- *Mycobacterium kansasii*
- *Mycobacterium fortuitum*
- *Mycobacterium bovis*
- *Mycobacterium avium-intracellulare*
- *Mycobacterium xenopi*

Pathophysiology

Generally primary infection is in form of pulmonary tuberculosis. Genito-urinary tract is believed to be involved secondarily, usually after an interval of several years.

Kidney

Tuberculosis may involve the kidney as a part of generalized disseminated infection or as localized genitourinary disease. Kidney is usually infected by hematogenous spread of bacilli from the primary focus of infection.

Multiple granulomas form at the site of metastatic foci. In the kidneys, they are typically bilateral, cortical, and adjacent to the glomeruli and may remain inactive for decades.[iii] Although both kidneys are seeded, clinically significant disease usually develops in only one kidney. The medullary hypertonic environment impairs the phagocytic function.

A single ulcer develops in cortex adjacent to blood vessels. This ulcer breaks into pelvi-calyceal system, spreading the bacilli to the renal pelvis, ureters, bladder, and other genitourinary organs. Depending on the status of the patient's defense mechanisms, fibrosis and strictures may develop with chronic abscess formation. Extensive lesions can result in nonfunctioning kidney. Hypertension in persons with renal TB is twice as common as it is in the general population.

Ureter

Tuberculous ureteritis is always an extension of the disease from the kidney. Ureteral TB develops in about half of all patients with renal TB. Ureteral TB often causes ureteral strictures and hydronephrosis. The commonest site is the lower third of ureter or the uretero-vesical junction. Occasionally, severe cases can cause stricture of virtually the entire ureter. Such type of strictured ureter takes the form of corkscrew or pipe stem ureter. In such patients, the kidney shows extensive disease, is often non-functioning, and may be calcified.

Bladder

Bladder lesions are without exception secondary to renal TB. The earliest forms of infection start around one or another ureteral orifice. It initially manifests as superficial inflammation with bullous edema and granulation. Fibrosis of the ureteral orifice can lead to stricture formation with hydronephrosis or scarification (i.e., golf-hole appearance) with vesicoureteric reflux.

Severe cases involve the entire bladder wall, where deep layers of muscle are eventually replaced by fibrous tissue, thus producing a thick fibrous bladder with progressive reduction of bladder capacity (Thimble bladder)[iv].

Prostate

Prostatic TB is also the result of hematogenous spread, but involvement is rare. In many cases pathologist diagnose it incidentally after TURP. On DRE it feels like a firm granulomatous nodule, and needs to be differentiated from malignacy. Very rarely in acute fulminating cases it spreads rapidly and presents as peri-anal sinus.

Epididymis and testis

The higher frequency of isolated epididymal TB lesions in children favors the possibility of hematological spread of infection, while adults seem to develop tuberculous epididymo-orchitis caused by direct spread from the urinary tract through retrograde route. The formation of a draining sinus is uncommon in developed countries, but epididymal induration and beading of the vas are common.

Involvement of the testis is usually due to direct extension. Infertility may result from bilateral vasal obstruction. Nodular beading of the vas is a characteristic physical finding. Orchitis and the resulting testicular swelling can be difficult to differentiate from other mass lesions of the testes.

Clinical Presenatation

Symptoms

The presentation is often vague, and physicians must have a high degree of awareness to make the diagnosis. Symptoms are generally chronic, intermittent, and nonspecific. Genitourinary tuberculosis (GUTB) often manifests as repeated urinary tract infections that do not respond to the usual antibiotics.

Persons with GUTB rarely display the typical symptoms of TB. The most common symptoms are urinary frequency, urgency, dysuria, suprapubic pain, blood or pus in the urine, and fever. Urinary urgency is unresponsive to all treatment when the bladder is extensively involved.
Gross hematuria occurs in approximately 10% of cases and is usually total and painless. Microscopic hematuria is present in around 50% of cases. Asymptomatic patients are not uncommon. Unexplained infertility in both men and women may be attributable to GUTB.

Examination
Physical examination is typically unremarkable. Renal tuberculosis usually does not present with any positive physical signs. Tender testicular or epididymal swelling, nodularity and beading of the spermatic cord and vas may be the most tell-tale physical signs of genitor-urinary tuberculosis one can find. In late cases, epididymo-cutaneous sinus formations may develop.

Investigations

Lab Studies

- **Tuberculin skin test** results are positive in about 90% of patients, but this finding denotes only prior exposure to mycobacteria rather than active disease.
- Complete blood cell count, sedimentation rate, serum chemistry, and C-reactive protein studies are helpful to assess the severity of disease, renal function, and response to treatment.
- **AFB smear**: Serial early-morning urine collection for acid-fast smear (at least 3) is a specific (89-96%)[v] but less sensitive (approximately 52%) tool.
- **AFB urine cultures** are still considered the criterion standard for evidence of active disease, with sensitivity of 65% and specificity of 100%. Every effort should be made to process the samples immediately after collection. Sending cultures before starting anti-tubercular treatment and adjusting therapy according to sensitivity in case of resistance is always recommended. The following methods are available:
- Solid media: The Lowenstein-Jensen medium yields results in more than 4 weeks.
- Radiometric media: The BACTEC 460 medium yields results in 2-3 days.
- **PCR**: The polymerase chain reaction (PCR) test has been extensively studied and has been proven highly sensitive, specific, and rapid. In various studies, data show sensitivity ranging from 87-100% (usually >90%) and specificity from 92-99.8% (usually >95%). Compare this with cultures (37%), bladder biopsies (47%), and intravenous pyelography (IVP) examinations (88%). Along with an accurate clinical assessment, PCR is the best tool available for avoiding a treatment delay because results are available in only about 6 hours. [vi, vii] The following PCR tests are available with near-equivalent quality:
  i) Genus-specific 16S rRNA PCR test
  ii) Species-specific IS6110 PCR test
  iii) Roche Amplicor MTB PCR test
  iv) Amplified *Mycobacterium tuberculosis* Direct Detection Test (AMDT)
- TB PNA FISH: Fluorescence in situ hybridization (FISH) using peptide nucleic acid (PNA) probes allows differentiation between tuberculous and non-tuberculous mycobacteria in smears of mycobacterial cultures. PNA molecules are pseudopeptides with DNA-binding capacity in which the sugar phosphate backbone of DNA has been replaced by a polyamide backbone.
- Nucleic acid amplification (NAA): Nucleic acid amplification allows both detection and identification of M tuberculosis through enzymatic amplification of bacterial deoxyribonucleic acid (DNA). The most widely used technique is PCR, but transcription mediated amplification (TMA) and strand displacement amplification (SDA) are also commercially used. The sensitivity of this test is higher than that of smear microscopy but it is slightly lower than that of culture techniques. The main advantage of these tests is that they offer quick results, paired with a high level diagnostic accuracy.
- Transcription mediated amplification (TMA). AMPLIFIED MTD (Mycobacterium Tuberculosis Direct) Test: TMA can identify the presence of genetic information unique to M tuberculosis directly from pre-processed clinical specimens. AMPLIFIED MTD Test (Gen-Probe, Hologic) detects Mycobacterium tuberculosis ribosomal ribonucleic acid (rRNA) directly and rapidly, with sensitivity similar to that of culture techniques. The sensitivity of this test is of 96% and its specificity is 100% for M tuberculosis on specimens that are smear-positive for acid-fast bacilli. One other disadvantage of the technique is that positive results are recorded for both viable and dead bacilli.

Imaging Studies
Radiography

- Chest and spine radiographs may show old or active lesions. In 50% of patients, chest radiographic findings are negative.
- Kidney, ureter, and bladder (KUB) radiographs reveal calcifications in the kidney and ureter in approximately 50% of patients. Calcifications are intraluminal, as opposed to

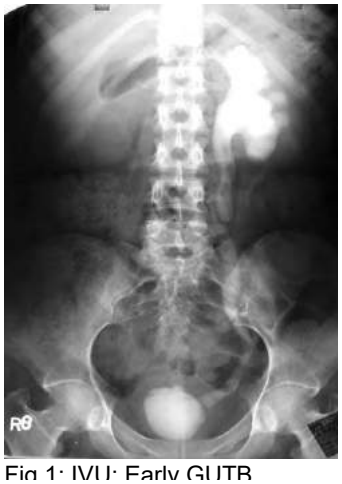
Fig 1: IVU: Early GUTB

schistosomiasis, which produces intramural calcifications. Calcifications in the bladder are uncommon.

Intravenous Urography

- These tests are the standard diagnostic imaging studies for renal TB and have 88-95% sensitivity. They also help define the extent and severity of disease. Approximately 10%–15% of patients who present with active renal **tuberculosis** will have normal urographic findings.[viii]
- The earliest radiographically detectable changes are cavitary lesions that progress to the papilla and invade the collecting system, causing calyceal disruption. Findings of infundibular stenosis and multiple ureteral strictures are highly suggestive of renal TB. Later findings may include calcifications, scarring, stricture formation. Triangular ring like calcificati**on**s within the collecting system are characteristic of papillary necrosis.[ix] A nonfunctioning or extensively diseased kidney indicates irreversible tuberculous disease. A small contracted bladder suggests extensive bladder TB. (Fig 1-2)

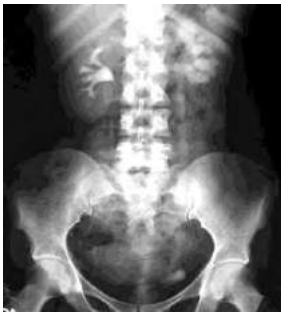
Fig2 IVU: Advanced GUTB

Sonograms

- Ultrasongraphy may reveal cystic or cavitary lesions, cortical scarring, hydronephrosis, and abscess in kidneys; ultrasonography is very sensitive in testicular TB.[x] (Fig 3)
- In recent years, high-resolution transrectal ultrasonography (TRUS) has become a very useful noninvasive technique. TRUS can reveal abnormalities in the seminal vesicles and ejaculatory duct and can help assess the status of the prostate.

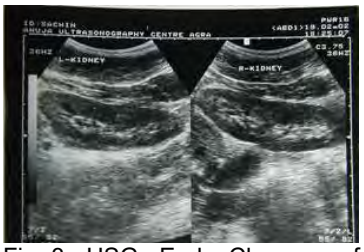

Fig 3: USG: Early Changes of GUTB

CT scan

This imaging test is increasingly being used as the primary modality of investigation in disorders of the genitor-urinary tract. It is a very sensitive investigation, and can detect disease in early stage (Fig 4). It is a useful adjunct to IVP and is helpful in late or advanced disease for assessing the extent of disease[xi] This study is very sensitive for detecting calcification and thickened walls of the ureter and bladder. [xii]

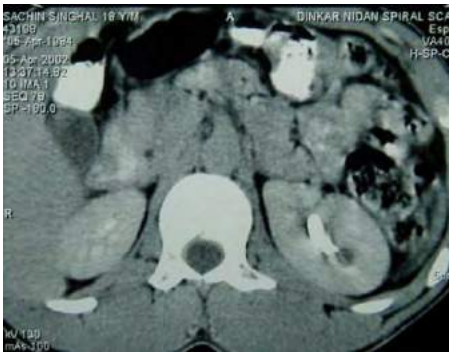
Fig 4: CT: Early Changes of GUTB

Retrograde pyelography is rarely indicated now except in patients with renal failure in whom the kidneys cannot excrete contrast and to evaluate stricture in the upper urinary tract. It also helps for sampling urine from individual kidneys for microbiology.

Diagnostic Procedures

- **Diagnostic Laparoscopy:** The discovery of peritoneal tubercles during tubal ligation is not uncommon in developing countries.
- **Biopsies** of genital ulcers; tubercles in the bladder, especially if scattered away from the ureteric orifice (an uncommon feature of bladder TB); and any lesion with even a slight possibility of malignancy. The yield of biopsy for TB is about 45%.
- **Fine-needle aspiration (FNA**) as a minimally invasive technique plays a prime role in the diagnosis of tubercular epididymitis and epididymo-orchitis. Acid-fast bacilli (AFB) may be detected on FNA smears in up to 60% of these patients.
- **Histology Findings:** Findings include granuloma with central Langerhans cells surrounded by lymphocytes, fibrocytes, and epithelioid cells, which later progress to central caseous formation and varying degrees of fibrosis and calcification

Treatment

Medical Care

Genitourinary tuberculosis (GUTB) responds better to a short course of treatment than pulmonary TB because GUTB carries a lower mycobacterial load. Also, isonicotinic acid hydrazide (INH) and rifampin penetrate well into the cavitary lesions associated with GUTB. A high concentration of INH, rifampin, and pyrazinamide are maintained in urine.

The primary aims of treatment are to preserve renal parenchyma and function, to make the patient noninfectious, and to manage co- morbid conditions. Standard treatment is rifampin, INH, pyrazinamide, and ethambutol for 2

months, then rifampin and INH for 4 more months unless resistance to either agent exists. In cases of resistance to first line drugs, culture and sensitivity reports need to be obtained and the regimen changed if necessary. Aminoglycosides and quinolones are the most commonly used second line / adjunct drugs.
Drug doses:

• INH (Isoniazid)	300 mg PO
• Rifampicin	600 mg PO
• Pyrazinamide	1.5 – 2.5 g PO
• Ethambutol	15 – 25 mg/kg PO
• Streptomycin	15 mg/kg

- In patients who are HIV-positive, continue treatment for a total of 9 months to one year.
- Special considerations apply to patients with impaired renal function. Rifampicin, isoniazid, pyrazinamide, ethionamide, and prothionamide may be given in normal doses because they are either eliminated in the bile or broken down to metabolites. Ethambutol and aminoglycosides should be avoided in these patients.

Steroids
Indications:
- Severe bladder symptoms
- Tubular structure involvement (e.g., ureter, fallopian tubes, spermatic cord)
  High-dose prednisone (i.e., at least 20 mg tid) for 4-6 weeks is recommended because rifampicin reduces effectiveness and bioavailability of prednisone by 66%.

Surgical Care

Although chemotherapy is the mainstay of treatment, surgical intervention, either as ablation or reconstruction, is often required during the course of GUTB. Generally, at least 4-6 weeks of chemotherapy with appropriate agents is first tried if immediate surgery is not necessary. In a recent European series, the overall frequency of surgical management in GUTB in the past 20 years was 0.5% of total urological surgical procedures.

A) Ablative surgery

a) Nephrectomy / Nephro-uretrectomy
Indications
- Non-functioning kidney with or without calcification
- Extensive disease involving whole kidney, with hypertension, UPJ obstruction
- Coexisting renal carcinoma

b) Partial nephrectomy
Indications
- Localized polar lesion containing calcification that has failed to respond after 6 weeks of intensive chemotherapy.
- An area of calcification that is slowly increasing in size and is threatening to destroy kidney.

c) Epididymectomy
Indication: Caseating abscess not responding to chemotherapy

B) Reconstructive surgery

a) **Ureteric stricture:** Reconstructive surgery is required most commonly for stricture of ureter either presenting at the time of initial diagnosis or developing during the course of anti-tubercular treatment due to fibrosis.
Strictures of the lower end of the ureter occur in approximately 9% of patients. If obstruction at the lower end of the ureter is present at the start of chemotherapy, careful observation is required. These strictures may result from edema, and they respond to chemotherapy. The patient should receive chemotherapy and should be monitored by ultrasonography and / or intravenous urograms at regular intervals. Corticosterioids can be added to chemotherapy if there is deterioration or no improvement after 3 weeks.

a) *Endoscopic management*: If there is deterioration or no improvement after a 6-week period, mild strictures in early stages of the disease can be managed by endoscopic means. **Balloon dilatation** and placement of **double J stent** can help resolve the obstruction and give permanent relief in a significant proportion of patients.

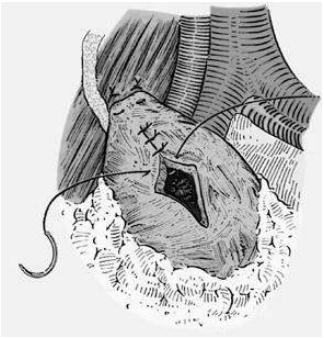
Fig 6: Psoas hitch procedure

b*) Surgical management*: Surgical repair of the stricture is carried out if an initial attempt at dilatation has failed. Since lower third of ureter including the uretero-vesical junction is the most common site of stricture in these cases, **ureteric reimplantation** into the urinary bladder is the most appropriate treatment. This can be done by either trans-vesical **Politano-Leadbetter** submucosal tunneling technique, or the **Lich** extra-vesical approach (Fig 5 a-c). **Psoas hitch** (Fig 6) or **Boari flap** (Fig 7) procedures may be required if the length of ureter is found to fall short for direct uretero-neocystostomy.

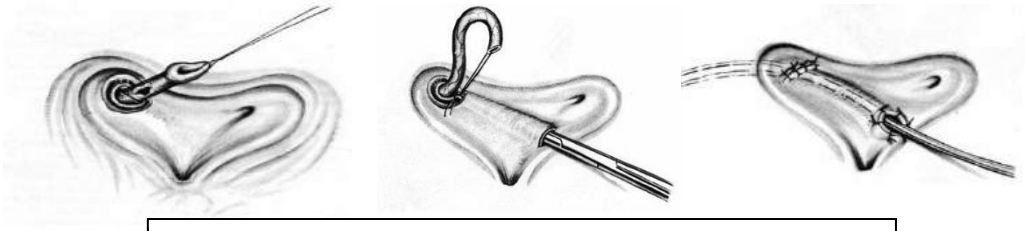

Fig 5 a, b, c : Politano-Leadbetter uretero-neo-cystostomy

For the less common strictures of the middle third of the ureter, excision of the stricture and spatulated end-to end **uretero-ureterostomy** is the first choice (Fig 8 a, b, c). Alternatively, especially in case of difficulty due to short length of ureter, the **Davis intubation ureterotomy** technique should be chosen. The stent should be left in place for at least 6 weeks.

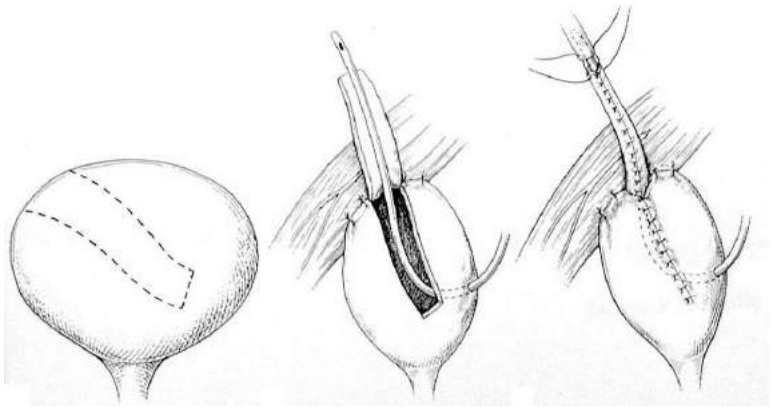

Fig 7 a, b, c : Boari flap procedure

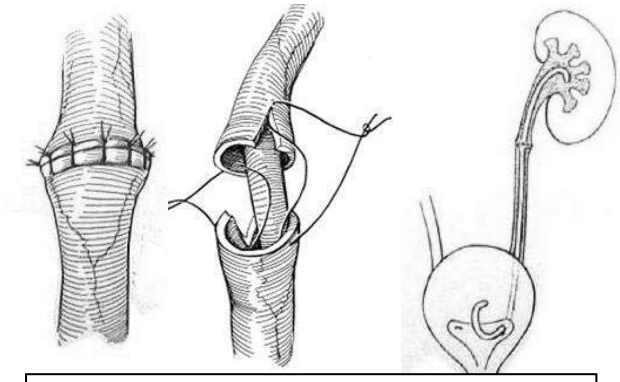

Fig 8 a, b, c : End-to-end Uretero-Ureterostomy

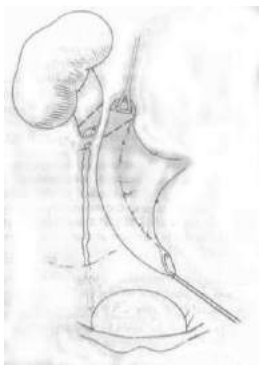

Fig 9: Ileal replacement of ureter

Finally, in patients where the entire length of ureter is strictured, and unsalvageable, the final choice may be **ileal replacement of ureter**, which is done transperitoneally, using a vascularised iso-peristaltic segment of ileum. (Fig 9) The proximal end of this defunctionalised ileal segment is anastomosed to the proximal unobstructed part of ureter or the renal pelvis, and the distal end is attached directly to the urinary bladder.

b) **Augmentation cystoplasty:** In advanced stages, the bladder capacity is severely reduced due to fibrosis, resulting in contracted (thimble) bladder. The patient typically presents with severe frequency of micturition, both day and night, together with pain urgency and hematuria. In early stages, symptoms can be relieved with medical treatment, but once fibrosis is advanced, no relief can be obtained by any medical therapy. The treatment of choice in these cases is augmentation cystoplasty. A vascualrised

segment of terminal ileum or sigmoid colon is defunctionalized, detubularised, and attached to the bivalved urinary bladder to increase its capacity. (Fig 10)

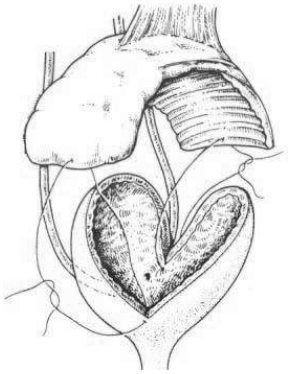

Fig 10: Augmentation cystoplasty

GUTB & Immuno-deficiency *(HIV-Positive Individuals)*

Approximately 10% of all cases of tuberculosis worldwide are HIV related, but in sub-Saharan Africa, the percentage is much higher, as high as 60% in some regions. The incidence is expected to rise in Africa and also in Asia. Tuberculosis was the cause of death in approximately 30% of the 3 million patients who were dying of AIDS in 1999[xiii]. In those who are only mildly immune-suppressed, the disease resembles that in HIV-negative individuals. In the more profoundly immune-suppressed, particularly those with CD4+ T-cell counts of 50/cu.mm or lower, a high viral load, and a negative tuberculin test, the disease often is disseminated and the kidney is involved incidentally with various pathologic manifestations, including granulomatous interstitial nephritis. The incidence of renal involvement may be higher than currently believed. In an autopsy study in India, 24 of 35 kidneys from patients who died of AIDS showed evidence of infection, including 17 cases of tuberculosis. In a similar study in Mexico City, renal disease was demonstrable in 87 of 138 (63%) autopsies on AIDS patients: infection was the cause of the renal disease in 36 cases, with 19 being due to *M. tuberculosis*.[xiv]

GUTB in CA Bladder

An acute mycobacterial cystitis commonly is induced by local instillation of BCG for the treatment of urothelial carcinoma *in situ* and superficial bladder cancer. Usually this causes only a self-limiting, low-grade, superficial cystitis, but sometimes the inflammatory reaction is more severe. Cases of disseminated infection have been recorded, and ureteric involvement with ureteric obstruction was observed in 0.3% cases in a large series [xv]. Renal involvement was found in 0.1% of the 2602 patients in this series, presumably from ascending infection rather than hematogenous spread. Histologically, the lesions caused by BCG are indistinguishable from those seen in classical tuberculosis, and caseation may be present. Organisms may be demonstrated by standard techniques such as Ziehl-Neelsen staining.

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Male Infertility

R.C.M Kaza, Manish Agrawal, Lovenish Bains, Rajesh Arora

Definition

"Infertility is the inability of a sexually active, non-contracepting couple to achieve spontaneous pregnancy in one year"[1] Studies of conception in normal couples reveal that 60% to 75% will conceive within 6 months of unprotected intercourse and 90% by 1 year.

Primary infertility may be defined as inability to conceive after one year of unprotected intercourse. The definition is based on a demonstrated monthly faecundability rate of 20-25% in normal couples attempting pregnancy. Secondary infertility is present when there is history of a conception.

Epidemiology

The World Health Organization (WHO) estimates that 60–80 million couples worldwide currently suffer from infertility.[2] Infertility varies across regions of the world and is estimated to affect 8–12% of couples worldwide.[3,4] The WHO estimates the overall prevalence of primary infertility in India to be between 3.9% and 16.8%.[2] Studies has shown equal prevalence of secondary infertility in India, which is an acquired problem and often preventable and treatable.[5] Estimates of infertility vary widely among Indian states from 3.7% in Uttar Pradesh, Himachal Pradesh and Maharashtra,[6] to 5% in Andhra Pradesh,[7] and 15% in Kashmir.[8] But , it should be kept in mind that these estimates used different definitions of infertility and done in different time , hence direct comparisons between these studies will be difficult. In a 1982–1985 WHO multicenter study, 20% of cases were attributed to male factors, 38% were attributed to female factors, 27% had causal factors identified in both partners, and 15% could not be satisfactorily attributed to either partner.[9] So man may be responsible for 47% of cases either directly or indirectly. In Indian couples seeking treatment, the male factor is the cause in approximately 23%.[8]

Etiology

Male infertility may be attributed following main factors:

- *Infertility of known cause*
  - *Maldescended testes*
  - *Varicocele*
  - *Sperm autoantibodies*
  - *Testicular tumour*
  - *Others*
- *Idiopathic infertility*
- *Hypogonadism*
  - *Klinefelter's syndrome*
  - *Primary hypogonadism of unknown cause*
  - *Secondary (hypogonadotropic) hypogonadism*
  - *Late-onset hypogonadism*
  - *Constitutional delay of puberty*
  - *XX male*
  - *Kallmann syndrome*
  - *Idiopathic hypogonadotrophic hypogonadism*
  - *Residual after pituitary surgery*
  - *Others*
- *Cryopreservation due to malignant disease*
  - *Testicular tumour*
  - *Lymphoma*
  - *Leukaemia*
  - *Sarcoma*
- *Disturbance of erection/ejaculation*
- *Obstruction*
  - *Vasectomy*
  - *Cystic fibrosis*
  - *Others*
- *General/systemic disease*

Diagnostic Evaluation

Prognostic factors for male infertility depend on duration of infertility, primary or secondary infertility, results of semen analysis and age, fertility status of female partner. Early evaluation and management of both partners are mandatory.

History & Physical Examination

Successful diagnosis and treatment of infertility requires a thorough history and physical examination.
Pertinent History in Evaluation of the Infertile Male must follow the following

- Reproductive history
  - Duration
  - Prior conceptions
  - Previous fertility evaluation and treatment
- Sexual history
  - Erectile function
  - Lubricants
  - Frequency/timing of intercourse
- Past history
  - Childhood- Cryptorchidism, Onset of puberty, Testicular Torsion/Trauma, Midline defects (cleft palate)
- Medical history
  - Diabetes mellitus,
  - Neurologic disease (Spinal cord injury, Multiple sclerosis),
  - Infection (Urinary infections, Sexually transmitted disease, Epididymitis/prostatitis, Tuberculosis, Mumps orchitis, Recent viral/febrile illness),
  - Renal disease,
  - Cancer (Chemotherapy/radiotherapy)
- Surgical history
  - Orchidopexy
  - Retroperitoneal/pelvic surgery
  - Herniorrhaphy
  - Vasectomy
  - Bladder neck/prostatic surgery
- Drug history
- Gonadotoxins
  - Environmental exposures (pesticides, heavy metals)
  - Radiation
  - Habits (tobacco, recreational drugs, anabolic steroids)
- Family history
  - Infertility
  - Cystic fibrosis
  - Androgen receptor deficiency

Female Partner history taking

Physical Examination

- General Examination- Body habitus, body hair, temporal pattern balding, gynecomastia, eunuchoid proportions, long exterimities, Thyroid & Liver palpation
- Genital Examination-
  - Penis- curvature, chordee, or hypospadias
  - Testis- size, surface, sensation
  - Epididymides- size, nodularity, Abnormal lesion, tenderness
  - Spermatic cord- Varicocele, vas deferens
  - Rectal examination- Prostrate, Seminal Vesicles

Reproductive history regarding any prior conceptions with his present or prior partner should be obtained to differentiate between primary and secondary infertility as secondary infertility are presumed to have normal embryologic development of their reproductive tract and genetic complement.
Sexual history regarding assessment of erectile and ejaculatory function and use of vaginal lubricants are part of the initial evaluation. A number of commercially available lubricants have been shown to adversely affect sperm motility and sperm DNA integrity. It remains optimal to avoid lubricant use if possible. The timing and frequency of intercourse are important. Intercourse frequency every 2 days near the time of ovulation (can be calculated with ovulation predictor kits, measure midcycle urinary luteinizing hormone surge) maximizes the chance of availability of viable sperm to the oocyte as viability of spermatozoa within the female reproductive tract is between 2 and 5 days in favorable cervical mucus. Too frequent intercourse does not allow replenishment of adequate numbers of spermatozoa within the epididymis, whereas infrequent intercourse may miss the potential window for fertilization.

Childhood history of cryptorchidism can have significant implications on eventual fertility. Undescended testis unilateral or bilateral has a long term impact on the fertility, regardless of the time of orchidopexy. Spermatogenesis tends to be lower with overall poor semen quality. This defect is present in the normally descended testis of a case of unilateral undescended testis. The timing of the onset of puberty may suggest underlying endocrinologic abnormalities. A history of delayed puberty, especially in conjunction with anosmia, is associated with the diagnosis of Kallmann syndrome, or primary hypogonadotropic hypogonadism. On the other hand, precocious puberty may be secondary to congenital adrenal hyperplasia, which may affect future fertility. Testicular torsion or trauma can result in testicular atrophy, as well as the development of antisperm antibodies, which are detrimental to sperm function and motility

Medical history of Diabetes mellitus, spinal cord injuries, and multiple sclerosis exert effects through impairment of both ejaculatory and erectile function. Both hyper and hypothyroidism affects steroid hormone metabolism and sperm quality. Inflammatory diseases can have profound effects on the patency of the genital tract and function of the spermatozoa. Infectious diseases such as prostatitis or sexually transmitted infections such as Chlamydia or Neisseria gonorrhea are associated with elevated seminal oxidative stress and leukocytospermia, resulting in abnormal bulk semen parameters, elevated sperm DNA fragmentation, and reduced fertility. A history of bilateral epididymitis with subsequent azoospermia suggests the possibility of epididymal obstruction. Epididymal granuloma may result from noninfectious diseases such as sarcoidosis or from the sequelae of an active tuberculosis infection. Epididymal sarcoidosis has been associated with azoospermia, which may be reversible with corticosteroid treatments. Although prepubertal mumps is unlikely to have detrimental effects on fertility, mumps occurring in the postpubertal timeframe is associated with unilateral or bilateral orchitis in up to 40% of children with potentially devastating testicular damage. Post pubertal orchitis results in a small and soft testis while prepubertal pathologies cause small and firm testis.

Surgical history of paediatric herniorraphy, scrotal or inguinal surgery might cause injury to the vas deferens. Vasal injuries from inguinal surgery have seen resurgence with the popularity of polypropylene mesh hernia repairs, which can induce dense fibroblastic reactions leading to vassal obstruction. There are now a large number of survivors of testicular cancer who have been exposed to radiotherapy and chemotherapy. If the treatment had occurred less than 5 years ago the affects are likely to be continuing. The recovery time is around 4-5 years. Classic retroperitoneal lymphadenectomy for testicular cancer frequently results in sympathetic nerve injury leading to anejaculation or retrograde ejaculation. Fortunately, with modifications in the surgical template and intentional nerve sparing, ejaculation can be preserved in almost all patients with low-stage disease and in selected patients with more advanced disease. Bladder neck surgery and transurethral resection of the prostate can lead to retrograde ejaculation due to bladder neck incompetence. In selected patients, transurethral incision of the prostate can allow preservation of antegrade ejaculation.

Drug history of Antibiotics including nitrofurantoin, erythromycin, tetracycline, and gentamycin intake may cause direct gonadotoxicity or impair sperm function. Androgen production is inhibited by spironolactone, ketoconazole, and cimetidine. Sulfazalazine are associated with reversible reductions in sperm concentration and motility. α Blockers are associated with retrograde ejaculation, an effect that may be more prominent with tamsulosin than with other selective α blockers. 5-α reductase inhibitors such as finasteride and dutasteride inhibit conversion of testosterone to the metabolically active dihydrotestosterone. Use of these agents has been associated with reductions in semen volume, as well as erectile and ejaculatory dysfunction. Psychotherapeutic medications including the selective serotonin reuptake inhibitors (SSRI), monoamine oxidase inhibitors, phenothiazines, and lithium can suppress the hypothalamic-pituitary-gonadal axis, impair ejaculation and erectile function, and reduce libido.

Gonadotoxins exposure by environmental and occupational factor such as heavy metals, pesticides such as dibromochloropropane, organic solvents, and heat may affect spermatogenesis. Industrial lead exposure exerts direct negative effects on both seminiferous tubules and the hypothalamic pituitary axis, resulting in asthenospermia, oligospermia, teratospermia, and ultimately reduced fertility. Smoking is associated with declines in basic semen parameters such as sperm concentration, viability, forward motility, and morphology, as well as declines in sperm penetration ability and hence fertilization rates. Exogenous testosterone and steroid supplementation can have detrimental effects on spermatogenesis. Androgenic agents induce hypogonadotropic hypogonadism leading to azoospermia, which can last 6 months or more after cessation of the supplements and, on occasion, may be irreversible. Testosterone replacement therapy in hypogonadal men desiring fertility should be avoided, and alternate regimens such as antiestrogens (clomiphene citrate, tamoxiphene) should be considered instead. Marijuana use is associated with gynecomastia, reductions in serum testosterone, decreased sperm counts, and elevated seminal leukocytes. Abnormal sperm morphology, decreased motility, and low sperm concentrations have been associated with cocaine use. Although longterm abuse of alcohol is associated with global suppression of the hypothalamic-pituitary gonadal axis and spermatogenesis, moderate intake is not associated with significant deterioration in fertility.

Family history of cystic fibrosis may suggest the diagnosis of congenital bilateral absence of the vas deferens with its associated vasal, epididymal, and seminal vesicle anomalies. Abnormalities of the androgen receptors should be considered in the setting of a family history of intersex disorders.

Finally, a complete history should also include an assessment of female factor fertility issues because almost two thirds of infertility can be attributed to the female side, either wholly or in combination with male factors. Risk factors for female subfertility include but are not limited to advanced age, irregular menstrual cycles, and a history of pelvic pathology including endometriosis and pelvic infections. Fecundity begins to decline sharply after age 35 and is less than 5% by age 40. Ovulatory dysfunction occurs in 40% of infertile women, accounting for the largest single cause of female infertility.

PHYSICAL EXAMINATION

General Examination

Body habitus provides clues to the adequacy of virilization with androgen deficiency suggested by decreased body hair, absence of temporal pattern balding, gynecomastia, and eunuchoid proportions. Abnormalities in these areas suggest possible endocrinopathies to include low serum testosterone, hyperprolactinemia, abnormalities in the estrogen to testosterone ratio, adrenal dysfunction, and genetic syndromes associated with subvirilization to include Klinefelter syndrome. Low androgen levels at the time of puberty may cause disproportionately long extremities due to delayed closure of the epiphyseal plates. Palpation of the thyroid gland will occasionally disclose nodules suggesting hyperfunction or hypofunction, which can affect fertility. Hepatomegaly on abdominal examination raises suspicion for hepatic dysfunction, which may induce altered sex steroid metabolism.

Genital Examination

Genital examination starts with a careful examination of the phallus. Penile curvature, chordee, or hypospadias may interfere with semen deposition in the vaginal vault. A careful examination of the scrotal contents is the most critical part of the examination. The testes should be examined with the patient in both supine and standing positions in a warm room to assist relaxation of the cremasteric muscle. Testicular size should be assessed with either an orchidometer, calipers, or sonographic measurement. Normal adult testicular measurements have been established to be at least 4 × 3 cm or 20 mL in volume. The epididymides should be carefully palpated for enlargement or induration, which can indicate downstream obstruction or inflammatory conditions such as epididymitis. Granulomatous changes of the epididymis have been associated with tuberculosis, and sarcoidosis. Small cystic lesions of the epididymis are common and are usually spermatoceles, which are often nonobstructing. Papillary cystadenomas are less commonly seen and may present in conjunction with von Hippel-Lindau (VHL) disease. Examination of the spermatic cord in the supine and standing position allows the detection of varicoceles, defined as abnormally dilated scrotal veins. Varicoceles are detected by palpation for assymetry of the spermatic cord, or an impulse, during the Valsalva maneuver. Gentle traction on the testis during this examination can be helpful in more difficult examinations such as patients with high riding testes or exaggerated cremasteric muscle response to Valsalva. Varicoceles are present in 15% of normal males, 19% to 41% in men presenting with primary infertility, and up to 81% of men with secondary infertility. Careful palpation of the vas deferens is also a critical component of the spermatic cord assessment. Inability to palpate the vas deferens is consistent with unilateral or bilateral vasal agenesis. Nodularity of the vas is also observed from prior infections such as tuberculosis. Vasal thickening is associated with prior scrotal surgery or downstream obstructions such as inguinal vasal obstruction, potentially from prior surgery or ejaculatory duct obstruction. Finally, a rectal examination should be performed to evaluate prostatic anatomy for midline cysts such as müllerian duct cysts, which can obstruct the ejaculatory ducts. Prostatic induration or tenderness may be seen in acute or chronic prostatitis. Under normal conditions, the seminal vesicles may not be palpable but may be prominent in the setting of ejaculatory duct obstruction.

INVESTIGATIONS

Laboratory investigations in infertility should be carefully chosen for their simplicity, relevance, cost effectiveness, and most important of all for their noninvasiveness and unobtrusiveness. An infertility couple is psychologically at a very difficult moment of their lives, a victim of both disease and society. So the magnitude of investigation should be carefully calculated.

Semen Examination: This is central to investigation of infertility and is the pivot on which all else moves. It is however not an index of fertility, which is a couple dependant phenomenon. So ideally both the husband and wife should be simultaneously investigated. The adequacy of seminal values is hard to define. However it is possible to state the minimal values below which pregnancy becomes statistically increasingly difficult.
Ejaculate analysis has been standardized by the WHO and disseminated by publication of the WHO Laboratory Manual for the Examination and Processing of Human Semen (5th edn.). It is the consensus that modern spermatology must follow these guidelines.

Lower reference limits (5th centiles and their 95% CIs) for semen characteristics

Parameter	**Lower reference limit**	**(range)**
Semen volume (mL)	1.5	(1.4-1.7)
Total sperm number (10^6/ejaculate)	39	(33-46)
Sperm concentration (10^6/mL)	15	(12-16)

Total motility (PR + NP)	40	(38-42)
Progressive motility (PR, %)	32	(31-34)
Vitality (live spermatozoa, %)	58	(55-63)
Sperm morphology (normal forms, %)	4	(3.0-4.0)

Other consensus threshold values

- pH > 7.2
- Peroxidase-positive leukocytes (10^6/mL) < 1.0
- Optional investigations
- MAR test (motile spermatozoa with bound particles, %) < 50
- Immunobead test (motile spermatozoa with bound beads, %) < 50
- Seminal zinc (µmol/ejaculate) ≥ 2.4
- Seminal fructose (µmol/ejaculate) ≥ 13
- Seminal neutral glucosidase (mU/ejaculate) ≤ 20

CIs = confidence intervals; MAR = mixed antiglobulin reaction NP = non-progressive; PR = progressive.

Frequency of semen analysis

If the results of semen analysis are normal according to WHO criteria, one test is sufficient. If the results are abnormal in at least two tests, further andrological investigation is indicated. It is important to differentiate between the following:

- oligozoospermia: spermatozoa < 15 million/mL;
- asthenozoospermia: < 32% progressive motile spermatozoa;
- teratozoospermia: < 4% normal forms.

Often, all three anomalies occur simultaneously, which is defined as oligo-asteno-teratozoospermia (OAT) syndrome. As in azoospermia, in extreme cases of oligozoospermia (spermatozoa < 1 million/mL), there is an increased incidence of obstruction of the male genital tract and genetic abnormalities.

Collection and Timing: The sample should be collected in a dry widemouthed and sterile container. The semen sample should be examined within 1 hour of production and receipt in the laboratory. Some of the semen parameters can be affected by a delay in assessment. Motility decreases significantly after 2 hours and progressively diminishes afterwards as free radical activity increases. There should be 2 to 7 days of sexual abstinence before collection. Two separate samples at least 7 days apart should be analyzed. The duration of abstinence should be constant, if possible, because each additional day can add as much as 25% in sperm concentration. Lubricants should be avoided because they may interfere with motility results. The method of collection is by masturbation, coitus interruptus or by special condom sheaths devoid of spermicidal jellys. Masturbation is the best method. Coitus interruptus should be discouraged because it often leads to inaccurate results (i.e., the first part of the ejaculate, which contains most of the sperm, may be lost). The glans and the penis should be cleaned with a wet paper towel (soap should be avoided). Some men may not be able to achieve adequate erection and ejaculation. Assistance can be provided to them by oral medications such as phosphodiesterase type 5 inhibitors given 30 to 60 minutes before collection, cavernosal and subcutaneous injections of prostaglandins for patients who have erectile dysfunction, Seminal pouches, Vacuum erection devices, Vibratory stimulation if T8 and above spinal cord lesion, and Rectal probe electro-stimulation.

In order to allow liquefaction and mixing, semen is placed in a 37° C gently shaking incubator for 30 minutes. The semen analysis characteristics can be classified into two groups: macroscopic and microscopic.

Macroscopic Features of Semen Analysis

PARAMETERS	NORMAL VALUES	ABNORMALITIES	CLINICAL SIGNIFICANCE
Ph	7.8	Acidic: <6.5-7	With low volume and noncoagulation: congenital bilateral absence of vas deferens Ejaculatory duct obstruction Partial retrograde ejaculation
Coagulation/ liquefaction	Coagulates and liquefies within 20 minutes at room temperature of 37° C	No coagulation Prolonged liquefaction	Congenital absence of the seminal vesicles Poor prostatic secretions
Color	Whitish-gray; pearl-white	Yellowish color Reddish brown	Jaundice, carotenemia, drugs Haemato-spermia secondary to urethral bleeding or inflammation of the seminal vesicles, exclude genitourinary tumors
Viscosity	4-mm threading	>6 mm No threading	Important when associated with low motility
Volume	2-4 mL	0 (aspermia) <2 mL (hypospermia) >4 mL	Retrograde ejaculation Incomplete collection Partial retrograde ejaculation Short duration of sexual abstinence Prolonged sexual abstinence

Macroscopic Assessment: The specimen usually liquefies within 30 minutes. However, semen obtained from patients with congenital bilateral absence of the vas usually does not form a coagulum and is acidic. Liquefaction is aided by the proteolytic enzyme fibrinolysin, secreted by the prostate. Viscosity and nonliquefaction are two different phenomena often confused. Viscosity relates to the fluid nature of the sample. It is measured by dropping the semen sample into a container using a pipette and observing the length of the thread formed. Measurement of pH is a standard component of semen analysis and is largely determined by the secretions from the seminal vesicles and the prostate. Because the secretions of seminal vesicles are alkaline, acidic pH indicates congenital absence of the vas with the associated seminal vesicle hypoplasia seen in azoospermic patients

Microscopic Assessment

Sperm Agglutination: The microscopic examination starts with the creation of a wet smear by placing a drop of semen on a slide covered with a cover slip and observing it under 1000× magnification. Sperm agglutination, sperm presence, and subjective motility can be assessed by this method.

Count and Concentration: Assessment of sperm concentration (number of sperm per milliliter) and sperm count (number of sperm per ejaculate) is conducted after liquefaction. Azoospermia (absence of sperm) may be the result of abnormal spermatogenesis, ejaculatory dysfunction, or obstruction. Polyspermia (abnormally elevated sperm concentration), although rare, may be caused by a long period of abstinence and is often associated with sperm of poor quality.

Motility. Motility is recognized as the most important predictor of the functional aspect of spermatozoa. Sperm motility is a reflection of the normal development of the axoneme and the maturation that it undergoes within the epididymis. The sperm motility is graded according to the WHO as follows: A—Rapid forward progress motility; B—Slow or sluggish progressive motility; C—Nonprogressive motility; and D—Immotility. The cutoff value for normal is 50% grade A+B or 25% grade A motility.

Morphology: Sperm morphology is the most subjective and most difficult-to-standardize semen parameter. Normal sperm possess an oval head with a well-defined acrosomal region composing 40% to 70% of the head area. The dimensions of the head are 4 to 5.5 µm in length and 2.5 to 3.5 µm in width. The normal sperm are free from head, midpiece, or tail defects. Sperm morphology is expressed as percentage of abnormal forms present in the semen.

Nonsperm Cells. Several nonsperm elements noted on seminal microscopic examination are immature germ cells, epithelial cell, and leukocytes. Epithelial cells when present in high numbers are indicative of poor collection. Leukocytes are the most significant nonsperm cellular elements in the semen and are a frequent finding in patients who have unexplained infertility. The WHO has defined leukocytospermia as levels above 1×10^6 WBC/mL.

Computer-Assisted Sperm Analysis: Computer-assisted sperm analysis (CASA) is a semiautomated technique that provides data on sperm density, motility, straightline and curvilinear velocity, linearity, average path velocity, amplitude of lateral head displacement, flagellar beat frequency, and hyperactivation. It has two distinct advantages over traditional manual analyses: high precision and quantitative assessment of sperm kinematics. Although this technology has theoretic advantages, it has not translated into benefits in clinical practice.

Limitations of Semen Analysis: Although the semen analysis is used as a surrogate measure of a man's fertility potential, it is not a direct measure by any means. Clinical research has shown that normal semen analysis may not reflect defects in sperm function (idiopathic infertility), and men with poor sperm parameters still may cause spontaneous pregnancies.

Sperm Function Assessment

Sperm-Mucus Interaction/Postcoital Test

Cervical mucus is a heterogenous fluid that is composed of 90% water. In order to reach the site of fertilization, the spermatozoon must be able to successfully traverse the cervix and the cervical mucus. The cervical mucus is shown to demonstrate cyclical changes in consistency and to be highly receptive around the time of ovulation. Increase in penetrability is often observed one day before the LH surge. Cervical mucus has been shown to protect the spermatozoa from the hostile environment of the vagina.

This test can assess cervical environment as a cause of infertility. Accurate timing is crucial. In this test, cervical mucus is examined 2 to 8 hours after normal intercourse. Progressively motile sperm greater than 10 to 20 per HPF is designated as normal. Poor-quality semen most likely will have poor PCT. Therefore
it is not recommended routinely for men who have abnormal semen analyses.

Acrosome Reaction
The Acrosome is a membrane-bound organelle that covers the anterior two thirds of the sperm head. Acrosome reaction is an important prerequisite for successful fertilization. It is an exocytotic event that involves fusion of outer acrosomal membrane and sperm plasma membrane, which enables the exposure of acrosomal contents through the formation of vesicles. Acrosome reaction testing is not widely practiced in laboratories and only remains a research interest.

Sperm Penetration Assays/Sperm

Zona Binding Tests
The sperm penetration assay (SPA) or the hamster egg penetration assay (HEPT) determines the functional capacity of the spermatozoa necessary to fertilize an oocyte. The assay is performed by incubating zona-free hamster oocytes in sperm droplets for 1 to 2 hours. The oocytes are examined microscopically for sperm penetration. Normally, 10% to 30% of ova are penetrated (WHO, 1999).

Advanced Semen Testing

Antisperm Antibody Testing
The tight Sertoli-cell junctions provide the testis with a barrier that prevents the immune system from coming in contact with the post-meiotic germ cells. However, in certain conditions such as testicular torsion, vasectomy, and testicular trauma, this unique barrier can be violated, resulting in an immune response to sperm, displayed as antisperm antibodies (ASABs). These antisperm antibodies can be several types—sperm agglutinating, sperm immobilizing, or spermotoxic. Acceptable normal values by WHO (1992) standards include less than 10% (IgG MAR (mixed antiglobulin reaction)) or 20% (Immunobead Test (IBT), which measures IgG, IgA, and IgM) of spermatozoa with adherent particles. Clinical implications of ASA on male infertility are varied. A weakly positive IgG MAR/IBT in men who have low motile sperm rules out immunologic factors, and no further testing is necessary

Electron Microscopy
Spermatozoa may test positive for viability even in the presence of ultrastructural defects. Ultrastructural details of the sperm can only be seen under the electron microscope (EM). Patients who have low sperm motility (<5% to 10%) with high viability (as determined by HOST or Eosin-Nigrosin staining) and density may be appropriate candidates for EM assessment.

Biochemical Tests
Acrosin is a serine protease-like enzyme that exhibits a lectin-like carbohydrate binding activity to the zona pellucida glycoproteins. Low acrosin activity has been associated with low sperm density, motility, and poor normal morphology. Zinc is necessary for chromatin stability and decondensation, as well as for head–tail detachment during fertilization. It is measured by colorimetric methods with a reference value of 13 mmoL per ejaculate. Reports on the effects of zinc in sperm function and semen parameters are quite conflicting. Dietary supplementation of zinc did not improve semen variables. The seminal vesicles contribute to the bulk of seminal fluid that serves as the transport medium for sperm and contribute to the nutrition in the form of fructose. L-carnitine is secreted by the epididymis and is concentrated in the seminal plasma at up to 10 times the serum levels. It has a role in sperm maturation. The levels of carnitine can possibly serve as indicators of the level of obstruction in the ductal system. Alpha glucosidase, tested by fluorimetric methods, has been used to distinguish nonobstructive from obstructive azoospermia. It is used as a specific marker for epididymal function and is believed to play a role in sperm maturation in the epididymis.

Patterns of Endocrine Testing by Diagnosis

DIAGNOSIS	FSH (mIU/mL)	LH (mIU/mL)	TESTOSTERONE (ng/dL)
Normal	Normal	Normal	Normal
Obstruction	Normal	Normal	Normal
Primary Testicular Failure Histology			
Hypospermatogenesis	High	Normal or high	Normal or low
Germinal cell aplasia	Very high	High	Low
Maturation arrest	Normal	Normal	Normal
Klinefelter syndrome	Very high	High	Low
Hypogonadotropic Hypogonadism	Low	Low	Low

FSH, follicle-stimulating hormone; LH, luteinizing hormone.

Endocrine
Endocrine evaluation in men with (1) an abnormally low sperm concentration, especially if less than 10 million/mL; (2) impaired sexual function; or (3) other clinical findings suggestive of endocrinopathy such as marked reduction in testicular size or gynecomastia. Initial endocrine evaluation in those with indications for testing should include serum follicle-stimulating hormone (FSH) and morning serum testosterone measurements.

Morning specimens are preferred due to a normal physiologic decline in testosterone and gonadotrophin levels throughout the day.

Hyperprolactinemia is usually associated with low serum testosterone often without associated increases in LH levels, suggesting that the hypothalamic-pituitary axis is unresponsive in the setting of elevated serum prolactin levels. Prolactin tests should be repeated due to marked physiologic variability in serum prolactin levels. Mild serum prolactin elevations (<50 ng/ mL) may be seen with medications, stress, and renal insufficiency or may be idiopathic. However, if the prolactin level is persistently elevated, a pituitary tumor such as a prolactinoma should be ruled out with a focused neurologic examination including visual field testing and magnetic resonance imaging of the pituitary fossa. Estrogen excess may be manifested by gynecomastia, decreased libido, erectile dysfunction, and low serum testosterone levels.

On rare occasions, endocrinopathies involving adrenal or thyroid functions may present with male subfertility. Patients with congenital adrenal hyperplasia (CAH) present with a history of precocious puberty and short stature due to premature closure of the epiphyseal plates. The common variant involving 21- hydroxy deficiency will have elevated serum levels of 17- hydroxyprogesterone and urinary pregnanetriol. Although CAH patients may retain fertility, many will have reduced testicular function due to suppression of gonadotropin levels from direct feedback inhibition of the pituitary from the excessive adrenal androgens.

Genetic Testing
Genetic testing is important for establishment of the etiology of infertility, identification of potential future medical issues for the patient, prediction of therapeutic efficacy from various fertility interventions such as varicocele repair and sperm retrieval, and counseling information to couples regarding transmission risk to offspring. Clinically relevant genetic testing for the infertile male include karyotype and y-linked microdeletion assessment, which are used for evaluation of both nonobstructive azoospermia (NOA) and severe oligospermia, as well as the cystic fibrosis transmembrane conductance regulator (CFTR) gene, which is assessed in men with obstructive azoospermia due to CBAVD

RADIOGRAPHIC EVALUATION

Radiographic evaluation of the infertile male focuses on identification of patients with genital tract obstruction in the vas deferens or ejaculatory duct, as well as ruling out associated pathologies in certain individuals such as testicular masses or renal anomalies.

Transrectal Ultrasonography

TRUS provides excellent definition of the prostate, seminal vesicles, ampulla of the vas deferens, and the ejaculatory ducts. TRUS is primarily employed to examine patients suspected to have ejaculatory duct obstruction (EDO). These patients usually have lowvolume azoospermia (volume <1 mL) with acidic pH and negative semen fructose. TRUS typically employs the 5- to 7-MHz endocavitary probe with scanning in both the longitudinal and transverse planes. Although not always present with ejaculatory duct obstruction, seminal vesicle width in excess of at least 12 to 15 mm or ejaculatory duct diameter greater than 2.3 mm is considered suggestive of obstruction. Seminal vesicle aspiration using a 20-gauge needle at the time of TRUS has been used to further increase the specificity of the diagnostic techniques. Findings of three or more sperm per HPF in the seminal vesicle aspirate support the diagnosis of EDO. Seminovesiculography using transrectal injection of radiopaque contrast (50% renograffin) into the seminal vesicles under TRUS guidance with postinjection radiographs can provide excellent anatomic detail of the seminal vesicles and ejaculatory ducts. Seminal vesicle chromotubation is a variation of seminovesiculography using the injection of dilute indigo carmine or methylene blue (1:5 dilution with saline) into the seminal vesicles via TRUS guidance followed by cystoscopic inspection of the ejaculatory ducts in the prostatic urethra to confirm patency.

Scrotal Ultrasonography

Scrotal ultrasound for the infertile male is primarily used to confirm the presence of clinical varicoceles. Although clinical varicoceles do not require confirmation with ultrasound examination, color Doppler ultrasound may be required when the clinical examination is difficult due to body habitus or when the examination is equivocal. Demonstration of reversal of venous blood flow with the Valsalva maneuver or spermatic vein diameters of 3 mm or greater support the diagnosis of varicocele. Scrotal ultrasound is not recommended for screening for subclinical varicoceles. In addition, ultrasound examination provides excellent anatomic details of the epididymis and testis, potentially disclosing a number of conditions that may affect fertility. Testicular germ cell tumors, Testicular microlithiasis can be detected.

Abdominal Ultrasonography

Abdominal ultrasound imaging in the infertile male is primarily indicated to rule out associated renal anomalies in patients with vasal agenesis.

Vasography
Vasography remains the gold standard test for assessing the patency of the male ductal system. Although procedures such as TRUS, seminal vesicle aspiration, and seminal vesiculography offer minimally invasive imaging to diagnose obstruction, properly performed vasography provides unequalled anatomic detail of the vas deferens, seminal vesicles, and ejaculatory ducts.
Absolute indications for vasography are:

1. Azoospermia
2. Normal testicular biopsy with normal spermatogenesis
3. Atleast one palpable vas.

Vasography is ideally performed at the time of anticipated reconstruction due to the potential to cause vasal scarring at the vasogram site. Either a puncture or vasotomy technique may be used to inject contrast into the vas deferens. The following possibilities exist once the vas deferens is opened and presence of sperm is looked for.

1. The vasal fluid may be rich in sperms and the vas itself may be dilated. This is suggestive of ejaculatory duct obstruction or distal vasal obstruction.
2. The vasal fluid may have no sperms suggestive of epididymal obstruction.
3. There may be thick white fluid with no sperms suggestive of ejaculatory duct obstruction with secondary epididymal obstruction.

Vasography can be achieved by one of the methods as under:

1. Intravasal injection of radiographic contrast which is rarely indicated.
2. Injection of Methylene blue with catheterisation of bladder. The dye will efflux into bladder via the ejaculatory duct if the vas and the ejaculatoey duct is patent.
3. Injection of 30 cc of plain saline.If the saline goes in freely than it is unlikely that any obstruction to vas exists.
4. The puncture technique

The puncture technique is preferred if possible because it avoids a full-thickness vasotomy, which necessitates subsequent microsurgical closure, although it is technically more difficult to enter the vasal lumen than with the vasotomy method. With the puncture procedure, a 30-gauge lymphangiogram needle is inserted directly into the proximal vas lumen and contrast is injected in an antegrade fashion. Alternatively, a microsurgical scalpel may be used to make a hemivasotomy incision through the anterior wall of the vas deferens to expose the vasal lumen and allow placement of a 25-gauge angiocatheter for contrast injection. This techique allows examination of the intravasal fluid for presence of sperm to confirm epididymal patency. If a hemivasotomy technique is used for the vasogram, the vas will require reconstruction at the end of the procedure with 9-0/10-0 nylon interrupted sutures using standard microsurgical technique. Once the vasal lumen has been intubated, 5 to 10 mL of full- or half-strength contrast (Renografin) is injected in an antegrade fashion. Retrograde injection is not recommended due to the potential for subsequent epididymal scarring or obstruction.

Vasography with contrast material is most useful when characterising obstructions proximal to the internal ring. For eg. ejaculatory duct obstruction, Mullerian cysts and distal vasal obstructions.

Transrectal vasography and seminal vesciculography
Transrectal ultrasonography will reveal midline leisons(cysts) or dilated seminal vesicles. These can be aspirated with fine needles under the guidance of ultrasonography. Aspirate is examined for the presence of sperms. Further, Methylene blue can be injected into this cyst/dilated seminal vesicle and a transurethral resection of a midline cyst can be done. The efflux of methylene blue from the site of resection will prove its completeness.
Aspirate from seminal vesicles/ Midline cyst can be cryopreserved for future IVF or ICSI (Intracytoplasmic sperm injection) in case surgery fails. This technique obviates the necessity to explore scrotum in case of transrectally accessible lesions.

Venography
Venography of the internal spermatic veins has been used to diagnose and treat varicoceles. As a diagnostic test, venography is arguably the most sensitive imaging modality but specificity remains its limitation. Although nearly 100% of clinical varicocele patients will demonstrate reflux on venographic examination, left internal spermatic vein reflux has been reported in up to 70% of patients without a palpable varicocele. Because of the high false-positive rate and the invasive nature of the test, venography is not indicated for routine screening in the subfertile male. It does have utility in patients with presumed postvaricocelectomy recurrence both for confirmation of the diagnosis and embolization of persistent vessels. Percutaneous embolization of varicoceles has been described using deployed coils, balloons, and sclerotherapy as a second-line therapy in cases of recurrence.

Testicular Biopsy
Testicular biopsy has two roles in the management of male infertility:

1. diagnostic for the differentiation of obstruction from nonobstructive testicular pathology

2. therapeutic for sperm harvest with the intention of use for ICSI.

Diagnostic testicular biopsy is primarily indicated for evaluation of the azoospermic patient presenting with a clinical picture suggestive of obstruction to include normal testicular size and consistency and normal serum FSH levels. Unilateral testicular biopsy is usually sufficient to assess the azoospermic patient for obstruction. Bilateral biopsy may be performed if there is suggestion of asymmetric pathology such as unilateral testicular failure from a situation such as cryptorchidism and contralateral obstruction such as from prior inguinal surgery with vasal injury. Testicular biopsy specimens should be placed in specific solutions such as Bouin's, Zenker's, or buffered glutaraldehyde because the normal formalin tissue preservative will introduce distortion artifacts into the specimen.

Normal
More than 85% of testicular volume consists of seminiferous tubules made up of progressively maturing germ cells and their supporting Sertoli cells. Blood vessels and Leydig cells in the interstitial areas provide the rest of the cellular complement. Spermatogenesis proceeds in an orderly fashion from spermatogonia along the basement membrane to spermatocytes and finally mature spermatozoa adjacent to the tubular lumen. In the setting of azoospermia, a normal testicular biopsy is considered pathognomonic of ductal obstruction.

Hypospermatogenesis
Hypospermatogenesis is associated with reduced numbers of all germ cells, but all stages of spermatogenesis remain present in the histologic section .The degree of reduction determines whether the patient is oligospermic or azoospermic. A critical level of sperm production is required before sperm can be detected in the ejaculate, accounting for the common observation of hypospermatogenesis in the azoospermic patient.

Maturation Arrest
As the name suggests, maturation arrest involves a block of sperm maturation at a specific stage anywhere along the path of spermatogenesis. Maturation arrest most commonly occurs at the primary spermatocyte or late spermatid stages. Complete maturation arrest will produce azoospermia, whereas patients with partial maturation arrest may present with severe oligospermia.

Germinal Aplasia
Germinal aplasia, also called Sertoli cell-only syndrome, has small seminiferous tubules that are completely devoid of germ cells. The interstitial component, as well as the Sertoli cells and basement membranes, are normal. The diagnosis of germinal aplasia is suggested in an azoospermic patient with small-volume testes and elevated levels of FSH consistent with primary testicular failure.

End-Stage Testes
Thickened basement membranes, tubular and peritubular sclerosis, and absence of both germ cells and Sertoli cells are characteristic histologic findings for end-stage testes. These patients will have azoospermia with profoundly small, soft testes (2- to 3-mL volume). This is characteristic of KS, but may be seen with cryptorchid testes.

DIAGNOSIS AND TREATMENT OF MALE INFERTILITY

The goal of the infertility evaluation is to cause a successful pregnancy in the safest, most natural, expeditious, and costeffective manner possible. Although advanced ART technologies such as ICSI are helpful tools in the armentarium for the management of infertility, all attempts should be made to correct underlying male factor etiologies before proceeding with these treatments.

Semen Parameter

Azoospermia: Azoospermia is defined as the absence of sperm in the ejaculate and is identified in 10% to 15% of infertile males. Before proceeding with further diagnostic procedures, the diagnosis of azoospermia should be confirmed with at least two centrifuged semen specimens to rule out severe oligospermia. Causes of azoospermia fall into three general categories: pretesticular, testicular, and post testicular. Pretesticular causes, also called secondary testicular failure, are usually endocrine in nature and relate to either congenital (Kallman syndrome) or acquired hypogonadotropic hypogonadism. Testicular etiologies, broadly termed as primary testicular failure, are intrinsic disorders of spermatogenesis. Direct testicular pathology may derive from genetic abnormalities such as Y-chromosome microdeletions or chromosomal abnormalities, varicocele-induced testicular damage, gonadotoxic effects from medications or environmental exposures, and idiopathic infertility, which constitute the majority. Ejaculatory dysfunction or obstruction of the genital tract account for the post-testicular pathologies, which constitute 40% of cases of azoospermia. Pretesticular and post-testicular causes are often amenable to treatment, which may restore fertility, whereas the success rates for intervention in testicular pathology are much more modest. Although both primary and secondary testicular failure will be associated with marked reduction in testicular volume, these entities can be distinguished by serum endocrine testing to include FSH, LH, testosterone, and prolactin levels. High serum FSH levels, typically greater than two times normal, are indicative of primary testicular failure, and diagnostic testicular biopsy is not required to rule out

obstructive etiologies. Primary testicular failure in conjunction with azoospermia, commonly termed nonobstructive azoospermia (NOA), is best managed with testicular sperm harvest for eventual ICSI. Obstructive azoospermia accounts for 40% of cases of azoospermia A normal testicular biopsy is pathognomonic for genital tract obstruction. If these patients desire restoration of patency, they will require scrotal exploration and vasography at the time of planned reconstruction to identify the site of obstruction. Genital tract obstruction may occur anywhere along the sperm transport system to include the rete testis, efferent ductules, epididymis, vas deferens, or ejaculatory ducts. Obstruction at the level of the epididymis or vas deferens may be successfully treated with microsurgical reconstruction, either vasoepididymostomy for epididymal obstruction or vasovasostomy for vasal obstruction. Elective vasectomy remains the leading cause of obstructive azoospermia and subsequent infertility. In the absence of prior injury to the vas either intentionally from vasectomy or iatrogenic injury of inguinal vas from hernia repair, most men with idiopathic ductal obstruction will be obstructed at the level of the epididymis. Epididymal obstruction may be due to prior trauma, infection, or the result of downstream vasal obstruction from an elective vasectomy. Although vasectomy usually results in a single obstructive site, the development of high intraluminal pressures after a vasectomy can result in rupture of the delicate epididymal tubule with secondary obstruction in the epididymis. Epididymal obstruction rarely occurs within 4 years of a vasectomy but is present in more than 60% of patients on one or both sides after 15 years of vasal obstruction. The absence of proximal vasal fluid or thick, viscous, pastelike fluid is indicative of a concurrent epididymal obstruction and such patients will require a vasoepididymostomy for their reconstruction. The outcome of reconstruction in vasectomized men depends on a number of factors including the obstructive interval, the quality of the fluid from the proximal vas at the time of surgery, and the surgeon's microsurgical experience. Azoospermia in conjunction with low semen volumes and palpable vas deferens is most likely caused by ejaculatory duct obstruction (EDO), although rarely, ejaculatory dysfunction can cause a similar presentation. Disorders of ejaculation such as retrograde ejaculation will more frequently cause oligospermia in conjunction with low semen volume and are readily diagnosed by the presence of sperm in a postejaculation urine specimen. The diagnosis of EDO is suggested by low semen volume with acidic pH and absent semen fructose. TRUS will often reveal midline prostatic cysts, dilated ejaculatory ducts, or dilated seminal vesicles (>1.5 cm in width), and seminal vesicle aspiration may producelarge numbers of sperm. Ultimately, EDO may be confirmed by vasography at the time of planned transurethral resection of the ejaculatory ducts (TUREJD) to relieve the obstruction.

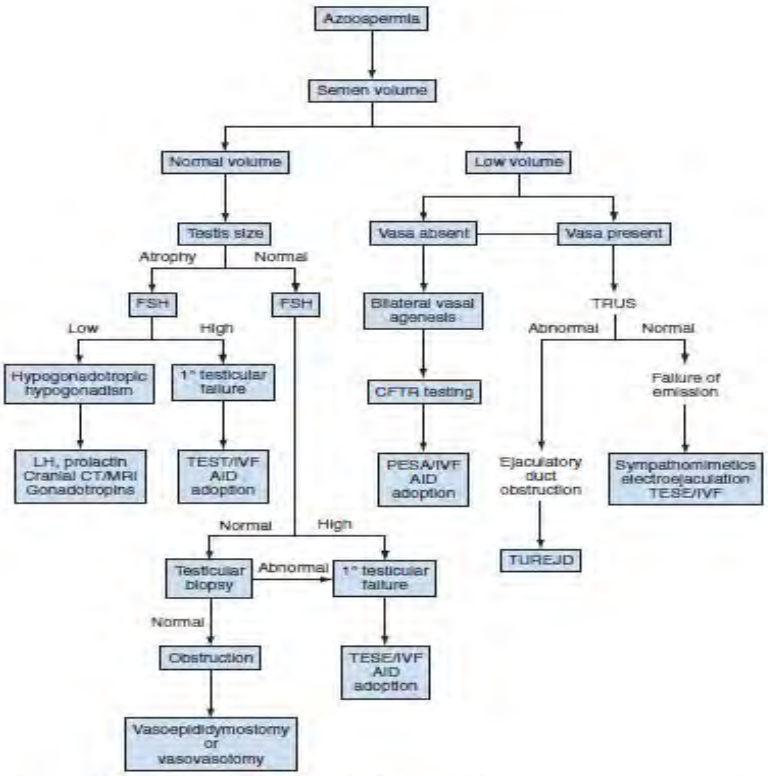


Figure 23–8. Algorithm for evaluation and treatment of azoospermia. AID, artificial insemination by donor semen; CFTR, cystic fibrosis transmembrane conductance regulator; CT/MRI, computed tomography/magnetic resonance imaging; FSH, follicle-stimulating hormone; IVF, in-vitro fertilization; LH, leuteinizing hormone; PESA, percutaneous epididymal sperm aspiration; TESE, testicular sperm extraction; TRUS, transrectal ultrasound; TUREJD, transurethral resection of the ejaculatory ducts.

Oligospermia: Oligospermia is defined as a sperm density of less than 20 million/mL. Oligospermia is rarely seen as an isolated seminal abnormality but is usually associated with disturbances in motility and morphology. Endocrinopathies are rarely observed in patients with concentrations higher than 10 million/mL. Testis biopsy is not indicated in the setting of mild to moderate oligospermia, although it can be considered in patients with sperm

concentrations under 1 million/mL in whom ductal obstruction is considered on the basis of history or physical examination findings.

Seminal Quality Abnormalities: Asthenospermia may be iatrogenic from delayed processing in the laboratory or may be due to a prolonged abstinence period. Persistent asthenospermia in a properly processed specimen, while often idiopathic, may be seen in association with varicoceles, genital tract infections, ultrastructural cilia abnormalities such as immotile cilia syndrome, and immunologic infertility in association with antisperm antibodies. Abnormal sperm morphology has not been correlated with recurrent spontaneous miscarriages or abnormalities in offspring. Relative acidity of the seminal pH and low semen fructose suggest absence of seminal vesicle contribution to the semen, pointing to either CBAVD or EDO as lead possible causes of subfertility.

Normal Bulk Semen Parameters: Up to 50% of men presenting for an infertility evaluation will have normal bulk semen parameters, representing a particularly difficult population to be assigned an etiology for subfertility and reinforcing the inherent inability of standard semen analyses to assess sperm function. In these couples, particular attention should be given to identifying occult female factor fertility issues, as well as assessing coital frequency to optimize reproductive timing for conception. On occasion, antisperm antibodies in the cervical mucus may inhibit sperm motility in vivo and prevent fertilization.

VARICOCELE

Varicoceles represent the most common attributable cause of primary and secondary infertility in the male. Varicocele treatment remains the most commonly performed surgery for the correction of male factor subfertility. Varicoceles have been attributed to turbulent venous flow related to the right angle insertion of the left testicular vein into the left renal vein, an explanation supported by the left-sided predominance of these lesions. In addition, incompetent or absent venous valves in the gonadal veins allow retrograde reflux of blood into the scrotum with the standing position. Venous pooling from a varicocele produces elevated intrascrotal temperature resulting in reductions in testosterone synthesis by Leydig cells, injury to germinal cell membranes, altered protein metabolism, and reduced Sertoli cell function. It has also been suggested that free reflux of renal and adrenal metabolites from the left renal vein are directly gonadotoxic. Other proposed mechanisms for varicocele induced subfertility include impaired venous drainage with resulting hypoxia, poor clearance of gonadotoxins, and elevated levels of oxidative stress. The various methods of varicocele treatment all involve ligation or occlusion of dilated gonadal veins. Surgical ligation has been approached through retroperitoneal, inguinal, and subinguinal dissection, whereas embolization is a radiologic procedure. The most current guidelines in 2008 by the Best Practice Committee of the American Society for Reproductive Medicine recommend treatment of a varicocele in the infertile patient when all of the following conditions are met: (1) varicocele is palpable on physical examination; (2) the couple has known infertility; (3) the female partner has normal fertility or a potentially treatable cause of infertility; and (4) the male partner has abnormal semen parameters or abnormal results from sperm function tests. Patients with subclinical varicoceles are not candidates for varicocele treatment due to a lack of demonstrated efficacy in this population. On occasion, large varicoceles will produce clinical symptoms such as dull hemiscrotal discomfort or sense of heaviness and these patients will benefit from varicocele treatment. Adolescent males with unilateral or bilateral clinical varicoceles and ipsilateral testicular hypotrophy are also candidates for varicocele repair. In the absence of testicular growth retardation, adolescents with varicoceles should be followed with annual testicular size assessments, as well as semen analysis if possible to assist early identification and intervention of varicocele-induced testicular damage. Spontaneous pregnancy rates after varicocele treatment have been reported to average between 30% and 50% in the larger series with pregnancies occurring at an average of 8 months.

CRYPTORCHIDISM

It is important to distinguish cryptorchid testes from retractile testes, a condition involving hyperactive cremasteric muscles causing the testis to periodically reside in the inguinal canal or high scrotum. Although retractile testes have been associated with depressed spermatogenesis, more severe reductions in semen quality have been identified in cryptorchid patients. Cryptorchidism is reduced testicular size and sperm concentration, as well as reductions in serum inhibin and elevations in serum FSH levels.

Suggested mechanisms for cryptorchidism-induced subfertility include testicular dysgenesis, impaired endocrine axis, immunologic damage, and obstruction. Controversies remain as to the exact effect on fertility from unilateral versus bilateral cryptorchidism and the protective effect and timing of orchidopexy. Unilateral cryptorchidism may be associated with modest or no significant impact on fertility. The level of the cryptorchid testis is predictive of spermatogenic impairment with germinal cell aplasia found in 20% to 40% of inguinal testes versus 90% of intraabdominal testes. Epidemiologic study comparing fertility in men with either unilateral or bilateral cryptorchidism versus age-matched controls reported paternity rates of 89% in unilateral cryptorchidism, 93% in age-matched controls, and 65% in patients with a history of bilateral cryptorchidism. Some studies have suggested that orchiopexy at younger ages, typically younger than 4 years of age, is associated with improved fertility outcomes, although the question still awaits large longitudinal studies.

Peripheral Vascular Disease

Lovenish Bains, Rajdeep Singh

Background & prevalence

Peripheral vascular disease (PVD) “a silent assassin” termed by an author is living up to its reputation by the increasing number of cases. Peripheral vascular disease (PVD is a nearly pandemic condition that has the potential to cause loss of limb or even loss of life. This disease spares no nation, the true burden of PVD is most likely underestimated. Longer life expectancy, as well as changing lifestyles, appears to be driving this steep rise in PAD rates, leading to a greater than 35% increase in cases involving patients older than 80 years. PAD now affects one in 10 people 70 years and older and one in six people older than 80 years worldwide.

PVD manifests as insufficient tissue perfusion initiated by existing atherosclerosis acutely compounded by either emboli or thrombi. It is among those non-communicable diseases that can be diagnosed without skilled technologists and at low cost by measurement of the ankle brachial index (ABI). Many people live daily with significant degrees of PVD; however, in settings such as acute limb ischemia, this latent disease can suddenly become life threatening and require emergency intervention to minimize morbidity and mortality.

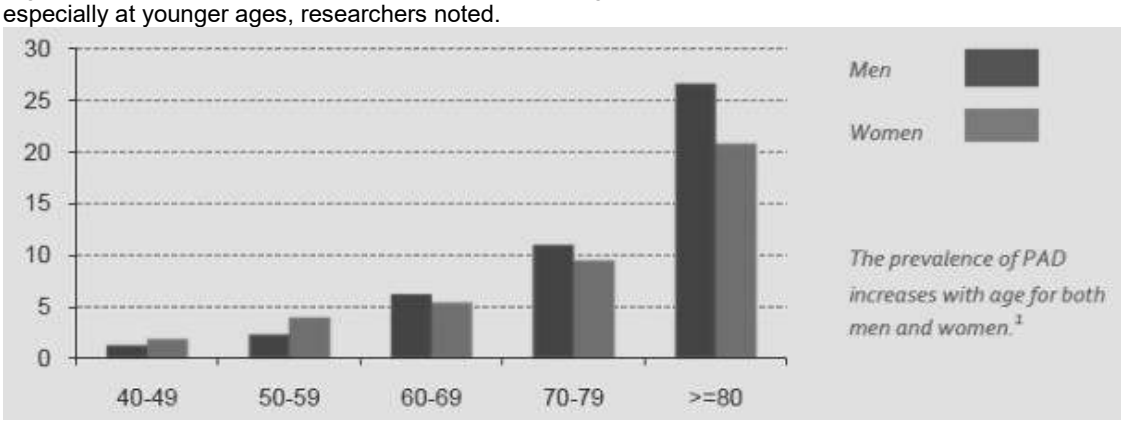
PAD affects 12%–14% of the general population and its prevalence increases with age affecting up to 20% of patients over the age of 75 (Hiatt et al 1995). The prevalence of PAD increases progressively with age, beginning after age 40. As a result, PAD is growing as a clinical problem due to the increasingly aged population in the United States and other developed countries. The prevalence rates of PVD were 2.7, 2.9, and 6.3% in individuals with normal glucose tolerance (NGT), impaired glucose tolerance (IGT), and diabetes, respectively. The overall prevalence rate was 3.2%. Known diabetic subjects had a higher prevalence of PVD (7.8%) compared with newly diagnosed diabetic subjects (3.5%). PVD was uncommon until middle-age and then the prevalence rate increased dramatically. The evidence of PVD in patients with type 2 diabetics is 14.3% as per a study from Delhi. (2012)

As in China (2006), the prevalence of PAD defined by intermittent claudication was 11.3% (men, 8.0%; women, 13.6%); 15.3% (men, 11.7%; women, 17.7%) by ABI, and 19.8% (men, 14.7%; women, 23.2%) by both criteria. About 40% of PAD patients were asymptomatic and unaware of their condition. The 2007 TASC II consensus document on the management of PAD made the following estimates for the prevalence of PAD in Europe and North America:

- 27 million affected individuals
- 413,000 hospital discharges of patients with chronic PAD per year with 88,000 hospitalizations involving lower extremity arteriography and 28,000 discharges for embolectomy or thrombectomy of lower limb arteries.

More than a quarter of a billion people in the world have peripheral artery disease (PAD), with poorer countries disproportionately affected, the first global analysis of the disease found. The global prevalence of PAD increased by 24% from 2000 to 2010, from 164 million to 202 million, nearly 70% of affected individuals, or 140.8 million, live in low-to-middle-income regions, a 29% increase during the decade-long span. (The Lancet) But high-income regions were not exempt from this rising pandemic -- they saw a 13% increase in PAD prevalence during the 10-year period. The increase in poorer regions occurred mostly in Southeast Asia, which counted 54.8 million cases in 2010, and Western Pacific areas, with a total of 45.9 million cases in 2010.

The "most striking differences in prevalence" were the higher prevalence of men with the disease in wealthier regions compared with men in poorer areas, and the higher prevalence in women than in men in poorer regions, especially at younger ages, researchers noted.

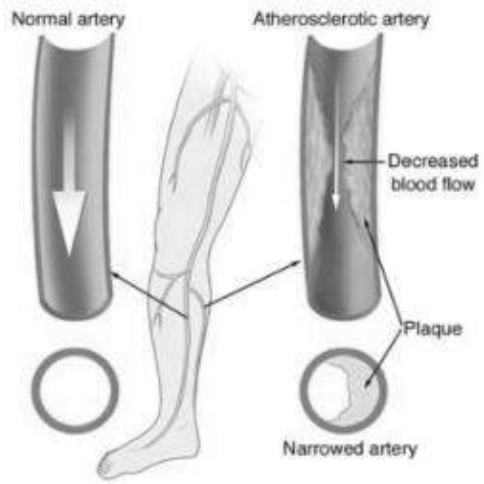


The prevalence of PAD increases with age for both men and women.[1]

PAD prevalence and incidence are both sharply age-related, rising >10% among patients in their 60s and 70s. With aging of the global population, it seems likely that PAD will be increasingly common in the future. Prevalence seems to be higher among men than women for more severe or symptomatic disease.

Prevalence of PAD (%) by Age Group (years)

(cdc.gov/dhdsp/data_statistics/fact_sheets)



The PARTNERS (Peripheral Arterial Disease Awareness, Risk, and Treatment: New Resources for Survival) program has evaluated 7000 at-risk individuals seen in primary care practices. In this population, the program uncovered several important facts related to PAD epidemiology.

- First, PAD is common (prevalence, 29%) in high-risk individuals (age older than 70 years without additional risk factors, or age 50 to 69 years with a history of cigarette smoking or diabetes) in the primary care setting.
- Second, PAD is poorly recognized—44% of cases were diagnosed after enrolment in the program, only 83% of patients with a prior diagnosis of PAD were aware of it and, surprisingly, only 49% of their physicians knew about it, despite documentation in medical records.
- Third, patients who had both PAD and CAD were more likely to have been diagnosed than patients with PAD alone.
- Fourth, despite being an independent risk factor for cardiovascular morbidity and mortality, patients with PAD were less intensively managed. Hyperlipidaemia, hypertension, and adequate antiplatelet therapy were less frequently prescribed compared with CAD patients.

RISK FACTORS

The risk factors that favor the development of peripheral artery disease (ie, hyperlipidemia, smoking, hypertension, diabetes) are similar to those that promote the development of coronary atherosclerosis. Cigarette smoking is a major risk factor for PAD, and smoking cessation substantially reduces the risk.

Data from the Framingham Heart Study of 381 men and women who were followed for 38 years revealed that the odds ratio for developing intermittent claudication was 1.2 for each 40 mg/dL (1 mmol/L) elevation in the serum cholesterol concentration, 1.4 for each 10 cigarettes smoked per day, 1.5 for mild and 2.2 for moderate hypertension, and 2.6 for diabetes mellitus. Patients with diabetes have more advanced arterial disease and poorer outcomes than nondiabetic patients.

Patients with PAD are more likely to have increased levels of triglycerides and/or cholesterol, apolipoprotein B, and very low density lipoprotein; all are independent risk factors. Conversely, high density lipoprotein cholesterol and apolipoprotein A-I and A-II values, the "protective" lipoproteins, are reduced in these patients. The risk of intermittent claudication may also be increased in patients with elevated plasma lipoprotein (a) and fibrinogen levels.

A diagnosis of metabolic syndrome (ie, obesity, hypercholesterolemia, hypertension, insulin resistance) is associated with increased risk of PVD. Not only are these atherosclerotic risk factors associated with an increased prevalence of PAD, they are also associated with earlier PAD onset. Patients who are 50 to 69 years with a history of cigarette smoking (more than 10 pack-years) or diabetes may have an incidence of asymptomatic PAD similar to patient’s ≥70 years of age.

The 2005 American College of Cardiology/American Heart Association (ACC/AHA) guidelines (updated in 2011) on PAD, which were produced in collaboration with major vascular medicine, vascular surgery, and interventional radiology societies, identified the following groups at risk for lower extremity PAD:

- Age ≥ 70 years.
- Age 50 to 69 years with a history of smoking or diabetes.
- Age 40 to 49 with diabetes and at least one other risk factor for atherosclerosis.
- Leg symptoms suggestive of claudication with exertion or ischemic pain at rest.
- Abnormal lower extremity pulse examination.
- Known atherosclerosis at other sites (eg, coronary, carotid, or renal artery disease).

PVD is more frequent in older adults, with a 1.5- to twofold increase in risk for every 10-year increase in age. Smoking or DM increases the risk of PAD independently by approximately threefold. In addition, smoking has a synergistic effect on other risk factors, and the number of pack/years is associated with disease severity. Smokers have at least double the risks of mortality, disease progression, and limb amputation rates compared with nonsmokers. Although diabetics often have extensive involvement, diffuse and advanced PAD appear to be related to the duration of diabetes rather than glycemic control.

ETIOLOGY

There are two types of PVD:

- **Functional PVDs** don't involve defects in blood vessels' structure. (The blood vessels aren't physically damaged.) These diseases often have symptoms related to "spasm" that may come and go.
- **Organic PVDs** are caused by structural changes in the blood vessels. Examples could include inflammation and tissue damage.

Etiology of lower extremity ischemia	Etiology of upper extremity ischemia
Major causes	**Large artery disease**
Atherosclerosis	Atherosclerosis
Thromboangiitis obliterans (Buerger's disease)	Arterial injury
Arterial injury	Arterial dissection
Arterial dissection	Thrombosed aneurysm
Atheroembolism	Atheroembolism
Thromboembolism	Thromboembolism
Thombosed aneurysm	Arterial fibrodysplasia
	Arterial tumor
	Arteritis
	Giant cell arteritis
	Takayasu's arteritis
	Repetitive injury
	Thoracic outlet syndrome (subclavian artery, often with cervical rib)
Other causes	Crutch injury (axillary artery)
Aorto-iliac	
Retroperitoneal fibrosis	**Small artery disease**
Radiation fibrosis	Vasculitis
Tumor	Rheumatoid arthritis
Iliac	Systemic lupus erythematosis
	Scleroderma
	Sjögren's syndrome
	Mixed connective tissue disease
	Repetitive injury
	Vibratory tool arterial injury
	Hypothenar hammer syndrome
	Drug-related
	Vasopressors
	Ergot toxicity
	Vasospasm
	Raynaud's syndrome
	Buerger's disease

Atherosclerosis etiology is common to both upper extremity and lower extremity. Buerger's disease is common in lower limbs whereas it is uncommon in upper limbs; vasospastic disorders and vasculitits form the major causative factors in upper limb ischemia after atherosclerosis. Upper extremity vascular disease are less common compared to lower extremity vascular disease, accounting for less than 10% of all cases of chronic arterial occlusions. Acute arterial occlusions of the upper limb have a less critical effect than those of the lower limb because of liberal collateral circulation and relatively small muscle mass.

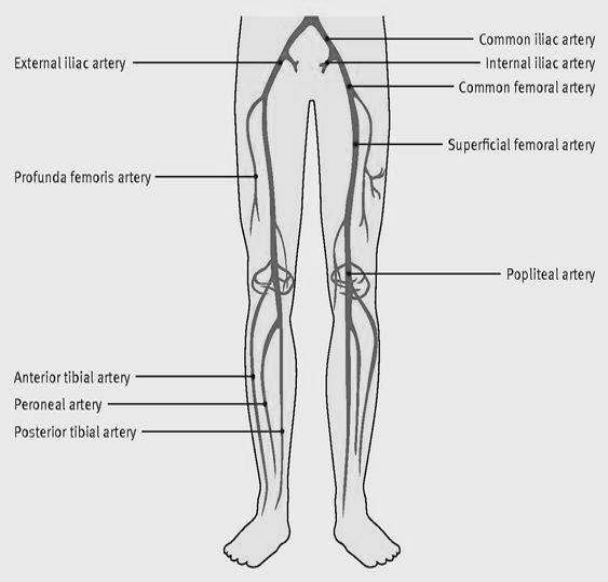
Chronic upper limb ischemia falls into six broad anatomical patterns:

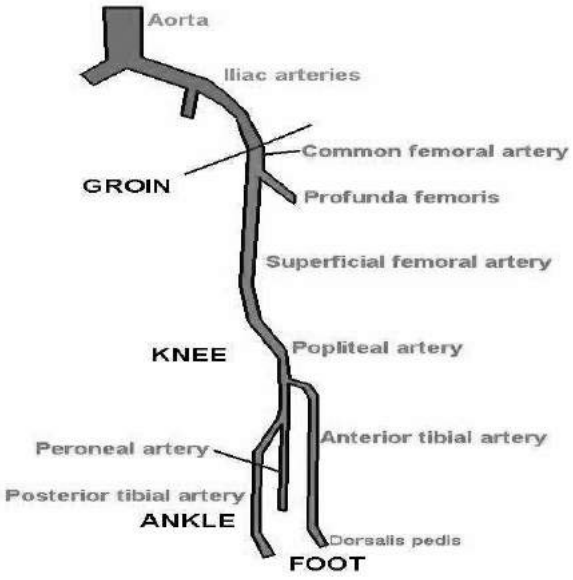
- Central causes: Delayed presentation of emboli from the heart lodging in the upper extremity vessels.
- Occlusion of vessels at the arch: atherosclerosis, Takayasu arteritis
- Causes at the root of the limb e.g. thoracic outlet syndrome
- Local causes: radiation injury, trauma, post-cannulation occlusion etc.
- Peripheral disorders affecting the small vessels of the hand: Raynaud's and Buerger's diseases, thermal or vibration injury
- Generalized systemic disorders e.g. arteritis or vasculitis.

This chapter focusses on the arterial insufficiency disorders of the lower limbs. A brief review of lower limb arterial anatomy is below.

LOWER EXTREMITY ANATOMY

The lower extremity is perfused by the common femoral artery. The common femoral artery branches into the superficial and deep femoral vessels. The superficial femoral artery runs anteriorly down the thigh between the adductor and quadriceps muscles within the anterior compartment. In the distal third of the femur, the superficial femoral artery is in close proximity to the femur. The superficial femoral artery passes through the adductor canal to become the popliteal artery which divides at the level of the tibial tuberosity into the anterior tibial artery and tibioperoneal trunk, which further divides into the posterior tibial and peroneal arteries. The anterior tibial artery accompanies the deep peroneal (fibular) nerve along the posterior margin of the tibia. The peroneal artery passes adjacent the medial margin of the fibula throughout its course distally. The posterior tibial artery is accompanied by the tibial nerve within the deep posterior compartment. The collateral circulation in the lower extremity is derived from the deep femoral artery (profunda femoris).





PRESENTATION

Critical limb ischemia is a state of arterial insufficiency manifested by chronic inadequate tissue perfusion at rest. To emphasize the chronic nature of ischemia, it is often termed chronic critical limb ischemia to distinguish it from acute limb ischemia, a relatively sudden process of severe limb hypoperfusion. The major manifestations of limb-threatening ischemia are *claudication, rest pain, ischemic ulcers, and gangrene.* Critical limb ischemia is most often seen when two or more levels of the distal arterial tree have either significant stenosis or occlusions. Multiple levels of disease promote severe ischemia by reducing the effectiveness of collateral flow and by lowering distal systolic driving pressures. From the pathophysiologic point of view, ischemia of the lower limbs can be classified as functional or critical.

Functional ischemia occurs when the blood flow is normal at rest but insufficient during exercise, presenting clinically as intermittent claudication. **Critical ischemia** is produced when the reduction in blood flow results in a perfusion deficit at rest and is defined by the presence of pain at rest or trophic lesions in the legs. The principal feature of chronic limb ischemia is claudication which may progress to rest pain, ulceration and lastly to gangrene of limb.

Classification of limb ischaemia

Terminology	Definition or comment
Onset:	
Acute	Ischaemia <14 days
Acute on chronic	Worsening symptoms and signs (<14 days)
Chronic	Ischaemia stable for >14 days
Severity (acute, acute on chronic):	
Incomplete	Limb not threatened
Complete	Limb threatened
Irreversible	Limb non-viable

CLAUDICATION

Claudication is a pain, cramp or sense of fatigue in a muscle group of the lower extremity related to sustained exercise and relieved by rest. The word claudication is from the Latin claudicare meaning "to limp," but it has been adopted in medical terminology to describe a painful limp associated with exercise. *Intermittent claudication is not a diagnosis but a symptom.* It refers to a condition of lameness and pain in the lower extremity precipitated by muscular exercise and relieved by 1 to 2 minutes of rest while the patient remains standing. When present, it is a rather specific and reliable indicator of arterial insufficiency of the leg.

Disease severity and functional impairment in patients with intermittent claudication is usually quantified by the measurement of pain-free walking distance or at onset of pain after covering certain distance (intermittent claudication distance, ICD) and maximal walking distance (absolute claudication distance, ACD); however the distance at which patient prefers to stop is defined as the functional claudication distance (FCD). FCD may better reflect the actual functional impairment. Some factors like Excess body weight, Walking uphill, Walking against wind and carrying load can adversely affect claudication distance.

The pathophysiology of claudication is explained as: in a situation of gradual arterial occlusion the blood flow may be adequate to maintain a comfortable limb at rest or with limited activity, but upon more vigorous exercise the muscle groups distal to a level of major arterial obstruction receive inadequate circulation to meet metabolic demands. The resulting pain is thought to be due to an accumulation of irritating metabolic products in the ischemic muscle, causing stimulation of sensory nerves. When claudicants [Substance P and calcitonin gene-related peptide (CGRP) are involved in nociception] stand still to rest, they achieve relief of pain by allowing the blood supply to catch up with the previously increased metabolic activity. Subjects may then walk again for the same distance, with the same sequence of events. Such pain does not occur in persons with normal circulation because metabolic products can be removed adequately by the abundant blood flow present in the normal exercising limb. While the pain of claudication is usually of a dull, aching type, on occasion it may be excruciating or totally disabling, especially if the individual persists in walking despite ischemic symptoms. Although a brief period of rest generally affords prompt relief of claudicatory pain, patients with more severe arterial impairment or those who do not yield to the pain signal may note persistent tenderness or soreness of the affected muscle for some time thereafter. This is presumably the result of ischemic myositis caused by forcing the muscle to perform beyond its blood flow limit.

Among symptomatic patients, the perception of claudication can vary from severe, debilitating discomfort at rest to a bothersome pain of seemingly little consequence. The severity of symptoms of claudication depends upon the degree of stenosis, the collateral circulation, and the vigor of exercise. Patients with claudication can present with buttock and hip, thigh, calf, or foot pain, either singly or in combination. The usual relationships between pain location and corresponding anatomic site of arterial occlusive disease can be summarized as follows:

- Buttock and hip – aortoiliac disease
- Thigh – aortoiliac or common femoral artery
- Upper two-thirds of the calf – superficial femoral artery
- Lower one-third of the calf – popliteal artery
- Foot claudication – tibial or peroneal artery

Physical examination in the patient with claudication can be normal, but commonly reveals diminished or absent pulses below the level of stenosis with occasional bruits over stenotic lesions and evidence of poor wound healing over the area of diminished perfusion. Other physical findings may include a unilaterally cool extremity, a prolonged venous filling time, shiny atrophied skin, and nail changes. Physical signs can also help determine the extent and distribution of vascular disease. These include an abnormal femoral pulse, lower extremity bruits, and the Buerger test (foot pallor with elevation of the leg and, in the dependent position, a dusky red flush spreading proximally from the toes).

Buttock and hip claudication — Patients with aortoiliac occlusive disease (Leriche's syndrome) may complain of buttock, hip, and, in some cases, thigh claudication. The pain is often described as aching in nature and may be associated with weakness of the hip or thigh with walking. Bilateral aortoiliac disease that is severe enough to cause symptoms almost always causes erectile dysfunction in men; another diagnosis should therefore be entertained if impotence is absent. Physical examination reveals bilateral diminished or absent pulses at the level of the groin, with occasional bruits over the iliac and femoral arteries. Other findings include muscle atrophy and slow wound healing in the legs. This vascular claudication (true) needs to be differentiated from spinal claudication or neurogenic claudication (false) which is due to compression of spinal nerves due to spinal stenosis.

Conditions that resemble aortoiliac occlusive disease are:

- Neurogenic claudication – Neurogenic claudication, also called pseudoclaudication, describes a pain syndrome due to lumbar neurospinal canal compression, which is usually due to osteophytic narrowing of the neurospinal canal. The clinical presentation often helps to distinguish vasculogenic (ie, true) claudication from pseudoclaudication. Unlike true claudication, which occurs with walking and is relieved by stopping, pseudoclaudication causes pain with erect posture (lumbar lordosis) and is relieved by sitting or lying down. Patients with pseudoclaudication may also find symptomatic relief by leaning forward and straightening the spine.

- Osteoarthritis of the hip or knee joints – Osteoarthritis can be distinguished clinically from aortoiliac disease because osteoarthritic pain may not disappear promptly after exercise, may be associated with weather changes, and may vary in intensity from day to day (usually worse in the morning or upon wakening).

Differential Diagnosis of Intermittent Claudication

Condition	Location of pain or discomfort	Characteristics of discomfort	Onset relative to exercise	Effect of rest	Effect of body position	Other features
Intermittent claudication	Buttock, thigh, or calf muscles and rarely the foot	Cramping, aching, fatigue, weakness, or frank pain	After same degree of exercise	Quickly relieved	None	Reproducible
Nerve root compression (such as herniated disc)	Radiates down leg, usually posteriorly	Sharp lancinating pain	Soon, if not immediately after onset	Not quickly relieved (also often present at at rest)	Relief may be aided by adjusting back position	History of back problems
Spinal stenosis	Hip, thigh buttocks (follows dermatome)	Motor weakness more prominent than pain	After walking or standing for same length of time	Relieved by stopping only if position changed	Relief by lumbar spine flexion (sitting or stooping forward)	Frequent history of back problems, provoked by intraabdominal pressure
Hip arthritis	Hip, thigh, buttocks	Aching discomfort, usually localized to hip and gluteal region	After variable degree of exercise	Not quickly relieved (and may be present at rest)	More comfortable sitting, weight taken off legs	Variable, may relate to activity level, weather changes
Arthritic, inflammatory processes	Foot, arch	Aching pain	After variable degree of exercise	Not quickly relieved (and may be present at rest)	May be relieved by not bearing weight	Variable, may relate to activity level
Venous claudication	Entire leg, but usually worse in thigh and groin	Tight, bursting pain	After walking	Subsides slowly	Relief speeded by elevation	History of iliofemoral deep vein thrombosis, signs of venous congestion, edema

Thigh claudication — Atherosclerotic occlusion of the common femoral artery may induce claudication in the thigh, calf, or both. Patients with occlusive disease of the superficial femoral or popliteal arteries have normal groin pulses but decreased pulses distally.

Calf claudication — Calf claudication is the most common complaint. It is usually described as a cramping pain that is consistently reproduced with exercise and relieved with rest. Cramping in the upper two-thirds of the calf is usually due to superficial femoral artery stenosis, whereas cramping in the lower third of the calf is due to popliteal disease. This type of cramping pain in the calf can be confused with two other conditions:

- Nocturnal leg cramps – Nocturnal leg cramps occur among older and infirmed patients and are not associated with exercise. This complaint is thought to be neuromuscular rather than vascular in origin.
- Calf pressure and tightness – This symptom is primarily seen in athletes, and is usually associated with chronic exercise. It is thought to be due to increased compartment pressure and may persist even after rest.

Foot claudication — Claudication of the foot is usually accompanied by occlusive disease of the tibial and peroneal vessels. Isolated foot claudication is rarely seen with atherosclerotic occlusive disease, but is commonly seen with thromboangiitis obliterans (Buerger's disease).

REST PAIN

Ischemic rest pain or diffuse pedal ischemia can be described as a severe pain which is not readily controlled by analgesics and which is typically localized in the forefoot and toes of the chronically ischemic extremity. A severe decrease in limb perfusion can result in ischemic rest pain. Such discomfort typically occurs at night and involves the digits and forefoot. The pain may also be felt more proximally; when this occurs, the pain usually does not spare the distal sites. The pain may be more localized in patients who develop an ischemic ulcer or gangrenous toe.

This is said to be the cry of dying nerves and is due to the ischaemia of the skin and subcutaneous tissues, which are richly supplied by nerves. Affected patients frequently find that the pain is relieved by hanging their feet over the edge of the bed or, paradoxically, by walking around the room because of the gravitational effect of dependence on limb blood pressure. Chronic tissue ischemia may also result in ischemic neuropathic pain that is frequently described as throbbing or burning with a superimposed severe shooting pain up the limb. Ischemic rest pain is brought on or made worse by elevation of the lower extremity and is ameliorated or relieved by limb

Characteristic	Arterial ulcer	Venous ulcer	Neuropathic ulcer
Location	Over toe joints, malleoli (over the bony prominence), anterior shin, base of heel, pressure points	Medial and lateral malleolar area above bony prominence, posterior calf, may be large, circumferential	Plantar surface of foot over metatarsal heads, heel, pressure points
Appearance	Irregular margins, base dry and often pale or necrotic (brown/black fibrous tissue)	Irregular margins, pink or red base that may be covered with yellow fibrinous tissue, exudate common (may be heavy); ulcers can be large, sometimes circumferential	Punched out ulcer, usually superficial but sometimes deep, red base
Ulcer within callus	Rare	No	Calloused border, ulcer can be underlying a callus
Foot temperature	Warm or cool	Warm	Warm
Pain	Yes, may be severe	Yes, usually mild but may be severe	No
Arterial pulses	Absent	Present	Present or absent
Sensation	Variable	Present	Absent tactile, pain, temperature and vibratory sensations
Foot deformities	No	No	Often
Skin changes	Shiny, taut, loss of hair Dependent rubor of leg and foot that becomes pale with leg elevation	Erythema, brown-blue hyperpigmentation can be spotty or diffuse: "stasis" changes; atrophie blanche (white sclerotic areas), edema; dry skin; varicose veins common; if lipodermatosclerosis is present, skin may be bound down; bilateral lower extremities often affected	Waxy or shiny, loss of hair, may be taut; dry skin; may have non-pitting edema, especially on dorsal foot
Reflexes	Present	Present	Absent

dependency. Thus, rest pain is often experienced at night or while reclining. Diffuse pedal ischemia is commonly associated with systolic arterial ankle pressures below 40 mmHg and toe pressures below 30 mmHg.

ISCHEMIC ULCERS

Ischemic ulcers often begin as minor traumatic wounds and then fail to heal because the blood supply is insufficient to meet the increased demands of the healing tissue. The ulcers are often painful and are associated with other manifestations of chronic ischemia including rest pain, pallor, hair loss, and nail hypertrophy.
Ischemic ulcers need to be distinguished from venous insufficiency and peripheral neuropathy, which are the other major causes of foot and leg ulcer.

GANGRENE

Gangrene is characterized by cyanotic, anaesthetic tissue associated with or progressing to necrosis; it occurs when arterial blood supply falls below that necessary to meet minimal metabolic requirements. Gangrene can be described as either dry or wet.

- Dry gangrene is characterized by its hard, dry texture, usually occurring in the distal aspects of toes and fingers, often with a clear demarcation between viable and necrotic tissue. This form of gangrene is more common in patients with atherosclerotic disease and frequently results from embolization to the toe or forefoot. The patient may often give a history of associated claudication or foot and toe pain.

- Wet gangrene is characterized by its moist appearance, gross swelling, and frequent blistering. It is a true emergency, often occurring in diabetics with decreased sensation who sustain an unrecognized trauma to the toe or foot. If sufficient viable tissue is present to maintain a functional foot, emergent debridement of all affected tissue often results in healing. If the wet gangrene involves an extensive portion of the foot, emergent guillotine amputation may be warranted, with revision to below knee or above knee amputation later.

The Rutherford and Fontaine symptom classification systems are the most widely used for chronic extremity ischemia. The walking distance that defines mild, moderate, and severe claudication is not specified in the Rutherford classification, but is part of the Fontaine classification as 650 feet (200 meters).

Rutherford	Fontaine
Stage 0 – Asymptomatic	**Stage 1** – No symptoms
Stage 1 – Mild claudication	**Stage 2a** – Mild claudication without pain on resting, but with claudication at a distance of greater than 650 feet (200 meters)
Stage 2 – Moderate claudication	**Stage 2b** – Moderate claudication without pain on resting, but with a claudication distance of less than 650 feet (200 meters)
Stage 3 – Severe claudication	**Stage 3** – Nocturnal and/or resting pain
Stage 4 – Rest pain	**Stage 4** – Necrosis (death of tissue) and/or ulceration/gangrene in the limb
Stage 5 – Ischemic ulceration not exceeding ulcer of the digits of the foot	
Stage 6 – Severe ischemic ulcers or frank gangrene	

ACUTE LIMB ISCHEMIA

According to the 2007 Inter-Society Consensus for the Management of Peripheral Arterial Disease (TASC II), **acute limb ischemia** is defined as a sudden decrease in limb perfusion that causes a potential threat to limb viability (manifested by ischemic rest pain, ischemic ulcers, and/or gangrene) in patients who present within two weeks of the acute event. Patients with similar manifestations who present later than two weeks are considered to have critical limb ischemia, which is by definition chronic. **Critical limb ischemia** is defined as persistent, recurring ischemic rest pain requiring opiate analgesia for at least 2 weeks, ulceration or gangrene of the foot or toes, and ankle systolic pressure less than 50 mm Hg or toe systolic pressure less than 30 mm Hg (or absent pedal pulses in patients with diabetes).

The natural history of critical limb ischemia usually involves inexorable progression to amputation unless there is an intervention that results in the improvement of arterial perfusion. This is in contrast to the often benign natural history of mild and moderate claudication. The SVS/ISCVS (Rutherford) classification stratifies limb ischemia based upon the presence and degree of sensorimotor deficits and Doppler findings.

SVS/ISCVS classification of acute extremity ischemia:

	Viable	Threatened	Nonviable
Pain	Mild	Severe	Variable
Capillary refill	Intact	Delayed	Absent
Motor deficit	None	Partial	Complete
Sensory deficit	None	Partial	Complete
Arterial Doppler	Audible	Inaudible	Inaudible
Venous Doppler	Audible	Audible	Inaudible
Treatment	Urgent work-up	Emergency surgery	Amputation

Viable — Viable limbs are under no immediate threat of tissue loss. There is no sensory loss or muscle weakness and both arterial and venous Doppler signals are audible.
Marginally-threatened — Marginally-threatened limbs are salvageable if treated promptly. There is minimal pain (in the toes) or no sensory loss, no muscle weakness, arterial Doppler signals are often inaudible, and venous Doppler signals are audible.

Immediately-threatened — Immediately-threatened limbs are salvageable with immediate revascularization. Sensory loss involves more than the toes and may be associated with rest pain. There is mild to moderate muscle weakness, arterial Doppler signals are usually inaudible, and venous Doppler signals are audible.

Irreversible (nonviable) — Irreversible limbs have major tissue loss and/or permanent nerve damage. Sensory loss is profound, muscle weakness is profound with paralysis and possible rigor, and arterial and venous Doppler signals are inaudible. These nonviable extremities require major amputation regardless of the therapy that is instituted. Revascularization may be required to permit healing of the amputation or amputation at a lower level.
A thorough history and physical examination is the first step in the evaluation of the patient with acute extremity ischemia. The **"5 Ps"** have been used as a mnemonic to remember the presentation of a patient with acute limb ischemia—**paresthesia, pain, pallor, pulselessness, and paralysis.** In some cases, a sixth P is added—**poikilothermia,** meaning equilibration of the temperature of the limb to that of the ambient environment (coolness).

Symptoms and signs of acute limb ischaemia

Symptoms or signs	Comment
Pain	Occasionally absent in complete ischaemia
Pallor	Also present in chronic ischaemia
Pulseless	Also present in chronic ischaemia
Perishing cold	Unreliable as ischaemic limb takes on ambient temperature
Paraesthesia	Leading to anaesthesia (unable to feel touch on foot or hand)
Paralysis	Unable to wiggle toes or fingers

History should include a description of the duration, location, intensity, and suddenness of the onset of pain and change over time. The past history should state whether or not the patient has a history of intermittent claudication, previous leg bypass or other vascular procedures, and history suggestive of embolic sources such as cardiac arrhythmias and aortic aneurysms. General atherosclerotic risk factors (smoking, hypertension, diabetes, hyperlipidemia, family history of cardiac or vascular events) should be recorded because these can be predictors of periprocedural mortality.

Pain — Pain associated with acute ischemia is usually located distally in the extremity, gradually increases in severity, and progresses proximally as the length of ischemia increases. Later, the pain may decrease in severity due to progressive ischemic sensory loss. Pain may either be constant or elicited by passive movement of the involved extremity. It is essential to determine if the patient had symptoms of chronic ischemia before the acute event occurred. Patients with an embolus usually have no pre-existing ischemic symptoms, and can frequently pinpoint the exact time that symptoms began. Thus, the sudden and dramatic development of ischemic symptoms in a previously asymptomatic patient is most consistent with an embolus, while gradually increasing symptoms in a patient with chronic ischemia is indicative of thrombosis.

Pulse — The quality and character of the peripheral pulses must be evaluated. If pulses are not palpable, a hand held Doppler should be used. It is rare to have acute limb-threatening ischemia without a major pulse deficit. The status of the pulses in the contralateral extremity is also important. The presence of a pulse deficit in an asymptomatic contralateral extremity is an indication of underlying chronic arterial occlusive disease and suggests that acute thrombosis of an already diseased vessel is the most likely cause of the acute occlusion. By

contrast, the presence of normal pulses in the contralateral extremity suggests the absence of chronic occlusive disease, and increases the likelihood that an embolus is the etiology of acute occlusion.

Skin — The skin of both the normal and affected extremity should be examined for temperature, color, and capillary refill. The skin of the ischemic extremity is typically cool and pale with delayed capillary filling. The level of arterial obstruction is usually one joint above the line of demarcation between the normal and ischemic tissue. Both extremities should also be examined for signs of chronic ischemia such as atrophy of the skin, hair loss, and thickened nails.

Neurologic examination — A careful neurologic examination must be performed. Subjective sensory deficits such as numbness or paresthesias are signs of early nerve dysfunction secondary to ischemia. Major loss of sensory or motor function is indicative of advanced ischemia. The anterior compartment of the lower leg is most sensitive to ischemia, and sensory deficits over the dorsum of the foot are often the earliest neurologic sign of vascular insufficiency.

In an effort to classify the extent of acute ischemia for standardization reporting of outcome, the Society for Vascular Surgery/International Society for Cardiovascular Surgery (SVS/ISCVS) (now SVS) ad hoc committee was established and published what has now come to be known as the *Rutherford criteria*, after Dr. Robert Rutherford, the lead author of the article. The following three classes were defined:

- Class 1: the limb is viable and remains so even without therapeutic intervention.
- Class 2: the limbs are threatened and require revascularization for salvage.
- Class 3: those limbs that are irreversibly ischemic and infarction has developed such that salvage is not possible.

The initial work of the reporting standards committee was revised several years later, dividing the middle category into two sub classifications: class 2A for limbs that are not immediately threatened and class 2B for those limbs that are severely threatened to the point where urgent revascularization is necessary for salvage.

Stages of Acute Limb Ischemia					
Stage	**Description and Prognosis**	**Findings**		**Doppler Signal**	
		Sensory Loss	*Muscle Weakness*	*Arterial*	*Venous*
I	Limb viable, not immediately threatened	None	None	Audible	Audible
II	Limb threatened				
IIa	Marginally threatened, salvageable if promptly treated	Minimal (toes) or none	None	Often inaudible	Audible
IIb	Immediately threatened, salvageable with immediate revascularization	More than toes, associated with pain at rest	Mild or moderate	Usually inaudible	Audible
III	Limb irreversibly damaged, major tissue loss or permanent nerve damage inevitable	Profound, anesthetic	Profound, paralysis (rigor)	Inaudible	Inaudible

Differentiating features of embolus and acute arterial thrombosis

Clinical features	***Embolus***	***Thrombosis***
Severity	Complete (no collaterals)	Incomplete (collaterals)
Onset	Seconds or minutes	Hours or days
Limb affected	Leg 3:1 arm	Leg 10:1 arm
Multiple sites	Up to 15%	Rare
Embolic source	Present (usually atrial fibrillation)	Absent
Previous claudication	Absent	Present

Palpation of artery	Soft, tender	Hard, calcified
Bruits	Absent	Present
Contralateral leg pulses	Present	Absent
Diagnosis	Clinical	Angiography
Treatment	Embolectomy, warfarin	Medical, bypass, thrombolysis

ATYPICAL SYMPTOMS

Some patients with PAD have atypical symptoms as a result of comorbidities, physical inactivity, and alterations in pain perception. This issue was addressed in a study of 460 men and women with known PAD. Symptoms were classified as follows:

- Classic claudication – Exertional calf pain that does not begin at rest, causes the patient to stop walking, and resolves within 10 minutes of rest; (33 percent)
- Atypical exertional leg pain type I – Pain similar to that of classic claudication, but does not cause the patient to stop walking; (9 percent)
- Atypical exertional leg pain type II – Pain similar to that of classic claudication, but does not involve the calves or does not resolve within 10 minutes of rest; (20 percent)
- Leg pain on both exertion and rest – (19 percent)
- No exertional leg pain, physically active (walked more than six blocks in previous week) – (14 percent)
- No exertional leg pain, physically inactive – (6 percent)

A brief review and pathogenesis of major conditions causing limb ischemia:

Atherosclerosis

Atherosclerosis is a multifocal, smoldering, immunoinflammatory disease of medium-sized and large arteries fuelled by lipids. Atherosclerosis derives its name from the Greek words ‘sclerosis’ meaning hardening and ‘athere’ meaning gruel (accumulation of lipid). The phenomenon is characterized by accumulation of cholesterol, infiltration of macrophages, proliferation of smooth muscle cells (SMC), accumulation of connective tissue components and formation of thrombus. Endothelial cells, leukocytes, and intimal smooth muscle cells are the major players in the development of this disease. The most devastating consequences of atherosclerosis, such as heart attack and stroke, are caused by superimposed thrombosis. The atherosclerosis process in peripheral arteries is thought to be similar to that described in the coronary and cerebral circulation, although the flow dynamics and stimulants may be different.

Cellular components of atherosclerosis

In lesion-prone areas, atherosclerotic lesions begin to develop under an intact but leaky, activated, and dysfunctional endothelium. Later, endothelial cells may vanish and de-endothelialized (denuded) areas appear over advanced lesions, with or without platelets adhering to the exposed subendothelial tissue. Depending on size and concentration, plasma molecules and lipoprotein particles extravasate through the leaky and defective endothelium into the subendothelial space, where potentially atherogenic lipoproteins are retained and modified (e.g., oxidized) and become cytotoxic, proinflammatory, chemotaxic, and proatherogenic. The endothelium becomes activated by atherogenic and proinflammatory stimuli, and the expression of adhesion molecules, primarily vascular cell adhesion molecule-1 (VCAM-1), are up-regulated, and monocytes and T cells are recruited. Besides VCAM-1, other adhesion molecules, such as intercellular adhesion molecule-1, E selection, and P selection, probably contribute to the recruitment of blood-borne cells to the atherosclerotic lesion. One of the earliest cellular responses in atherogenesis is the focal recruitment of circulating monocytes and, to a lesser extent, T lymphocytes. The mere adhesion to the endothelium is, of course, not enough for blood-borne cells to arrive in the lesion, transendothelial migration also is required. As to that, one or more chemokines (chemotactic cytokines) are necessary. Experimental studies indicate that the most important atherogenic chemoattractants are oxidized LDL and MCP-1 (Monocyte chemotactic protein-1). Within intima, the monocytes differentiate into macrophages and internalize the atherogenic lipoproteins, the development of lipid-loaded macrophages containing massive amounts of cholesteryl esters (foam cells) is a hallmark of both early and late atherosclerotic lesions. With continuing supply of atherogenic lipoproteins, the macrophages eat until they die because, the death of macrophages by apoptosis and necrosis contributes to the formation of a soft and destabilizing lipid-rich core within the plaque. Only endothelial cells, macrophages, and a few T cells participate in the development of the early and asymptomatic foam-cell lesion, the fatty streak. In disease progression, the immunoinflammatory response is joined by a fibroproliferative response mediated by intimal smooth muscle cells. These cells are responsible for healing and repair after arterial injury. If the atherogenic stimuli persist over the course of years, as they often do, the reparative response may become so voluminous and dominating that lumen is lost, blood flow is reduced, and ischemia sets in.

Risk factors for atherosclerosis

Positive risk factors	*Negative risk factors*
Advancing age	Regular physical activity
Smoking	Moderate alcohol intake
Diabetes (level of glycemic control and impaired glucose tolerance)	
Hypertension	
Fibrinogen	
Hyperlipidemia (elevated LDL, low HDL, elevated LP[a])	
Homocysteinemia	

Thromboangiitis obliterans (Buerger's disease)

Definition

Thromboangiitis obliterans or Buerger's disease is a nonatherosclerotic, segmental, inflammatory disease that most commonly affects the small to medium-sized arteries and veins of the extremities. Thromboangiitis obliterans is characterized by highly cellular and inflammatory occlusive thrombus with relative sparing of the blood vessel wall. The disease is strongly associated with the use of tobacco products and smoking cessation is important to decrease the risk for amputation.

Prevalence: The disease is found worldwide, the prevalence among all patients with peripheral arterial disease ranges from values as low as 0.5 to 5.6% in Western Europe to values as high as 45 to 63% in India, 16 to 66% in Korea and Japan, and 80% among Ashkenazi Jews.

Etiology: The etiology of thromboangiitis obliterans is unknown, but use or exposure to tobacco is central to the initiation and progression of the disease. If the patient smokes, stopping completely is an essential first step of treatment. By using an antigen-sensitive thymidine-incorporation assay, Adar et al. showed that patients with TAO have an increased cellular sensitivity to type I and III collagen, compared to that in patients with arteriosclerosis obliterans or healthy males. De Moerloose et al found a marked decrease in frequency of the HLA-B12 antigen in patients with Buerger's disease (2.2% *vs*. 28% in controls). Most investigators feel that Buerger's disease is an immune-mediated endarteritis. Recent immunocytochemical studies have demonstrated a linear deposition of immunoglobulins and complement factors along the elastic lamina. Peripheral endothelium-dependent vasodilation is impaired in patients with Buerger's disease, while non-endothelial mechanisms of vasodilation seem to be intact.

Diagnostic criteria: Several different criteria have been proposed for the diagnosis of thromboangiitis obliterans.

Diagnostic criteria of Shionoya (1998)	**Diagnostic criteria of Olin (2000)**
• smoking history; • onset before the age of 50 years; • infrapopliteal arterial occlusions; • either arm involvement or phlebitis migrans; • absence of atherosclerotic risk factors other than smoking.	• age under 45 years; • current or recent history of tobacco use; • the presence of distal-extremity ischemia indicated by claudication, pain at rest, ischemic ulcers or gangrenes and documented by non-invasive vascular testing; • exclusion of autoimmune diseases, hypercoagulable states and diabetes mellitus; • exclusion of a proximal source of emboli by echocardiography or arteriography; • consistent arteriographic findings in the clinically involved and non-involved limbs.

Pathogenesis: Although the disease was recognized and the pathology described over 100 years ago, its pathogenesis is poorly understood. While the clinical criteria of TAO are relatively well defined, there is no consensus on the histopathological findings. Pathologically, the condition is distinguished from other forms of vasculitis by a highly cellular, inflammatory intraluminal thrombus with relative sparing of the vessel wall and, more specifically, sparing of the internal elastic lamina. Three pathologic phases are described:

- In the acute phase, inflammatory thrombi develop in the arteries and veins, typically of the distal extremities. The thrombus is occlusive and polymorphonuclear leukocytes, micro-abscesses, and multinucleated giant cells may be present, but there is no evidence of fibrinoid necrosis. Although the external elastic lamina may show some disruption, the internal elastic lamina is intact. Biopsy of an involved superficial vein that demonstrates acute thrombophlebitis will likely show the characteristic acute phase lesion and is diagnostic of the disease.

- The intermediate (subacute) phase is characterized by progressive organization of the thrombus in the small to medium-sized arteries and veins
- In the chronic phase (later end stage), inflammation is no longer present and only organized thrombus and vascular fibrosis remain. The pathological appearance in the chronic phase is indistinguishable from all other types of arterial disease.

Raynaud's phenomenon

It is a condition resulting in discoloration of fingers and/or toes when a person is exposed to changes in temperature (cold or hot) or emotional events. The skin discoloration occurs because an abnormal spasm of the blood vessels causes a diminished blood supply. It was described by French physician Maurice Raynaud in 1962 as the condition afflicting a 26-year-old female patient: "Under the influence of a very moderate cold . . . she sees her fingers become ex-sanguine, completely insensible, and of a whitish yellow color. This phenomenon happens often without reason, lasts a variable time, and terminates by a period of very painful reaction, during which the circulation is re-established little by little and recurs to the normal state. The term 'Raynaud's disease' was used to describe these vascular events until Hutchinson, who argued that multiple etiologic factors could be responsible, introduced the concept of 'Raynaud's phenomenon.'

Although results vary according to sex, local environmental climate, and work exposures, most population based surveys estimate the prevalence of the disorder in the general population at 3 to 5%. Surveys show that approximately 30 to 50% of patients with primary Raynaud's phenomenon have a first-degree relative with the condition, which suggests a yet-to-be-defined genetic susceptibility.

It is classified into two groups:

- Primary Raynaud's phenomenon, which is diagnosed when no underlying disease is found;
- Secondary Raynaud's phenomenon, which is diagnosed when there is associated disease.

The **causes** of Raynaud's phenomenon are:

Primary RP	Secondary RP
Idiopathic	Vascular (usually proximal large vessel disease, often unilateral symptoms) Compressive (e.g., cervical rib) Obstructive: non-inflammatory (i.e., atherosclerosis) Inflammatory vascular disease (e.g., thromboangiitis obliterans (Buerger's disease)) Handarm vibration syndrome (vibration white finger) Autoimmune conditions Systemic lupus erythematosus Sjogren's syndrome Mixed connective tissue disease/overlap syndromes Undifferentiated connective tissue disease Idiopathic inflammatory myopathies Drug-related Amphetamines Beta blockers Bleomycin Cisplatin Clonidine Cyclosporine Interferon α and β Methysergide Polyvinyl chloride Conditions associated with increased plasma viscosity and reduced digital perfusion Cryoglobulinemia Cryofibrinogenemia Paraproteinemia Malignancy (including as a paraneoplastic phenomenon) *Other causes and associations* Carpal tunnel syndrome Frostbite Hypothyroidism

Pathogenesis: Raynaud's phenomenon is highly localized and affects the arterial inflow of specific skin area such as fingers, toes, and tips of the nose and ears. These sites are distinct from other skin areas in that they have specialized structural and functional features for thermoregulation. They have a high density of arteriovenous anastomoses, which bypass capillaries and provide direct connections between arterioles and venules. Arteriovenous anastomoses therefore do not contribute to capillary blood flow, which provides essential nutritional support to the skin, but instead function as thermoregulatory structures.

Arteriovenous anastomoses are richly innervated by sympathetic nerves and are normally exposed to increased sympathetic vasoconstriction under resting thermoneutral conditions and when sympathetic activity is increased during stress or exposure to cold. In persons with Raynaud's phenomenon, the already-heightened sympathetic vasoconstriction in these specialized areas is further amplified in intensity and scope: exposure to cold can evoke intense sympathetic-mediated vasoconstriction throughout this vascular network, including upstream arteries, which undergo vasospasm, arteriovenous anastomoses, and arterioles providing nutritional support to the skin. Vasoconstriction that is mediated by α2-adrenoceptors is markedly increased at reduced temperatures, which enables local cold-induced potentiation (amplification) of sympathetic vasoconstriction. The characteristic pallor that is observed in patients with attacks of Raynaud's phenomenon reflects the intense constriction of arterial inflow and arteriovenous anastomoses, combine with the mobilization of venous blood, whereas other color changes (bluing or reddening) can reflect distinct vasomotor changes occurring in arteries, veins, and arteriovenous anastomoses.

Diagnostic criteria for primary Raynaud phenomenon include the following:

- Attacks triggered by exposure to cold and/or stress
- Symmetric bilateral involvement
- Absence of necrosis
- Absence of a detectable underlying cause
- Normal laboratory findings for inflammation
- Absence of antinuclear factors

Vasculitis

Large Vessel Vasculitis (LVV)

Takayasu Arteritis (TAK)

[Granulomatous inflammation of the aorta and its major branches. Usually occurs in patients younger than 50.]

Giant Cell Arteritis (GCA)

[Giant-cell (temporal) arteritis Granulomatous arteritis of the aorta and its major branches, with a predilection for the extracranial branches of the carotid artery. Often involves the temporal artery. Usually occurs in patients more than 50 years old and is often associated with polymyalgia rheumatica.]

Medium Vessel Vasculitis (MVV)

Polyarteritis Nodosa (PAN)

[Necrotizing inflammation of medium sized or small arteries without glomerulonephritis or vasculitis in arterioles, capillaries, or venules.]

Kawasaki Disease (KD)

[Arteritis involving large, medium-sized, and small arteries and associated with mucocutaneous lymph node syndrome. Coronary arteries are often involved. Aorta and veins may be involved. Usually occurs in children.]

Small Vessel Vasculitis (SVV)

ANCA-Associated Vasculitis (AAV)

-Microscopic Polyangiitis (MPA)
-Granulomatosis with Polyangiitis (Wegener's) (GPA)
-Eosinophilic Granulomatosis with Polyangiitis (Churg Strauss) (EGPA)

Immune Complex SVV

-Anti-GBM Disease
-Cryoglobulinemic Vasculitis (CV)
-IgA Vasculitis (Henoch-Schönlein) (IgAV)
-Hypocomplementemic Urticarial Vasculitis (Anti-C1q Vasculitis)

Variable Vessel Vasculitis (VVV)

Behçet's Disease (BD)
Cogan's Syndrome (CS)

Single Organ Vasculitis (SOV)

Cutaneous Leukocytoclastic Angiitis
Cutaneous Arteritis
Primary CNS Vasculitis
Isolated Aortitis
Others

Vasculitis Associated with Systemic Disease

Lupus Vasculitis
Rheumatoid Vasculitis
Sarcoid Vasculitis
Others

Vasculitis Associated with Probable Etiology

Hepatitis C Virus-Associated Cryoglobulinemic Vasculitis
Hepatitis B Virus-Associated Vasculitis
Syphilis-Associated Aortitis
Drug-Associated Immune Complex Vasculitis
Drug-Associated ANCA-Associated Vasculitis
Cancer-Associated Vasculitis
Others

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Skin Cover

PS Bhandari

Anatomy of Skin

Skin is the largest organ in the body with a surface area of approximately 1.72 square meters in an adult male. It varies in thickness depending on the age and sex of the individual and the anatomic location on the body. Thus, the skin is thinnest in children, gradually increasing in thickness from 2nd decade to 4th-5th decades of life and thereafter, starts thinning.. Males have thicker skin than females in all anatomic areas. Skin is thicker in some regions and thinner in others in any given individual. Thus, skin of soles of feet and palm of hands is thickest while that of eyelids, post auricular region and prepuce is very thin.

The skin consists of two layers, epidermis (derived from ectoderm) and dermis (derived from mesoderm), intimately attached to each other. Epidermis constitutes approximately 5% of the skin while the remaining 95% is dermis. Being avascular, epidermis depends on the underlying dermal layer for all its nourishment by diffusion.

The dermis or the deeper layer is more complex vascular layer and is further sub-divided into superficial papillary dermis and deeper reticular dermis The reticular dermis contains fibroblasts, mast cells, nerve endings, lymphatics and some dermal appendages.These dermal appendages are sweat and sebaceous glands and hair follicles which are lined with epithelial cells.They act as source of epithelial cells whenever epidermis and part of dermis itself is damaged due to injury or after their surgical removal as in skin grafting. . The interface between the epidermis and dermis is ridge and groove interdigitations with specialized anchoring structures linking the two layers to prevent the stripping off of the epidermis from the dermis due to shearing forces.

SKIN GRAFT

A Skin Graft is a piece of skin (epidermis and dermis) which is completely separated from the body and transplanted onto another site from where it regains its blood supply. Skin grafting is a fundamental reconstructive surgical procedure.

History

Sushrata, the great Indian Surgeon, practicing near modern day Varanasi (Benaras) in 600 BC, wrote about skin grafts in Sushrata Samhita (a compilation of surgical knowledge of his times). Grafts were obtained from buttocks after repeated slapping with wooden paddles (flagellation) to repair an amputated nose.

In1804, Baronio, an Italian surgeon, did the first successful autograft in sheep. Sir Astley Cooper (1817) grafted a full thickness piece of skin from man's amputated thumb onto the stump for recovery. First successful skin autograft on nose in humans, in modern times, was done in 1823 by Bunger.

Reverdin (1869) used allograft by pinch grafting with very thin pieces of epidermis ('epidermic' grafts) while Ollier, (1871) included dermis in Reverdin's graft and showed better outcome ('dermoepidermic' grafts). In1875, Wolfe, described the use of full thickness skin graft to treat ectropion of the eyelid.

Types of Skin Graft

A skin graft may be classified in different ways. Thus,

(A) On the basis of their origin, a skin graft may be an:
- (i) Autograft: A skin graft transferred from one part of the body to another in the same individual is called an autograft. An isograft is a graft between two genetically identical individuals like identical twins and behaves like an autograft.
- (ii) Allograft (Homograft): A graft transferred from one individual to another of the same species. This will "take" (see later) exactly like an autograft and survive temporarily but will ultimately get rejected.
- (iii) Xenograft (Heterograft): A graft transferred from one species to another, e.g., pig to humans. This graft will never 'take' and act as temporary skin substitute only.

(B) On the basis of their dermal content, a skin graft may be:
- (i) Partial Thickness Skin Graft (Split Thickness Skin Grafts, STSG or SSG): These consist of whole of epidermis and part of dermis. They have been further classified into thin, intermediate and thick split thickness skin grafts depending on the amount of dermis included. Thin grafts, also known as Thiersch grafts, are 0.008-0.012 inch thick while intermediate grafts are 0.012-016 inch thick. Thick grafts, also known as Padgett grafts, are 0.016-0.020 inch thick and are almost equivalent to full thickness grafts in properties without the problem of closure as their

donor areas can heal of their own Thicker the graft from a given site, the more it matches the characteristics of normal skin.

(ii) Full thickness Skin Graft (Full Thickness Skin Graft, FTSG or FTG): They have the full component of epidermis and the dermis. They are also known as Wolff-Krause grafts. The donor site of FTG is closed primarily but when very large, needs thin SSGs to heal

Mechanism of Skin Graft "take"

Revascularization of skin graft at its new recipient site leading to its permanent survival is known as "take" of the graft. Classically, three phases/mechanisms of graft "take" have been described:

(i) Phase of Plasmatic/Serum Imbibition…..The plasma which leaks from the recipient bed fills the space between the graft and the raw area. The fibrinogen in the plasma forms a glue-like substance helping in adhesion of the graft to the bed. The remaining serum from the bed enters into the empty graft capillaries and nourishes the graft for first 24-48 hours by serum imbibition.

(ii) Phase of 'inosculation' ('to kiss'): By the end of 48 hours, the fine capillary buds from the graft bed have made end to end contact with the graft capillaries through the fibrin layer. Open channels are formed and blood flow is established. By day 4, blood flow through the graft is established and the graft appears pink. The blood flow through the graft continues to improve over a month when the revascularization is said to be complete.

(iii) Phase of revascularization: The revascularization and establishment of circulation in the skin graft is believed to occur by one or all the three processes described below. First, after inosculation, the graft consists of its original vasculature which has formed anastomoses with the vasculature of the recipient bed. The second process is that host vessels grow into the degenerated graft vasculature which acts as conduits only. Thirdly, the host vessels enter de novo into the dermis of the graft. Probably, all the three contribute in revascularization. The circulation is restored in the graft by 4^{th} to 7^{th} day. Restoration of lymphatic circulation parallels that of the blood supply.

Donor Sites

- the split skin grafts: Generally the split skin grafts are harvested from the lower extremities especially the thighs. However, in extensive avulsion injuries, limited donor sites may be available and graft may have to harvested from upper limb, back, buttocks or even scalp or scrotum
- Full thickness grafts: They are usually harvested from post/pre auricular region or supraclavicular area or medial arm.

Instrumentation For Harvesting of graft

(a) For full thickness skin graft, no special instrument is required and it is generally harvested with a number 15 blade mounted on a Bard Parker handle.

(b) For split skin graft, various instruments are available.
(i) Mechanical Dermatomes: They are usually called knives with detachable blades. Humby skin grafting knife is one of the earliest ones. Various improvements have been done in this model with Watson's skin grafting knife incorporating all the advantages and is one of the most commonly used hand held instrument. Their disadvantages are harvesting of grafts with irregular edges and of variable thickness.It is difficult to cut split skin grafts from trunk and scalp with Humby skin grafting knife

(ii) Power driven dermatomes. These may be air or electric powered. Brown dermatome is operated by air pressure. Electrical dermatomes (e.g., Brown, Zimmer) are better for cutting thinner and longer strips of skin with a more homogeneous thickness. They use an electrically driven blade which vibrates rapidly. Different widths can be set on the dermatome as per need.

Healing of Donor sites of Partial Thickness Skin Grafts

In split skin graft, the donor site from where graft has been harvested heals of its own from epithelial remnants of the epidermal appendages, the sweat and sebaceous glands and hair follicles. It must be noted, however, that the dermis does not regenerate. Only the epidermis forms over the residual dermis. Thus, the skin of the donor area becomes thinner to an extent depending upon the thickness of the dermis in the graft harvested. A donor site for an intermediate graft usually takes about 2 weeks to heal.

Preparation of Wound Bed

Any area which is capable of producing granulation tissue will take the graft. A skin graft will not 'take' over a bone denuded of periosteum, cartilage devoid of perichondrium, a tendon denuded of paratenon as they do not develop granulations. Membranous bones of skull do accept a graft because if left raw, granulations form on

them. All healthy granulating areas accept grafts readily except very long standing chronic granulating wounds which have been replaced extensively by fibrous tissue and have poor vascularity.

Skin Graft Expansion

In patients with extensive avulsion injuries and also in extensive post burn raw areas, there may be a shortage of the amount of skin graft required compared to the size of recipient area. In these patients, various techniques have been devised to expand the graft. It has been observed that after grafting, the epithelium from the graft margin can spread for up to 5 mm. The skin graft can be meshed using mechanical devices (skin graft mesher) so that the graft on stretching becomes a uniform mesh and expands.

Skin Graft Application and Initial Care

For the procedure of skin grafting to succeed, recipient bed should be free of infection, and absolute haemostasis should be achieved .The graft should not move over the recipient bed once it is placed lest the delicate vascular connections get disrupted with the resultant loss of graft. Several techniques are employed alone or in various combinations to achieve complete immobilization in different types of wounds.

Causes of Skin Graft Failure

There are a number of reasons for its failure, where graft "take" may be less than satisfactory.

a) Graft Bed: A skin graft will not "take" on an area without blood supply. Thus, bare tendon, bare bone, bare cartilage and bare nerve, i.e., devoid of paratenon, periosteum, perichondrium and epineurium respectively, do not accept grafts The graft 'take' is unsatisfactory over poorly vascularized tissues (e.g., chronically fibrosed granulating areas), exposed fat (adipose tissue), crushed tissues, irradiated areas, etc.

b) Poor graft to bed contact: Formation of hematoma, seroma or wound exudates between the recipient site and the graft prevent the vascularisation of graft with consequent loss.

c) Movement: Absolute immobility between the graft and the recipient bed is a must for a successful graft "take'. This is because of the extremely delicate mechanism of graft revascularization. To achieve this, a number of techniques are applied either alone or in combination. (see above).

d) Infection: A skin graft may be applied over electively created raw areas, like after release of a contracture or excision of a benign or malignant lesion, in which case the recipient area is considered to be sterile. More commonly, the skin graft is applied to close extensive raw areas following trauma where the wound cannot be expected to be sterile. In these cases, if the number of bacteria is less than 10^3/gram of tissue, graft 'take' is uneventful. However, as the bacterial load increases, there are greater chances of graft loss and it may become unacceptable beyond 10^5/gram of tissues. The presence of β-hemolytic *Streptococcus* in the wound is an absolute contraindication for grafting as the fibrinolysin produced does not allow the graft to adhere to the wound bed at all. The presence of *Staphylococcus aureus* is also a contraindication because after a successful 'take', the graft gradually gets lost and this may be an unacceptably large area requiring regrafting later after eradication of these bacteria.

e) Technical Errors

f) Miscellaneous factors: Malnutrition, anemia, use of steroids, antineoplastic agents, anticoagulants etc. may lead to unfavorable results.

FLAPS

Classically, a flap has been defined as a "tongue of tissue containing skin and sub cutaneous tissues which carries its own blood supply and remains attached to the body at all times for its nourishment". However, the evolution of flap surgery in the last five decades has been so rapid that this definition has become not only inaccurate but also highly inadequate. Thus, with the increasing knowledge of cutaneous vascular supply, development of microvascular techniques, increasing refinements in available flaps and rapid description of new flaps, a part of fibula or even omentum with its nutrient vascular pedicle is also now termed a flap. For a flap to survive, it must have a pedicle which remains attached to the body at all times or else is separated from the body for a very short while only (may be a few hours) and its vascularity restored by microvascular anastomosis as is done for free flaps.

History

Sushrata not only described the skin graft but also is credited with the first use of skin flaps. He is rightly regarded as the father of Plastic Surgery in the world. Reconstruction of chopped off noses (for theft and adultery) was done using flaps from the forehead and cheeks. The term flap originated in 16^{th} century from the Dutch word 'flappe', something that hangs broad and loose, joined only on one side. Tagliacozzi, an Italian surgeon in 16^{th} century, used a laterally based flap from the arm to reconstruct nose. During World War I, Sir Harold Gilles (now

known as father of modern Plastic Surgery) from England and other workers like Filatov from Russia and Ganzer from Berlin described the tube flap and this was extensively used to treat War victims

Cutaneous Vasculature

Within the deeper layer of the skin, i.e., dermis, two distinct vascular arcades are present. These are (i) superficial vascular plexus that runs between the reticular and papillary layers of the dermis; it supplies the epidermis by diffusion, and (ii) a more robust deep vascular plexus, commonly called as subdermal plexus, which runs between the dermis and the subcutaneous tissues and is responsible for the subdermal bleeding.

The skin receives blood supply from various sources. The blood reaches the skin by the following routes:

(1) The direct cutaneous system: Here, the vessel runs in subcutaneous tissues after its origin from the source vessel. Thus, groin flap is supplied by superficial circumflex iliac artery which is a direct branch of femoral artery.
(2) The musculocutaneous system: A named vessel supplying the subcutaneous muscle divides into various smaller vessels which run perpendicular to the muscle, perforate it to come out and reach the skin. This type of blood supply is more common in the trunk region where the muscles are broad and flat. For example, the latissimus dorsi is supplied by thoracodorsal artery and the skin over the back of the trunk overlying this muscle gets supplied by its musculocutaneous perforators.
(3) The septocutaneous system: The named major arteries of the extremities give out branches which traverse the fascial septa (septocutaneous perforators) separating the various compartments containing the long and thin muscles and supply the deep fascia. The deep fascia, in turn, supplies the skin.

The blood, thus, reaches the subcutaneous tissues and the subdermal plexus by one or more of the above three routes. The proportionate contribution of each of these systems varies in different regions of the body.

Classification

The flaps have been classified according to various considerations:

(i) ***Relation of donor to recipient site***: Thus, they may be local, regional or distant flaps

(ii) ***Type of Movement***: Local flaps can be further divided on the basis of their movement into the defect. The three basic movements are advancement, transposition and rotation.

There may be a combination of two or even all the three movements in various flaps. Thus, a flap which moves purely in a rotation design is called a rotation flap while the one who combines rotation and advancement movements is called a rotation–advancement flap. Although traditionally, these flaps were designed in a random pattern fashion (see later), with the increasing knowledge of cutaneous vascularity, more and more flaps clinically used include either a named vessel or deep fascia, muscle etc. to enhance their vascularity and length and survival chances.

An advancement flap has a linear configuration and moves into the defect by being stretched into the defect. The flap is designed adjacent to the defect and moves into the defect at right angles to its linear axis.

The transposition flap and the rotation flap are pivotal flaps with a curvilinear configuration.

(iii) ***Vascular source and pattern***: Random versus axial pattern flaps:

Random pattern flaps:

To begin with, all the flaps described were random pattern flaps because the blood supply of the skin was not known. Hence, they were also called local cutaneous flaps. The maximum surviving length of these flaps, as is now known, is directly related to the perfusion pressure of the vessels in the flap. This was unpredictable but with experimental studies and experience gained from the success/failure of clinical cases is considered to be 1:1 in extremities and approaches 3-4:1 in head and neck region which are highly vascularized regions of the body.The random flaps receive the blood supply from the perforator myocutaneous vessels terminating in the dermal-subdermal plexus which nourishes the skin. They can also receive the supply from direct cutaneous system or fasciocutaneous system. The flap is raised at the subcutaneous level. Based on their movement they were divided into advancement, transposition and rotation flaps.

Axial pattern flap:

It is a flap of skin and subcutaneous tissues that includes a direct cutaneous vessel and its accompanying venous drainage in such a way that the vessel runs parallel to the long axis of the flap. The length of the flap which survives is equal to the length of the vessel plus the random extension equal to the breadth of the flap (i.e., 1:1 ratio). The length to breadth ratio and chances of complete survival of all flaps whether random or axial pattern can be improved by the delay procedure.

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(iv) ***Composition or Tissue types:*** The initial flaps were all skin and subcutaneous tissues only. Gradually, muscle and deep fascia were added onto them to add blood supply to the skin. Thereafter, bone or nerve was added to it for reconstructing parts requiring bone or sensation respectively. With increasing knowledge of vascular pattern in the body and the blood supply to the skin, the vessels were isolated more and more and only tissues required were dissected out to decrease the donor site morbidity leading to perforator flaps. With the development of microvascular surgical techniques, flaps are now detached completely from their donor site along with their vascular pedicle and taken to distant sites and blood supply restored with microvascular surgical methods. At present, according to composition, the flap may contain:

- skin and subcutaneous tissues,
- skin, subcutaneous tissues and deep fascia (Fasciocutaneous flap)
- skin, subcutaneous tissues and muscle (Myocutaneous or Musculocutaneous Flap)
- skin, subcutaneous tissue and bone (Osseocutaneous Flap)
- Muscle only (muscular flap)
- Bone only (e.g., Free fibular flap)
- Skin, subcutaneous tissues and nerve (Neurocutaneous Flap)
- Omentum, part of small bowel when used to reconstruct with microsurgical techniques etc. are also considered flaps.

A composite flap contains more than one tissue. Thus, myocutaneous, fasciocutaneous, osseo-myo-fascio-cutaneous flaps are all composite flaps while gastrocnemius flap or fibular flap are not. Some flaps have also been named after the person who first described their design and use. Thus, we have Limberg's flap, Ponten's flap, Abbe's flap etc.

Myocutaneous or Musculocutaneous Flaps

A myocutaneous flap consists of skin, subcutaneous tissues and the underlying muscle which is supplied by a vascular pedicle. Mathes and Nahai(1981) classified the myocutaneous flaps into five groups based on the vascular supply to the muscles. Thus,

Type 1: Single pedicle e.g., Gastrocnemius, Tensor fascia lata
Type II: One dominant pedicle and one minor pedicle e.g., Trapezius, Gracilis
Type III: Two dominant pedicles, e.g., Serratus anterior, Gluteus maximus
Type IV: Multiple segmental pedicles e.g., Tibialis anterior, Sartorius
Type V: One dominant pedicle with multiple segmental pedicles .e.g., Latissimus dorsi, Pectoralis major

Muscle Flaps

Ralph Ger was the first to use the muscle alone as a flap for the difficult areas in the lower limb. These flaps not only provided the bulk to fill the cavity left after the infected, osteomyelitic bone was curetted out but also were more useful to clear infection than all other flaps.

Fasciocutaneous Flaps

Almost one hundred years back, Gilles and Esser had independently suggested that inclusion of deep fascia in a random pattern flap may be advantageous. Unfortunately, this was never studied methodically till Ponten in 1981 published clinical cases and showed the benefits of including deep fascia in flaps raised in lower extremities. The deep fascia is sandwiched between two layers of vascular network, the suprafascial and the subfascial plexus. The suprafascial plexus has the capability of nourishing both the underlying deep fascia and the overlying skin via the connections to the subdermal plexus.

Cormack and Lamberty classified fasciocutaneous flaps into four types based on their vascular supply: Type A flap, Type B flap, Type C flap and Type D flap

Microvascular Free flaps

A microvascular free flap is a type of distant axial pattern flap in which the flap along with vascular pedicle is divided completely from its donor site and donor vessels and the latter are anastomosed to vessels at the recipient site using microvascular techniques. Thus, the original definition of the flap given in the beginning above, viz. "…and remains attached to the body at all times for its nourishment", gets modified in case of free flaps. These flaps may have any of the composition as given above. These flaps have revolutionized the various reconstructive tissue transfer procedures which were earlier either not possible or extremely cumbersome and time consuming. Microsurgical anastomosis of vessels, quite naturally, started with the availability of operating microscope, experimental replantation of severed extremity in animals, clinical reimplantation, experimental transfer of free flaps in animals culminating in partial success of first clinical free flap by Antia and Buch (in India) and lastly the first successful free flap by McLean and Buncke (1970) and Daniel and Taylor (1973).

Island Flap

A pedicled flap whether random pattern or axial pattern usually have a broad base. While this broad base is required for the survival of a random pattern flap, an axial pattern flap can be islanded by skeletonising its nutrient vessels so that it is attached to the body only with its vascular pedicle. The corollary is that it can be used

as a free flap as well. The advantage is that the donor as well as recipient sites can be closed all around in the same sitting as the flap transfer.

Perforator flaps

In the last one decade, perforator flaps have become the most widely used flaps and have acquired the distinction of being positioned on the top of the reconstructive ladder. This is because they include only the exact amount of tissue required and its immediate vascular pedicle without sacrifice of any passive tissue just for the sake of vascular supply to the flap as is done in myocutaneous, fasciocutaneous flaps, etc. They are not only thin, pliable and moldable providing excellent wound coverage but also have the least donor site morbidity. The era of perforator flaps began with the publication of Koshima and Soeda (1989) who used inferior epigastric artery skin flap without taking the rectus femoris muscle. However, these flaps do require a very careful dissection of the perforator through the muscle akin to a microvascular surgery minus the anastomosis for even a pedicled perforator flap.

Propeller Flaps

Use of propeller flaps in defects of lower extremity has become very common in recent times. It is basically an islanded fasciocutaneous flap with the pedicle entering the flap perpendicularly in such a way that it divides the flap in one longer and the other shorter segment. When rotated at 180 degrees with the perforator forming the pivot point for rotation, the smaller segment replaces the longer side and vice versa, covering the wound in turn. The donor area is skin grafted. This has been likened to a propeller and hence given the name of propeller flap. It is obvious that the pedicle has to be dissected upto its maximum length and has to be single lest the two pedicles form a twisted or braided cord jeopardizing the circulation.

Uses of Flaps

Last 50 years have seen a tremendous change in our knowledge about the cutaneous vascular supply from its origin in the aorta to the most distant capillary in the skin in all regions of the body. This has led to the development of a very large number and variety of flaps, probably more than we actually need. Combined with the availability of operating microscope with great magnification, fine instrumentation including microsutures and microsurgical techniques, this has completely revolutionized the way we look at the management of a large number of surgical defects. So much so, a modern Orthopedic Surgeon cannot think of life without an associate Plastic Surgical colleague! In Orthopedic surgery, the flaps are required in following situations:

(i) Closure of wounds where graft will not ‘take’: As stated earlier, grafts will not ‘take’ over denuded tendons, bone, cartilage and poorly vascularized wound bed. Wounds over tibia usually have very poor circulation and a stable cover in the form of a flap is often required.

(ii) Reconstruction of composite defects e.g. in defects of head and neck region following excision of tumours

(iii) Reconstruction of organs e.g. in breast reconstruction, Mandibular reconstruction , Reconstruction of thumb:

(iv) Closure of wounds with exposed and fractured bone, tendons, implants etc.: Closure of exposed open joints: After excision of tumors or in skin avulsion injuries, the joints often get exposed with risk of loss of function, if not covered immediately by a flap cover.

(v) Management of chronic osteomyelitis: After thorough debridement and sequestrectomy, muscle flaps are placed in the resulting defect leading to an increased local vascularity with clearance of the infection and a healed wound.

(vi) A bone or joint cannot be exposed for any surgical intervention through a scar/adherent skin graft ..

(vii) Reconstruction of sole defects: Weight bearing regions of sole need cover with a flap even if they can be skin grafted or have been earlier split skin grafted because the sole skin is so special. Instep island flap is ideal but often not available

(viii) Reconstruction of bone defects: Segment of long bones lost due to trauma or excised in conservative excision of bone tumors can be bridged using vascularized bone transfer (e.g., fibula) using microvascular techniques.

(ix) Provision of padding in finger tip injuries and pressure sores: Finger tip injuries, even if graftable, often require a reconstruction with a flap to restore padding and restore contour or else the tip becomes painful whenever it touches something. Pressure sores with their deep cavity left after ostectomy/ bursectomy require well vascularized large flaps to fill the cavity and provide additional blood supply for their healing and stability.

(x) To restore circulation to distal extremity in case of damage to vascular structures: A flow through flap ,e.g., radial forearm flap , can often save the limb if a segment of the vasculature along with cutaneous cover is destroyed due to injury or is excised in the removal of a lesion.

(xi) Functional muscle transfer: Pedicled and free ‘functional muscle transfer’ can be done to restore function of a muscle. Thus, pedicled latissimus dorsi muscle can be used after dividing its insertion and attaching it to elbow to restore function of triceps muscle

(xii) Major vessels when exposed after an avulsion injury or excision of a lesion also need coverage by a flap to prevent blow out.

Complications

Complications following reconstructive procedures using can infection, seroma, haematoma, partial or total necrosis of flap, bulky flap and aesthetically not acceptable.

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Surgical Site Infection

Arun Gupta

Introduction

Infections that occur in the wound created by an invasive surgical procedure are generally referred to as surgical site infection (SSI). Prevalence studies tend to underestimate SSI because many of these infections occur after the patient has been discharged from hospital. It is important to recognise that SSI can range from a relatively trivial wound discharge with no other complications to a life-threatening condition.

Definition

The Centers for Disease Control and Prevention (CDC)[1] considers SSI to include both incisional SSI and organ space SSI. The incisional SSI is subdivided into superficial and deep SSI.

Superficial Incisional SSI.
Infection occurs within 30 days after the operative procedure and involves only the skin and subcutaneous tissues. At least one of the following must be present:

1. Purulent discharge
2. Organisms isolated from fluid or tissue
3. Pain, localized swelling, redness or heat AND incision deliberately opened by surgeon.

Deep Incisional SSI
Infection occurs within 30 days after the operation if no implant is left or within 1 year if implant left AND involves deep soft tissues of the incision. At least one of the following must be present:

1. Purulent discharge
2. Wound dehiscence or the surgeon deliberately opens the incision in the deeper plane
3. Evidence of infection involving the deep tissues by radiological examination or during reoperation

Organ/Space SSI
Infection occurs within 30 days after the operation if no implant is left or within 1 year if implant left and the infection involves the part of body that is opened or manipulated during the operative procedure. At least one of the following must be present:

1. Purulent discharge from the drain in the organ space.
2. Organisms isolated from fluid or tissue
3. Evidence of infection involving the organ or space by radiological examination or during reoperation.

Risk Factors

A. The microbes

The microbes responsible for SSI settle into the wound in the operating room. They may originate from the skin of the patient, the surrounding tissues and organs or the operation theatre (OT) environment. The CDC defines the wounds into 4 classes focussing primarily on the degree of contamination likely to be present during the operation [2].

1. ***Clean wounds***. A wound in which no inflammation is encountered and the respiratory, alimentary, genital or the urinary tract is not entered. Only organisms from the skin or the external environment are likely to be introduced into the wounds.
2. ***Clean-contaminated***. A wound in which the respiratory, alimentary, genital or the urinary tract is entered under controlled conditions and without unusual contamination. There should be no indication of major break in technique during surgery.
3. ***Contaminated***. Gross spillage from the gastrointestinal tract. Also included are open fresh accidental wounds. If there were a major break in the sterile technique during surgery, it would also fall into this category.
4. ***Dirty.*** Surgery for existing clinical infections or where, perforated viscera is encountered, will fall into this category.

Besides the endogenous route the microbes can gain entry into the wound during surgery because of perioperative factors. This could be the surgeons' hands, operating room air and the operating instruments.

B. Factors allowing the microbes to flourish

Poor surgical technique like inadequate hemostasis, failure to obliterate dead space and excessive tissue trauma can allow the organisms to flourish. Another important factor is the presence of foreign material.

C. Patient factors

The age of the patients, the nutritional status including obesity, presence of Diabetes mellitus, a history of smoking or coexistent infections in other areas of the body have been associated with higher incidence of SSI.

Prevention of SSI

Microbial factors
Some of these factors have been debated with no clear consensus.

Pre-operative showering

Randomised controlled trials comparing antiseptic preparation used for preoperative full-body bathing or showering with non-antiseptic preparations in people undergoing surgery were searched for and reported by Webster and Osborne[3]. There were three trials involving 7791 participants that compared chlorhexidine with a placebo. The review showed that there was no statistically significant reduction in the rates of SSI.

Hair removal

The removal of hair may be necessary to adequately view or access the operative site and it is sometimes undertaken because of a perceived increased risk of microbial contamination of the operative site from the presence of hair. However, micro-abrasions of the skin caused by shaving using razors may actually allow multiplication of bacteria, within the skin and on the skin surface, particularly if undertaken several hours prior to surgery. An increase in the number of microorganisms colonising the skin surrounding the operative site may facilitate contamination of the wound and subsequent development of SSI.

Tanner et al [4] did a review of published studies on this aspect. This review found no statistically significant effect on SSI rates of hair removal. They concluded that when it is necessary to remove hair, clippers are associated with fewer SSIs than razors. They found that there was no significant difference in SSI rates between depilatory creams and shaving, or between shaving or clipping done the day before surgery or on the day of surgery.

Hand decontamination

Hand decontamination prior to surgery is required to minimise the risk that either the resident flora that normally colonise the skin or transient organisms acquired by touch contaminate the surgical wound. While transient microorganisms are readily removed by soap and water, antiseptics such as alcohol or detergent solutions are required to eliminate resident microorganisms that reside in deep crevices and hair follicles.

Perienti et al [5] did a randomized equivalence trial to compare the effectiveness of hand-cleansing protocols in preventing surgical site infections during routine surgical practice at six surgical services from teaching and non-teaching hospitals in France. A total of 4387 consecutive patients who underwent clean and clean-contaminated surgery between January 1, 2000, and May 1, 2001 were taken.

Surgical services used 2 hand-cleansing methods alternately every other month: a hand-rubbing protocol with 75% aqueous alcoholic solution containing propanol-1, propanol-2, and mecetronium etilsulfate; and a hand-scrubbing protocol with antiseptic preparation containing 4% povidone iodine or 4% chlorhexidine gluconate. The two protocols were comparable in regard to surgical site infection risk factors. Surgical site infection rates were 55 of 2252 (2.44%) in the hand-rubbing protocol and 53 of 2135 (2.48%) in the hand-scrubbing protocol. They concluded that hand-rubbing with aqueous alcoholic solution, preceded by a 1-minute non-antiseptic hand wash before each surgeon's first procedure of the day and before any other procedure if the hands were soiled, was as effective as traditional hand-scrubbing in preventing surgical site infections. The hand-rubbing protocol was better tolerated by the surgical teams. They concluded that hand-rubbing with liquid aqueous alcoholic solution can be safely used as an alternative to traditional surgical hand-scrubbing.

Wound preparation

Randomised controlled trials evaluating the use of preoperative skin antiseptics applied immediately prior to incision in clean surgery were evaluated and reported [6]. Iodine in alcohol was compared to alcohol alone in one trial; one trial compared povidone- iodine paint after preparing with soap and alcohol. Six studies compared different types of iodine-containing products with each other and five compared iodine-containing products with chlorhexidine- containing products. There was evidence from one study suggesting that pre-operative skin preparation with 0.5% chlorhexidine in methylated spirits led to a reduced risk of SSI compared with an alcohol based povidone iodine solution. There were no other statistically significant differences in SSI rates in the other comparisons of skin antisepsis.

Use of plastic drapes
Using plastic adhesive drapes to protect the wound from organisms that may be present on the surrounding skin during surgery is one strategy used to prevent surgical site infection. Results from non-randomised studies have produced conflicting results about the efficacy of this approach. In a review by Webster and Alghamdi [7] which included five studies involving 3082 participants comparing plastic adhesive drapes with no drapes and two studies involving 1113 participants comparing iodine-impregnated adhesive drapes with no drapes, a significantly higher proportion of patients in the adhesive drape group developed a surgical site infection when compared with no drapes.

Antibiotic prophylaxis
Using prophylactic antibiotics when the risk of contamination during surgery is high, as happens in contaminated and dirty wounds, is an important aspect of preventing SSI. In clean wounds the usage is controversial.

The general principles are the following:

1. Select the antibiotic based on the likely pathogen likely to contaminate the wound at the time of closure.
2. In clean wounds antibiotic coverage may be used if a foreign body is left like an implant or a mesh or there are significant associated co-morbidities in the patient.
3. The antibiotics should be started just before the commencement of the operation. In a Trial to Reduce Antimicrobial Prophylaxis Errors (TRAPE) twenty-nine hospitals prospectively obtained information from 4472 randomly selected cardiac, hip/knee arthroplasty, and hysterectomy cases. Surgical site infections (SSIs) were ascertained through routine surveillance, using National Nosocomial Infections Surveillance system methodology. SSI risk increased incrementally as the interval of time between antibiotic infusion and the incision increased. The infection risk following administration of antibiotic within 30 minutes prior to incision was 1.6% compared with 2.4% associated with administration of antibiotic between 31 to 60 minutes prior to surgery[8].
4. The antibiotic in clean and contaminated cases could be given as a single shot or may be continued for at the most 24-48 hours after the surgery.
5. In patients with dirty wounds the patients often present with sepsis. Sepsis bundles have been designed to standardize critical care as per Surviving Sepsis Campaign practice guidelines [9]. Administration of early intravenous antibiotics to optimize outcomes, including prevention of SSI, have been recommended. Current guidelines [10] recommend initiating *empiric* antimicrobial therapy within the first hour using one or more drugs that have activity against ALL LIKELY pathogens. The antibiotics can be deescalated to an *appropriate* antibiotics after the availability of culture reports. This has resulted in a marked improvement in the survival rates and reduced the incidence of SSI including wound dehiscence.

Patient Factors
Patient comorbidities can contribute significantly to the development of SSI. Preoperative optimization of these patient related factors is the key to the prevention of SSI. Many of these factors are, however, non modifiable specially in emergency situations.

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Intestinal Fistulas

Shaji Thomas

A *fistula* is defined as an abnormal communication between two epithelialised surfaces. Advances in fluid and electrolyte / acid-base therapy, blood administration, critical care, ventilator management, antibiotic regimens, and nutritional management have brought about a remarkable reduction in mortality in these patients over the last few decades. In the present era, morality is largely attributable to uncontrolled sepsis and sepsis-associated malnutrition. 75% to 85% of acquired gastrointestinal fistulas are of iatrogenic origin and occur as a result of dehiscence of anastomoses, intraoperative injury to the bowel or blood supply, erosion from indwelling tubes, retention sutures or prosthetic mesh, and misplacement of a suture through the bowel during abdominal closure, or after percutaneous drainage of an abscess. They remaining 15% to 25% are spontaneous in origin and may be as a result of radiation, inflammatory disease, diverticular disease, appendicitis, ischemic bowel, perforation of gastric and duodenal ulcers, pancreatic and gynecologic malignancies and intestinal tuberculosis.

General Considerations

Gastrointestinal fistulas result from perforations that communicate with adjacent organs or intestine (internal fistulas) or communicate externally with the abdominal wall (enterocutaneous fistula). Multiple factors make them a complex and potentially lethal condition. These patients are usually systemically ill. Sepsis is a recognized antecedent risk factor. Malnutrition is also a common occurrence resulting both from the hypermetabolic state, and also from the large volume of protein rich fluid produced. Fluid and electrolyte abnormalities, including hypovolemia, hypokalemia, hypomagnesemia and metabolic acidosis are common. Malabsorption and malnutrition from bacterial overgrowth further complicates matters. Finally, local wound excoriation and discomfort from the enzymatically active intestinal effluent can complicate potential abdominal wall reconstruction and recovery.

Etiology

A. *Gastric and duodenal fistulas*
Majority of gastric and duodenal fistulas occur after surgical, endoscopic or interventional procedures. Post-operative anastomotic or suture line leaks account for 80% to 85% of all such fistulas. Inflammatory causes are rare; Crohn's disease, gallstone erosion resulting in cholecystoduodenal fistula, necrotizing pancreatitis, and neoplastic causes make up most of them.

B. *Small intestinal fistula*
Almost any surgical procedure involving the abdomen can result in iatrogenic injury to the small intestine and subsequent fistula formation. External small intestinal fistulas (enterocutaneous fistulas) are the most frequent type of small intestinal fistula, and commonly follow postoperative complications. The ileum is the most common site of origin of an enterocutaneous fistula.

Diagnosis of Perforations and Fistulas

Postoperatively, unrecognized perforations caused during surgery or leaks are manifested as instability or failure to improve as expected. Fistula formation is frequently heralded by fever and abdominal pain until gastrointestinal contents are discharged through an abdominal incision or the umbilicus. If the diagnosis if uncertain, the patient may be given activated charcoal or indigo carmine by mouth and the drainage inspected for these substances.

Staging and Classification

Gastrointestinal fistulas can be classified by their anatomic characteristics, and they are either internal or external (enterocutaneous). Typically, the name of a fistula is derived from the involved and connected organs or structures, eg., gastrocolic, gastrojejunal fistulas.

Fistulas can be classified physiologically in terms of output over a 24-hour period. They can be classified as low (<200 ml/day), moderate (200-500 ml/day), and high (>500 ml/day).

The anatomic and etiologic factors are much more important in predicting spontaneous closure than the actual output of the fistula.

Complications

A. Fluid and electrolyte abnormalities
Secretions from the salivary glands, stomach, duodenum, pancreas, liver and small intestine amount to 8 to 10 L/day, and this fluid is rich in sodium, potassium, chloride, and bicarbonate. The degree of volume

depletion and electrolyte imbalance depends on the anatomic location of the fistula and can vary from 50 to 3000 ml/day. High-output duodenal or jejunal fistulas continue to carry a mortality of around 35%, and are particularly prone to volume and electrolyte loss, and aggressive fluid management is necessary.

The most common abnormalities seen are hypovolemia, hypokalemia, and metabolic acidosis. Hypokalemia occurs primarily from potassium loss in the fistula effluent, although hypovolemia also contributes by causing renal retention of sodium in exchange for potassium secretion. Sepsis also contributes to the hypovolemic state. Metabolic acidosis is caused by the loss of pancreatic juice rich in bicarbonate, and is thus more common in conjunction with proximal intestinal fistulas. Gastric fistulas, especially in conjunction with gastric outlet obstruction, will cause a hypokalemic, hypochloremic metabolic alkalosis secondary to loss of a large volume of hydrochloric acid.

B. Malnutrition

The small intestine contains fluid rich in ingested nutrients and endogenous proteins, such as enzymes and albumin. Thus, protein-calorie malnutrition and mineral and micronutrient depletion develop in almost all patients with a small intestinal fistula when a substantial absorptive surface area is bypassed or the enteric contents are lost externally. The loss of luminal nutrients also has a major impact on gut growth and nutrition.

Magnesium, selenium, and zinc depletion are common in patients with high-output fistulas. Nutritional deficiency may be exacerbated by the extra metabolic demands of sepsis or additional surgery.

C. Sepsis

Sepsis remains the major determinant of mortality in patients with fistulas of the small intestine.

D. Abdominal wall and wound abnormalities.

Skin erosion and excoriation commonly occur from an externally draining gastrointestinal fistula. The local digestive action of the gastrointestinal secretions, particularly pancreatic secretions, depends on the output and contents of the fistula effluent. Malnutrition contributes to this process by delaying the formation of scar or granulation tissue.

E. Other complications

Massive gastrointestinal hemorrhage can result from the formation of a fistula between the small intestine and a blood vessel. More commonly, anemia develops chronically and is associated with slow blood loss from a friable fistula tract.

Colonization and overgrowth of the small intestine by colonic bacteria can occur with enterocolic fistulas and may result in malabsorption and severe, malodorous diarrhea.

Finally, carcinoma has been reported in chronic fistulas, especially those associated with Crohn disease.

Management

Management of a gastrointestinal fistula is a difficult and complex process. In general, management can be compartmentalized in to five stages: stabilization, investigation, decision, definitive therapy, and healing.

A. Stabilization

The first step in the management of these patients is stabilization which should be accomplished in the first 24 to 48 hours. These patients are in a vulnerable state of health. They may be febrile and septic. The wound drainage contains succus entericus and the patient may be deteriorating. They may be immunocompromised secondary to steroids, cancer radiation, or chemotherapy.

Patients require correction of obligate third space losses, as well as emesis, fistula output, urine output, or a combination of these. Initial steps should be directed towards fluid resuscitation, control of infection, ongoing measurement of fistulous and urine output, and protection of surrounding skin. Identify the fistulous source, nature of the tract, and associated fluid collections or abscesses.

B. Resuscitation

Restoration of normal circulating blood volume and correction of electrolyte and acid-base imbalances are a top priority. Initial management should address any existing hypovolemia, anemia, hypoalbuminemia, sodium, chloride or potassium depletion, bile salt losses and acid-base disorders. Strict intake and output measurements are essential and CVP monitoring and urinary catheterization are especially helpful. Urine output should be restored to greater than 0.5 ml/kg/hr. Ongoing fluid losses should be fully replaced, and potassium, calcium, phosphorus, and magnesium deficits should be corrected.

Often these patients are in a severe catabolic state and have extremely low protein and albumin levels. This will result in low capillary oncotic pressure, which may contribute to profound edema, especially after resuscitation has begun. Severe hypoalbuminemia will take weeks to correct through nutritional repletion alone. Short-term supplemental intravenous salt-poor albumin administration will help increase oncotic pressure and minimize edema and may improve wound healing.

C. Nutrition

Malnutrition continues to be a major clinical problem in 55% to 90% of patients. Nutritional support should begin as soon as the patient has stabilized. Full caloric and nitrogen replacement can be provided within a few days of instituting nutritional support. Either enteral tube feeding or parenteral nutrition will be required. It is advantageous to provide at least a portion of the calories through the enteral route because the gastrointestinal tract is a much more efficacious way of providing nutrition, maintaining the intestinal mucosal barrier and immunologic integrity, and stimulating hepatic protein synthesis, which has been found to be essential in determination of outcome in patients. Enteral nutrition can be given for upper gastrointestinal fistulas, especially when the feeding tube can be placed beyond the fistula.

D. Control of sepsis (and control of Fistula effluent)

Uncontrolled sepsis remains the major factor contributing to mortality in patients with small intestinal fistulas. Tachycardia, persistent fever, and leukocytosis usually portend inadequate control of the fistula or abscess formation. Frequent physical examination and judicious use of ultrasonography and computerized tomography (CT) are mandatory. Typically, drainage of an intraabdominal abscess is required, which is ideally accomplished in an image-guided percutaneous fashion. Adequate drainage of an abscess cavity must be accomplished.

In addition, fistula drainage must be controlled, and the skin of the abdominal wall protected. Suction aspiration via placement of a nasogastric tube or a nasoenteric tube positioned proximal to the fistula may be helpful with enteric fistulas involving the duodenum or proximal jejunum. Drainage should be collected to measure the output and provide a gauge for fluid and electrolyte replacement. Once skin excoriation occurs, healing is difficult in the presence of ongoing drainage. Use of an ostomy bag or other device to collect and monitor fluids and protect the skin, specialized nursing assistance by an enterostomal therapist or wound care specialist, use of sump suction catheter, or a wound vacuum drainage system may be required. Gastrointestinal fistulas can be associated with serious abdominal wall infections leading to necrotizing fasciitis and gas gangrene requiring aggressive management measures like surgical incision and drainage, debridement, and appropriate antibiotic therapy.

E. Pharmacological support

Somatostatin, a 14-amino-acid peptide, is a well established inhibitor of gastrointestinal secretion, inhibiting both endocrine and exocrine pancreatic secretion and reducing pancreatic blood flow. Use of long-acting somatostatin analogue octreotide decreases fistula output by 40% to 60%, regardless of fistula site or volume of output, and is particularly helpful in decreasing secretions in high output fistulas to a manageable level.

Proton pump inhibitors or histamine H2-receptor antagonists are advisable to reduce gastric acid production, slow transit, and to reduce gastric secretions, and may be useful in decreasing fistula output in proximal high output fistulas.

Antiperistaltic agents like loperamide (8-16 mg/day) are helpful in reducing intestinal transit times and decreasing intestinal volume losses.

Patients with refractory fistulas related to Crohn disease have been successfully treated with short courses of cyclosporine.

Investigation

After stabilization is accomplished in the first 24 to 48 hours, investigation takes place over the next 7 to 10 days. Investigation implies a thorough evaluation of the gastrointestinal tract, definition of the anatomy of the fistula, and identification of any complicating features such as abscess, stricture, or distal obstruction.

Oral administration of indigo carmine or charcoal will demonstrate a communication between the gastrointestinal tract and the abdominal wall or urinary tract.

Probably the most important first test is a fistulogram which will determine the site of the fistula, intestinal continuity with the fistula, presence of distal intestinal obstruction, nature of intestine immediately adjacent to the fistula, and probably the presence of an intraabdominal abscess. Performing the fistulogram first is prudent because contrast from an upper gastrointestinal series, contrast enema, or CT may make it difficult to interpret a fistulogram. Fistulogram should be followed by a complete contrast study of the gastrointestinal tract.

CT and ultrasonography are additional useful tests in the early stage of investigation that can define the anatomy in the vicinity of the fistula and evaluate for any ongoing or unrecognized intraabdominal abscesses, as well as distal obstruction. CT scanning with oral and intravenous contrast media is highly sensitive and specific for intraabdominal free air and will assist in locating the fistula and identifying adjacent fluid collections and concomitant bowel obstruction. CT scanning is also highly recommended for suspected duodenal perforations, and is also the most sensitive study for identifying a colovesical or enterovesical fistula.

Endoscopic evaluation may be helpful in certain clinical situations. Endoscopy is however not advised if there is suspicion of acute perforation.

Decision

The next step in fistula management is a decision on management and the timing of such management. The likelihood of spontaneous closure must be determined. The likelihood of closure depends on several factors. The first is anatomic location. Anatomic locations that are favorable for closure are the oropharynx, esophagus, duodenal stump, pancreas, biliary tree, and jejunum. Unfavorable locations include stomach, lateral duodenum, ligament of Trietz, and the ileum. Poor nutritional status and the presence of sepsis make spontaneous closure less likely. The cause of fistula is also predictive of closure. Postoperative fistulas and fistulas secondary to appendicitis or diverticulitis are likely to close. Fistulas associated with active Crohns disease, cancer, retained foreign bodies are unlikely to close. Total disruption of the bowel, distal obstruction, abscess, malignancy or irradiation (or both), epithelialisation of the fistula tract, and active disease negate closure. A long narrow tract fistula is more likely to close than a short wide tract. A fistula with an everted or ostomised appearance is unlikely to spontaneously close. The odds of spontaneous closure are three times greater with low-output fistulas than with high-output fistulas.

Failure of an enterocutaneous fistula to close spontaneously is associated with a number of factors (represented by the acronym FRIENDS): presence of *foreign* body, previous *radiation* exposure, *inflammation or infection*, *epithelialisation* of the tract, *neoplasm, distal obstruction*, and use of *steroids.*

After considering all the relevant factors, one has to decide whether to observe the fistula for spontaneous closure, or plan an early operation after stabilization. A fistula that has not closed by 4 to 6 weeks is unlikely to do so and surgery is indicated.

Definitive Therapy

The next important decision is to determine whether definitive operative therapy is necessary and the timing of such therapy. Whenever possible, the operation should not take place until the patient is stable, not septic, and in an adequate nutritional state. The most favorable time to reoperate on patients is either within 10 days of diagnosis or after 4 months.

A. Gastric and duodenal perforations and fistulas

Anastomotic leaks usually occur 1 week after surgery. The decision to operate will be influenced by the ability to drain associated abscesses percutaneously and the presence of peritonitis. Ongoing sepsis, poorly drained collections, or generalized peritoneal signs should mandate reexploration, debridement, drainage, and management of the perforation.

If the gastric or duodenal defect is too large to allow primary closure or the fistula originates in conjunction with the ampulla and pancreatic duct, a Roux-en-Y gastrojejunostomy or duodenojejunostomy is a flexible and valuable technique. A feeding jejunostomy distal to the enteroenterostomy should always be considered.

Treatment of a duodenal stump fistula is based on the condition of the stump and surrounding tissue and the surgeon's judgment. Options include primary suture closure, mobilization of the stump with resuture or stapling, lateral tube duodenostomy for duodenal decompression, direct tube drainage through the fistula, a serosal patch, or the use of a Roux jejunal limb.

Fistulas associated with recurrence of Crohns disease or malignancy are managed by resection.

B. Enterocutaneous fistula

Many enterocutaneous fistulas close spontaneously if infection is controlled, nutrition is adequate, and distal obstruction is not present. Definitive operative correction remains the final step in the management of non-healing small intestinal fistulas. The preferred operation is resection of the involved segment of intestine and primary end-to-end anastomosis. In the setting of extensive sepsis, primary anastomosis may not be appropriate – exteriorization of both the proximal and distal ends of the intestine may be performed.

Gastrointestinal fistulas associated with large abdominal wall defects are most difficult to manage surgically and most likely to result in mortality. The wound VAC device works well – protects the bowel, preserves the fascia, limits the loss of domain, reduces the need for dressing changes, removes excess fluid, decreases bacterial counts, and increases the vascularity of the wound. The fistulas located in the midst of a fixed visceral block should not be intubated as the tubes can result in more damage. The VAC may be coupled with the use of isolative techniques to wall off the fistula from the large granulating abdominal wound. Placement of ostomy pouches can capture the fistula effluent while VAC allows the remainder of the wound to be covered. The patient may be a candidate for split-thickness skin graft over the controlled granulated portion of the wound.

Musculocutaneous flaps and the application of abdominal wall reconstruction techniques involving component separation and prosthetic materials may be required to obtain adequate coverage. The use of synthetic prosthetic materials is contraindicated.

C. Enteroenteric fistulas

An enteroenteric fistula occurs when the small intestine joins with either another segment of small intestine or the colon. They are usually caused by Crohn disease, diverticulitis, or colon cancer. Symptoms are nonspecific – diarrhea, abdominal pain, weight loss, and fever, and are caused by the underlying disease process as well as the fistula. They are usually discovered incidentally on imaging or during laparotomy. Surgical intervention is necessary in most of these patients - the operation of choice is en bloc resection of the diseased intestine along with the fistula tract. In the presence of acute inflammation or abscess, the initial intervention may be proximal diversion and percutaneous drainage of any associated abscess.

General Considerations

When planning operation for fistula patients, allow adequate time for a difficult and prolonged procedure. Component release and other reconstructive maneuvers may be required; enlist the expertise of a plastic surgeon for closure of the abdominal wound. Contaminated conditions contraindicate use of prosthetic material for abdominal wound closure. Preoperative preparation should include mechanical bowel preparation and preoperative antibiotics directed towards bowel and skin flora.

Reentry into the abdominal cavity should be through a new incision or extension of the previous incision over virgin abdominal wall. The entire intestinal tract should be mobilized and complete enterolysis should be performed. An intestinal fistula cannot be repaired primarily; they require complete resection back to healthy tissue with enteroenterostomy. The choice between hand-sewn or stapled anastomosis does not matter. The anastomosis should not be under tension, there must be adequate blood supply, and distal obstruction should not be present. A feeding jejunostomy or nasoenteric tube should be placed.

Prolonged postoperative ileus commonly occurs, and decompression via a gastrostomy tube, while downstream enteral nutrition is given is beneficial. Methods for decreasing intraabdominal adhesions using hyaluronic acid – carboxymethylcellulose may be beneficial. It is essential that the abdominal wall be closed with autologous tissue (using component separation or musculocutaneous flaps) or an absorbable bioprosthesis consisting of human acellular dermal matrix, porcine dermal collagen, bovine pericardium, or porcine small intestinal submucosa.

Corrosive injuries of the Oesophagus

Tushar Kanti Chhattopadhyay

Injuries of the oesophagus due to corrosive ingestion is not uncommon. This is particularly so in developing countries. Such injuries may have devastating effects on the upper aerodigestive tracts, pose serious problems in their management and drain scant health resources.

Corrosives, by definition, are substances which can damage all living tissues on contact. In the context of esophageal injuries these can be acid, alkali or combination. Injuries of the esophagus have been documented with acids like sulfuric acid (used in jeweller's shop and in batteries), hydrochloric and muramic acid (used as toilet cleaner), hydrofluoric acid (used as rust remover and used in computer industry for etching) and phosphoric acid (used as metal cleaner). Similarly alkalies like NaOH (used as drain cleaner), NaOCl2 (used for bleaching), NH4OH (used as household cleaner) and Na_2CO_3 (used as dish washer) can produce oesophageal injuries. Combination of both acid and alkali can also damage the oesophagus through heat generated by exothermic reaction (unrelated to their pH).

Epidemiology

In the United States approximately 35,000 patients are treated each year for corrosive injuries. Exact incidence from developing countries is not available. There is geographic variation as to the cause of the injuries. In India, for instance, while acid injuries are predominant in the south, alkali burns occur with almost equal frequency in the north. In Nigeria caustic soda is a common cause of oesophageal burn. Chlorine bleach has been reported to cause corrosive injuries of the oesophagus in France.
These injuries can occur either due to accidental ingestion, commonly in children or in adults, when consumed for suicidal purposes. The victims of these injuries are usually young . There is somewhat higher frequency in females.

Pathogenesis

Alkalies cause liquefaction necrosis on contact with the esophageal mucosa. As a result deeper burns are more common; not infrequently resulting in full thickness burn causing perforation and/or mediastinitis. Acids on the other hand cause coagulation necrosis of the oesophagus. The coagulum thus formed prevents further penetration of the acid.

On entering the stomach these agents, particularly acids, produce intense pylorospasm resulting in stasis in the stomach allowing these substances to penetrate deeper. This causes either frank perforation immediately or antral stricture subsequently.

Corrosive burns of the oesophagus progress through three phases. *Phase I* is the phase of inflammation. *Second phase* is the phase of healing either by mucosal regeneration or granulation and in the *third phase* fibrosis occurs. These burns are classified into three degrees. In 1st degree burns there is only mucosal hyperaemia and oedema. These injuries usually heal completely without forming a stricture. In the 2nd degree burn superficial ulcers as well as pseudomembrane form. These ulcers heal both by granulation as well as mucosal regeneration. Strictures rarely form in the 2nd degree burns. The3rd degree burns are deep burns with necrosis of muscular coat of the oesophagus of variable depth. Eschars are commonly seen. Submucous vascular thrombosis is also common in this category. When there is full thickness necrosis of the oesophageal wall frank perforation occurs.

The extent of burn is decided by the volume and concentration of the agent ingested. The physical state of the agent is also important. While solid corrosives cause minimal damage; liquids, both acid and alkali can cause extensive injury. Injuries of the oral cavity, pharynx and larynx are common with liquids particularly acid.

Clinical presentation

In the presence of a relevant history, the diagnosis is obvious. Accidental injuries are common both in children and adults. Suicidal injuries are seen exclusively in adults. It is not uncommon to see a patient with history of unsound mental health.

Patients of corrosive oesophageal burns complains of intense oropharyngeal and chest pain. This is often associated with vomiting, excessive salivation, and drooling. The patients may have respiratory stridor as well. Retrosternal or epigastric pain and upper gastrointestinal bleeding too can be present. On examination they are restless. There can be eschars in the mouth and pharynx. In presence of oesophageal perforation respiratory distress, pleural pain and surgical emphysema can be present. Similarly, following gastric perforation patients can have abdominal guarding and rigidity with obliteration of liver dullness.

Emergency Management

When patients come to the casualty, they should be evaluated for air way patency. If inadequate, endotracheal intubation should be done. It is to be remembered that intubation may be difficult or impossible particularly in a restless patient. A tracheostomy may therefore be safer.

These patients are in great pain. Therefore all patients should be sedated and relieved of pain. It will be easier to assess a quiet patient.

Patients of oesophageal burn should not initially be allowed to take anything orally; instead they should be given intravenous fluids. Once adequately resuscitated, intravenous nutrition should be provided because they are unable to take anything by mouth.

Following resuscitation, a chest and abdominal X-ray should be obtained so as to rule out oesophageal and/or gastric perforations. Contrast studies of the oesophagus with either barium or water soluble dye has been suggested by some but everyone does not recommend these. This is because they are not very accurate. Barium, if escapes into the pleural space, can initiate severe inflammation. Water soluble agent has higher risk of aspiration.

While managing patients of corrosive burns of the esophagus certain “don’t”s are to be remembered. It is not wise to attempt passing a nasogastric tube or initiate gastric lavage. These measures may complicate matters by causing perforation of the esophagus rendered soft by the corrosive. For the same reason no neutralising agent should be used. The exothermic reaction resulting from their use can produce thermal burn of the esophagus.

The practise of emergency endoscopy lacks consensus. It is difficult though feasible. Its safety has been claimed by some but the frequent need of general anaesthesia dissuades others. Moreover the benefit of such practice does not seem too great. The proponents claim that by endoscopic evaluation the injuries (the depth of burn) can be accurately assessed which can predict whether a patient is going to develop a stricture or not.. The injuries have been classified as 1st to 3rd degrees as listed earlier. It has been observed that all 1st and most 2nd degree injuries almost always heal without forming a stricture. The 3rddegree burns on the other hand invariably form

strictures. Thus, assessment of the depth of burn can predict which patient is likely to form stricture. Moreover patients with endoscopic evidence of black eschar and vascular thrombosis have been claimed by some to have higher chance of perforation. To avoid such eventuality their removal has been advocated. The opponents of this view feel that since 1st and 2nd degree burns are more frequent and since they usually heal there is no advantage doing an emergency endoscopy for them. The eschar seen in the 3rddegree burn does not always indicate full thickness burn. Therefore to advocate emergency operation on the basis of a finding of doubtful significance does not seem a rational proposition. The decision of urgent surgery to save life can be based on monitoring the clinical course of the patients. Thus, after adequate resuscitation all patients should be monitored for any ominous sign when proper surgical treatment should be undertaken. All patients should be given broad spectrum antibiotics to prevent secondary infection. Analgesics and anti-inflammatory drugs can reduce pain and should be used. Use of steroid has not been shown to do any good. Once ability to swallow returns while recovering, patients should be encouraged to resume oral feeds; initially liquids gradually increasing to solids. Patients of superficial burns usually resume oral diet early when a barium swallow should be done by the second week to evaluate the injured oesophagus. Patients with third degree burns are usually unable to swallow. Endoscopic evaluation should be done in them and dilatation should be started early. Soft silastick nasogastric tube can be passed for enteral feeding. Regular dilatation schedule should be started in them and the result periodically assessed for future course of action.

Emergency Surgical Treatment

If patients develop surgical emphysema, massive pleural effusion and or pneumoperitoneum diagnosis of oesophageal &/or gastric perforations can be made and documented by chest and abdominal x-rays and pleural aspiration. Having confirmed the diagnosis all such patients should be explored. Abdomen is opened and the stomach evaluated. If already necrosed it should be removed. After closing the duodenal stump a feeding jejunostomy is done. The oesophagus is then exposed in the neck, opened and transhiatal esophagectomy done. In the end a cervical esophagostomy is done. Once the oesophagus and the stomach are removed mediastinal and abdominal drains are placed and the wounds closed. If the patient survives oesophageal continuity can be restored at a later date, several weeks or months later.

Emergency Management of Corrosive Oesophageal Injuries in AIIMS

Being a tertiary care referral centre, we have to manage all difficult forms of corrosive injuries in our hospital. Over a twenty year period we have managed 14 patients of very severe degrees of oesophageal burns. These patients had evidence of pneumomediastinum and / or pneumoperitoneum (10cases). Concomitant air way obstruction was present in 5 cases needing tracheostomy. All these patients were managed surgically. Cervical esophagostomy and feeding jejunostomy were done in -all these cases. Transhiatal esophagectomy along with total gastrectomy were done in--2 cases. Whipple's operation for associated bile duct and duodenal injuries were done in 1 case. Ten patients needed total gastrectomy. All patients had their mediastinum, pleural and peritoneal cavities drained. Six patients died of the operation. The remaining patients who survived the operation had their oesophageal continuity restored with left colic artery based colonic transposition. Over a mean follow up of 66 months (range 6 to 120 months), all surviving cases could swallow. However three cases had grade 1 dysphagia and required dilatation for anastomotic stricture.

Corrosive strictures of the Oesophagus

Development of stricture is sequelae of corrosive burns of the oesophagus. All deep burns (with ulceration of various depth and extent) heal by fibrosis resulting in strictures.

Magnitude of the problem of corrosive strictures is enormous. Firstly, the victims of corrosive strictures are usually very young with long productive life lying ahead. Secondly, though benign, the impact of these strictures is as devastating as malignancies of the oesophagus. As a result these patients too suffer from dysphagia, inanition, aspiration and sialorhhoea. All together the patients lead a miserable life.

Classification of strictures: We classify these strictures as:

- Short segment
- Segmental strictures
- Diffuse or extensive or long segment strictures

The stricture can be associated with scarring of the oropharynx and hypopharynx. Not infrequently the stricture can be associated with narrowing of airway. Concomitant abnormalities of the vocal cords (through fibrosis of various laryngeal folds) can also be present.

Presentation: As mentioned earlier the patients of oesophageal stricture present with dysphagia. As a result they continuously spit. They are frequently malnourished and dehydrated. Features of aspiration pneumonia can also be present. Occasionally patients can develop a lung abscess. Because of aspiration patients can have persistent disturbing cough.

Evaluation of the strictures is done by barium esophagogram. Depending on the severity of the stenosis the oesophagus is variably opacified. At times the stricture can be so tight that while attempting to swallow patients aspirate the dye and the entire tracheobronchial tree gets opacified.

Management of corrosive strictures: Treatment of oesophageal stricture can be either dilatation or surgical. Most patients of short segment stricture respond very well to dilatation therapy whereas long segment strictures or segmental strictures at multiple sites do not. To understand why extensive strictures do not respond to dilatation one has to go into the pathogenesis of these strictures. Following extensive burn of the oesophagus the entire muscle layer is destroyed and replaced by dense fibrous tissue. This fibrosed muscle does not have any propulsive activity. Essentially such oesophagus is a peristaltic inert tube functionally incapable of emptying itself. Following extensive burn even the lower oesophageal sphincter is destroyed facilitating reflux which in turn aggravates the stricture. Dilatation for this group does the same and hence potentiates the stricture. Moreover not only the muscle even the nerve bundle responsible for muscular activity are destroyed in extensive burns of the oesophagus. Thus it is not difficult to appreciate why patients of extensive stricture do not get the benefit of dilatation therapy. It is worth remembering that even if the stricture is dilatable since the oesophagus is rendered a- peristaltic and inert, patients will not be able to swallow normally. Dilated, this way patients at best can swallow liquids but not solids for which active peristalsis is necessary which is lacking in these patients.

Dilatation: Starting approximately 3-4 weeks after recovery from oesophageal burn, dilatation of the strictures are done on a regular basis and continued for at least 6 months before abandoning it .Attempts should be made to achieve oesophageal diameter of at least 18mm. Those who respond should be dilated every month for two years. Subsequently every 2-3 months for another 1 year. Following such a schedule Gundogdu et al have reported that 49% of patients are stabilised by one year, 51% requiring dilatation for more than a year and as many as 14% requiring dilatation for 5 years. Approximately 80% of short segment strictures can be dilated. The predictors of good results of dilatation are: patients younger than 8 years, length of stricture less than 5 cms and strictures at proximal site.

Classifying results of dilatation as excellent, good, fair and poor, Ananthakrishnan and others have reported good results in 52.4%. 38% of patients had fair and 9.5% poor results. The criteria followed are given below:

Table showing criteria for functional ranking following dilatation

Criteria	Ranking			
	Excellent	Good	Fair	Poor
Dysphagia	Nil	nil	Solids	Both
Weight loss	Nil	nil	+	++
Other symptoms (Fullness, Belching, Heart burn, Diarrhoea)	Nil	+	+	+
Ba-Swallow	Free flow	free flow	Stasis+	Obstruction
Diltn. Required	None	None	Infrequent <3mthly	Frequent >3mthly

Dilatation can be done either in ante grade or retrograde fashion. For ante grade dilatation olive point Savary or Hurst mercury filled bougies are preferred. Gum elastic bougies are also good for this purpose. In recent times however dilatations are done using flexible endoscope and placing guide wires over which dilators can be passed. Occasionally retrograde dilatation may have to be done when a silk thread is passed through the nose and retrieved from the stomach by a gastrostomy. A Tucker's dilator is then fixed to the silk thread coming from the stomach and pulled upwards to reach the oral cavity. Dilatation performed this way is convenient for the patients and can be done at home also. Whether antegrade or retrograde, dilatation is not free of complications. Perforation rate of 24 – 81% with mortality of 3-18% has been reported.

Surgical treatment: As mentioned earlier not all patients respond to dilatation. For them surgery remains the only option. Indications of surgery are:

- All extensive and segmental strictures
- Failure of dilatation
- Too frequent dilatation
- Complications developing after dilatation
- Increasing difficulty of dilatation
- Failure to thrive in spite of adequate dilatation
- Patient refusal to any further dilatation

Operative treatment can restore normal swallowing avoiding inconvenience and danger of repeated dilatation. However one has to balance this against the mortality and morbidity of a major operation.

Having decided surgical treatment one has to consider the type of surgery – oesophageal resection, bypass or esophagoplasty. Oesophageal resection has been advocated for a long time because of the estimated high risk

of cancer. However the real incidence of cancer developing in a corrosive oesophageal stricture is not exactly known. Very long latent period (over 30 years by some estimate) makes it very difficult to ascertain. Moreover no study is available which makes adequate correction for more established causative factors like smoking and alcohol consumption in these patients. Along side this there are authors who on a long term follow up have not recorded cancer in any of the patients. Moreover it is interesting to note that even when cancer has been detected, it is in the no bypassed oesophagus. As of now only three cancers have been reported in the bypassed segment. This only proves that cancer development is a rare event. This is the view of most surgeons dealing with corrosive stricture and they consider oesophageal bypass an adequate surgical option in the management of difficult oesophageal strictures. Hugh and colleagues introduced esophagoplasty for these strictures. They argue that the oesophagus can not be periodically assessed endoscopically for early detection of cancer following oesophageal bypass. With esophagoplasty this problem can be avoided.

Oesophageal resection: Oesophageal resection for corrosive strictures is technically difficult and demanding. The procedure can be done through the transthoarcic or transhiatal routes. The associated dense peri oesophageal fibrosis makes transhiatal resection extremely difficult and hazardous with significant danger of bleeding from the azygos vein or the aorta, damage to thoracic duct, recurrent laryngeal nerve and the tracheobronchial tree. Because of these problems, many authors do not recommend it.

Reconstruction following resection can be done either with the stomach, colon or jejunum depending on the availability of these organs for such purposes. If available the stomach is the most favoured organ. But in corrosive injuries it is often affected by the corrosive making it unsuitable for oesophageal substitute. Various gastric tubes have been created in the past but not many surgeons are using these in current surgical practice unless other organs are unavailable. The preferred organ thus is the colon either the left or the right. Use of jejunum is restricted for bridging defects located in the distal third of the oesophagus. A short segment gap usually in the neck can be bridged by isolated segment of jejunum with free vascular pedicle. This needs microvascular technique of reconstruction which may not be available every where. The relative merits of each organ are given in the following table:

Table showing advantages and disadvantages of each organ

Stomach	Colon	Jejunum
Good blood supply	suitable length	suitable bl.supply
Adequate length	reflux better tolerated	minimal reflux
one anastomosis	multiple anatomy	multiple anast
Quick & simple	time consuming	cumbersome
High reflux rate	inconstant blood sups.	Unfriendly
nutritional problem	preop. bowel prepn.	
respiratory problem	graft necrosis risk	high rate of graft necrosis;with leak & fistula

Before operation all patients should receive preoperative build up with particular reference to nutritional improvement if need be with feeding jejunostomy. Pulmonary physiotherapy with incentive spirometry and steam inhalation should be given to improve the chest condition. Since patients often have chest infection they should receive antibiotics as well. Bronchodilators may at times be needed. Concomitant hypopharyngeal stricture should always be ruled out before operation for esophageal stricture. Details of the operation and possible outcomes should be duly discussed with all patients.

We have surgically managed 101 cases of corrosive strictures at the All India Institute of Medical Sciences between 1980 to 2004.All these patients were previously managed with dilatation for variable duration ranging from one month to as long as 20 years. In the beginning of our experience we had managed the patients with oesophageal resection because of the fear of malignant transformation in the residual oesophagus. Since the incidence is not all that great we currently practise oesophageal bypass. For bypass we have used the stomach in 27/68 cases and colon in 27/68 cases. Jejunum had been used in only 2 cases. Ten patients underwent gastric bypass only. Thirty three patients underwent oesophageal resection in the beginning of our experience. Operative mortality was 7 (%) in the entire surgically treated group. .Postoperative complications noted are graft necrosis 2%, anastomotic leak 20%, anastomotic stricture in 20%, intestinal obstruction 5%, gastric outlet obstruction 5%,Chest infection 20% and features of aspiration 15% of cases. Five per cent of our patients failed to swallow all together. Results of surgery were considered excellent /good in 56%, fair in 18% and poor in 14% of cases. Following discharge from the hospital all the patients were followed up. Mean follow up was 27months (range being 3 months to 20 years).

Based on our experience we conclude that corrosive injuries of the oesophagus are difficult problems. Following successful emergency management all such patients should be properly evaluated as many of them develop strictures. All small segment localised strictures should be initially managed with oesophageal dilatation and the results noted. All patients who do not respond to adequate dilatation as well as all patients of segmental and extensive strictures should not receive unduly long dilatation therapy which amounts to procrastination. To

restore normal swallowing at the earliest they should be offered surgical treatment. Before operation adequate attention should be paid to build these patients nutritionally. Due attention should also be paid to improve their chest condition which is likely to be bad due to repeated aspiration. Surgery performed with such care is likely to give good results. The operation can be complex and not without complications. But performed with care these can be minimised and the end result is likely to be really rewarding.

Mammary Paget Disease

Naveen Sharma

Sir James Paget, a British Surgeon, first described Paget disease in 1874. Since the first account, multiple reports have described this relatively uncommon condition, and the understanding of the disease has improved considerably now. It is classified as T*is (Paget's; Carcinoma* in situ) and part of the phenomenon of multicentricity of breast cancer.(1)

Men are rarely affected with this disease and women constitute the vast majority of patients afflicted with mammary Paget disease (MPD). (Yes, there is extra mammary Paget disease but we shall confine ourselves to the MPD in this monograph.)

The mean age at diagnosis is about 55 years, although the condition has been described in adolescents and in octogenarians.(2) The lady presents with an eczema, bleeding, ulceration and itching of the nipple. There may be crusting or weeping lesions as well. All too often, this is mistaken for eczema of the nipple. Other differential diagnoses are erosive adenomatosis of the nipple, cutaneous extension of breast carcinoma, psoriasis, atopic dermatitis, contact dermatitis, chronic eczema, lactiferous ducts ectasia, Bowen's disease, basal cell carcinoma, melanoma and intraductal papilloma. (3) The confirmation of diagnosis is by obtaining a punch biopsy under local anaesthesia. (A video of punch biopsy can be seen on https://www.youtube.com/watch?v=vBBnq4Fu26M)

The pathological feature consists of epidermal Paget cells, PDCs are large, atypical, and have abundant, pale-staining cytoplasm that may contain mucin secretion vacuoles and bulky heterochromatic nuclei. They are commonly concentrated along the basal layer and stain for EMA, CAM5.2, cytokeratin 7, and HER2/neu oncoprotein.(4). These cells appear organized in groups, with nest-like patterns or gland-like structures, and are usually located in the epidermal basal layer. The number of cells varies from a few to large quantities; even completely replacing the epidermal cells. Invasion of adnexal structures can sometimes occur. (3)

Two theories have been proposed in regards to pathogenesis of Paget's disease: (I) epidermotropic theory and (II) in situ malignant transformation theory. The epidermotropic theory claims that changes typical for Paget's disease arise in the ductal cells, and spread along the basement membrane to the nipple. This theory is supported by the fact that most patients with Paget's have underlying breast cancer, and the cells from the nipple are histologically similar to the associated invasive carcinoma. (5)The in situ malignant transformation theory claim holds that Paget's disease originates in the epidermal cells of the nipple by malignant transformation of keratinocytes and is not associated with any coexisting neoplastic process in the affected breast.(6) (7)

MPD is associated with underlying DCIS or infiltrating duct carcinoma in about 90% cases. Once MPD is diagnosed, it is important to evaluate for underlying breast lump by clinical examination and imaging. Although mammography does play a role in diagnosing nonpalpable areas of abnormality in the breast, recent literature has come out heavily in support of MRI as the superior imaging modality when evaluating MPD. (8)(9)

The management of MPD traditionally involved mastectomy with axillary dissection. Even now, this is a reasonable management of MPD - whether associated with underlying DCIS/ malignancy. In case no underlying lesion is detected on clinical/radiological evaluation, the excision of nipple and areola followed by radiotherapy to the breast is a safe treatment option.(10) Any areas of abnormality within the breast are subjected to core needle biopsy. If DCIS or invasive cancer is detected, the management is directed towards this diagnosis and the area of nipple and areola is resected along with the lesion. The underlying lesions are often multifocal/multicentric.(11) The wide local excision of tumor/ modified radical mastectomy always involves excision of the nipple areola complex.

Earlier MPD associated DCIS and invasive cancer were largely managed by mastectomy.(12) In the last decade, there has been a trend towards offering Breast conserving surgery (BCS) to these patients. (13) (14) Analysing SEER data, Wong et al concluded that over the last decade, more BCS has been offered to patients with MPD associated DCIS/ invasive cancer. (15) Oncoplastic techniques have been successfully used in the reconstruction of central breast defects.(16)

The management of the axilla is less clear. Older studies noted a sizable number of patients with isolated MPD who had positive sentinel lymph nodes in the axilla. (17)(18)

However, these studies had not utilized MRI to look for underlying breast lesions associated with MPD. With MRI detecting most underlying lesions with management directed primarily towards the lesion, it is unlikely that patients with isolated MPD will benefit from an axillary Sentinel lymph node biopsy (SLNB).

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Surgery for Carcinoma Breast

Gaurav Agarwal, Chaitra Sonthineni

Carcinoma breast is one of the earliest documented malignancies, first mentioned in the Edwin Smith papyrus and Ebers papyrus of Ancient Egypt, dating back to the 2nd millennium, BC. While in the times of Hippocrates of Ancient Greece it was considered omitting any form of treatment would prolong life, the first century AD saw the beginning of surgical management of breast cancer by an operative technique described by Leonidas. The management of this ancient disease has come a long way since then. Currently, the norm is to **treat breast cancers in a comprehensive, multi-modality manner**, incorporating appropriate surgery, chemotherapy, radiotherapy, hormonal therapy and/or targeted therapy, which is best decided by a **'Multi-Disciplinary Team'** (MDT). Such an apporach is standard in most high quality cancer centers across the globe (1), and is gradually picking up in our country too. It is vital to have evidence based, pragmatic treatment protocols in place to achieve optimal outcomes for majority of breast cancer patients. The SGPGIMS Lucknow protocol for management of early opearable (EBC) and locally advanced (LABC) breast cancer are summarized in ***tables 1 & 2.*** While the primary modality for EBC and LABC is Surgery, the disease control achieved surgically needs to be augmented by adjuvant radiation therapy to improve loco-regional control; and systemic therapy- chemotherapy and hormone therapy (for ER, PR positive tumors), and trastazumab treatment (for HER 2-neu positive tumors) for improving systemic control and overall survival of the patients.

A basic pre-requisite before surgery and other treatment of breast cancer is to arrive at an irrefutable diagnosis. The standard diagnostic work up for a suspected breast mass or other symptoms includes **triple assessment** which has the following components:

- *History and Clinical Examination*
- *Radiological Imaging- Mammogram, Ultrasound, and possibly MRI*
- *Pathological diagnosis- Core Biopsy (preferred) and/or FNAC*

Investigations

Mammography is the imaging of choice but may not be adequately informative in young patients with dense breasts and may not be possible in locally advanced cancers due to large, non-pliable or ulcerated tumours. A core biopsy using a spring loaded core needle biopsy gun, or other similar biopsy needles/ equipment is preferable over fine needle aspiration cytology, and should be done only once imaging has been done as tumour morphology gets distorted after a biopsy has been performed. Stereotactic biopsy is another option while diagnostic surgery, such as incisional biopsy, should be avoided. The core biopsy is done with the intention of documenting the histology of carcinoma, its histological type, invasion, grade, lympho-vascular invasion and the basic histological bio-markers, namely estrogen and progesterone receptor (ER and PR) and HER2neu by immuno-histo-chemistry, which should be part of every breast histopathology report.

Having diagnosed the breast cancer, patient needs to **stage the disease** using the standard TNM staging system. Based on the clinical stage a comprehensive treatment plan needs to be chalked out, preferably in a multi-disciplinary team (or breast tumor board) meeting. The treatment plan should include the sequence of different modalities- i.e. whether patient's disease will be best treated with primary surgery or post-neo-adjuvant chemotherapy (NACT) surgery. The patient must be involved in the decision making and treatment planning, and should be provided all information to help her make an informed decision about nature of her own surgical and adjuvant treatment. NACT is an effective strategy of making large and locally advanced cancers operable, and facilitating breast conservation surgery by reducing the tumor size and making any matted axillary nodes operable. NACT is being increasingly employed in most centers, not only for LABC patients, but even in relatively large but operable breast cancers.

Surgery for the primary breast tumour

It can be of either curative intent or palliative intent, and the decision for which of the two is appropriate for an individual breast cancer patient rests largely on the stage of breast cancer, and more specifically on the **stage group** the patient can be attributed to, namely, early operable (stages I and II), locally advanced (stages III), or metastatic (stage IV) breast cancer. Surgery is part of the multimodality management of non-metastatic carcinoma breast.

However, the **role of surgery of the primary tumour in patients with metastatic breast cancer** beyond the indication of treating locally symptomatic tumours such as those causing pain, fungation, ulceration or bleeding or necrotic tumours or tumours with impending local complications is controversial. There are two schools of thought when it comes to surgical management of primary tumour in metastatic breast cancer: pro-surgery and no-surgery. The biological rationale of those pro-surgery, as is that surgical removal of the primary is supposed to reduce the overall tumour burden and source of metastatic spread (2, 3). The hypothesis of "cancer self-seeding" i.e., tumour cells may be able to recirculate from metastatic sites to their original site of production, favouring both

systemic and loco-regional disease progression also supports this argument (4). Also, Surgery may restore immune-competence, as the primary tumour modulates anti-cancer immune responses by releasing immunosuppressive factors. Systemic therapy may be more effective in presence of reduced tumour burden by decreasing the emergence of chemo-resistant clones and removing necrotic tumour tissue scantily accessible to drugs. There are only some retrospective studies showing benefit for surgery of primary tumour in metastatic breast cancer. Some recent prospective studies show no benefit of surgical removal of primary tumour (5, 6).

In patients with non-metastatic breast cancer, surgery plays a pivotal role in achieving cure in a large proportion of early stage cases. Surgery for breast cancer in these patients can be performed as primary procedure i.e. the first treatment modality implemented, or surgery may follow neoadjuvant chemotherapy (NACT). Patients with early breast cancer (stages T1-2) usually have tumour size amenable for primary surgery. Patients with large operable (stage T3) and locally advanced breast cancer (LABC, stages T4, and/or N2-3) would require NACT in the majority, especially if planned for breast conserving surgery (BCS). Exceptions would be patients with operable tumours opting for mastectomy and easily operable BCS due to favourable breast tumour ratio. Upfront Palliative/Salvage Surgery in locally advanced breast cancer can be offered to:

- Those in whom NACT cannot be offered safely
- Non-responders to NACT (includes progressive disease)
- Major bleeding, Tumour necrosis

Surgery for local disease in non-metastatic breast cancer consists of surgery on the breast and surgery for the axilla. The surgery for the primary breast tumour can extend from wide local excision of the lump, no ink on tumour being currently acceptable margin (7), to mastectomy. In early breast cancer, recent population based studies have shown breast cancer specific survival advantage in patients undergoing **breast conservation surgery** (BCS) with radiotherapy when compared with patients undergoing mastectomy alone in patients undergoing primary surgery (8, 9). BCS may be done without any additional oncoplasty, with local tissue displacement or with a regional flaps eg, latismuss dorsi flap. Any more than 20% volume deficit post BCS would require some form of oncoplastic procedure. Other indications of reconstruction in BCS are central, medial and lower pole resections, axillary dissection through lumpectomy incision, peri-areolar incisions in inferior quadrants and incomplete mobilisation of breast parenchyma to allow reshaping of the breast. In patients undergoing NACT, the decision of BCS should be taken prior to initiation of NACT and pre-NACT tumour mapping or marking either the core of the tumor or the margin(s) using radio-opaque clips or markers should be done. This is needed to assist safe and complete excision of the post-NACT residual tumor or in patients with complete tumor response- excision of the post-NACT foot-print of the now non-existent tumor. It should be explained to the patient that opposite breast might also require surgery such as reduction mammoplasty. Three types of patterns of positive response after NACT

- Pathologic complete response -tumour has totally disappeared.
- Concentric shrinkage- tumour has shrunk to a small volume and there is no residual nodule in the peripheral area.
- Mosaic pattern (multifocal residual)-tumour has shrunk to small volume but it has many small nodules in the edge of the tumour- Mastectomy should be preferred

BCS should be offered to most patients with breast cancer, unless there is a strong contraindication of breast conservation which are diffuse microcalcifications, extensive DCIS, indiscrete tumor, and multi-centric tumors; or contraindications for post-operative radiation therapy such as connective tissue disorders such as SLE. BCS is aimed at maintaining cosmetically acceptable shape, contour and symmetry of the breasts. Achieving this goal is possible in a large proportion of patients by utilizing appropriate breast conservative and oncoplastic surgical techniques. However, in a sizeable proportion of patients there are less than ideal results, and BCS can result in deformed breasts. The less than ideal cosmetic sequelae of BCS are classified into following categories:

- Type I -asymmetrical breasts with no deformity of the treated breast.
- Type II -deformity of the treated breast, compatible with partial reconstruction and breast conservation.
- Type III -major deformity of the breast, requiring mastectomy

While an ever increasing proportion of EBC and many post-neo-adjuvant chemotherapy (NACT) large operable breast cancer (LOBC) and LABC patients are now being offered and treated with breast conservation surgery, **Modified radical mastectomy (MRM)** still remains the most common surgical procedure employed in definitive management of breast cancer. Mastectomy is indicated in all EBC and LABC patients who can not be offered breast conservation (e.g. multi-centric cancer, contraindication for radiation- pregnancy, certain connective tissue disorders etc.) or those who are not willing to undergo breast conservation. MRM can be performed in following settings:

- Primary MRM: for EBC patients, selective large operable or LABC patients
- Post-NACT MRM: following adequate down-staging with NACT in Large operable and LABC
- Palliative MRM/ Toilet mastectomy: in patients with LABC/ metastatic breast cancer to address quality of life issues in patients with fungating tumors/ those with imminent fungation/ ulceration.

Mastectomy can be with or without reconstruction. Reconstruction can be autologous, such as TRAM flap or can be with an implant. Reconstruction can be single staged or two staged procedures. Immediate breast reconstruction after mastectomy does not affect the overall survival and disease-free survival of breast cancer, however surgical site infection is more common when compared to mastectomy alone (10). Skin-sparing mastectomy can be performed for implant reconstruction. However, long-term results for nipple sparing mastectomy (NSM) are not available. NSM appears to be an oncologically safe option for appropriately selected patients, with low rates of locoregional recurrence. For NSM to be performed, tumours should be peripherally located, smaller than 5 cm in diameter, located more than 2 cm away from the nipple margin, and human epidermal growth factor 2-negative. A separate histopathological examination of the subareolar tissue and exclusion of malignancy at this site is essential for safe oncological practice (11).

Surgery of the axilla

It is an essential and vital component of the breast cancer surgery. It can be for staging of the axilla alone in clinically node negative (cN0- defined as no palpable axillary lymph nodes, and none found enlarged/ suspicious on mammography and/or axillary ultrasonography) or for therapeutic intent in patients with clinically positive axilla (stage cN1 or N2/3 following –NACT) or in those where the ***sentinel lymph node biopsy*** (SLNB) results prove metastatic node(s) in the axilla. SLNB if done prior to NACT, contributes to the clinical staging of the disease as per 7th edition of AJCC staging and when done at the time of primary surgery contributes to the pathological staging of disease and a decision for further axillary clearance. It is done only in clinically node negative patients. The accuracy and detection rate of SLNB reduces post NACT (12), however detection rates of sentinel node in stage III tumours is similar to those of early breast cancer (13). An ***axillary clearance*** can be performed in those with clinical axillary nodes or those in whom SLNB is positive for metastatic deposits. Level I and II axillary clearance is standard and level III clearance is usually restricted to those in whom level III (apical) nodes are found to be enlarged intraoperatively (14). ***Axillary reverse mapping*** (ARM) to reduce the chance of lymphedema of the ipsilateral arm can be done intraoperatively along with SLNB or axillary clearance. In ARM, the lymphatics and lymph nodes draining the ipsilateral upper limb are identified and spared from the dissection, thereby reducing the chance of lymphedema.

Bilateral oopherectomy in breast cancer patients

In premenopausal women having hormone receptor positive cancers, ovarian function suppression is a highly effective treatment strategy. It can be offered in form of surgical bilateral salpingo-oophorectomy plus tamoxifen or aromatase inhibitor- which is a safe and practical treatment in low- and middle-income countries as other forms of ovarian suppressive treatment modalities e.g. Goserlin- a GNRH analogue- may not be affordable. Surgical oopherectomy can be offered to women who have completed their families and may be performed in post NACT women at the time of breast surgery. It can also be offered to premenopausal women with metastatic breast cancer.

Metastasectomy

For oligometastases may be tried in select patients. Isolated liver or lung metastasectomy has been shown to improve 5 year survival rates in some retrospective studies (15, 16) and no prospective data is available to this regard. However, brain metastasectomy is not widely recommended. In a study by Ho VK et al, patients with synchronous CNS metastases, surgery for the primary tumour and the metastases also improved survival. In patients with metachronous metastases, younger age (<50 years), lower initial tumour stage (I), ductal carcinoma, a prolonged time interval until diagnosis of CNS metastasis (>1 year), and absence of extracranial metastases were associated with improved survival in a study by Ho VK et al. Metastasectomy and radiation therapy did not provide benefit beyond the first six months.

Prophylactic and Risk-reducing surgery in genetically predisposed individuals

Prophylactic surgeries such as bilateral mastectomy (NSM may be performed) and risk reducing salpingo-oophorectomy (RRSO) have a proven role in women having BRCA 1 and 2 mutations. They, however, do not completely eliminate the possibility of cancer occurrence (17). Breast cancer rates following bilateral prophylactic mastectomy in BRCA mutation positive women is 5% and the occurrence of primary peritoneal carcinoma ranges from <1% to 1.5% following RRSO.

Contralateral prophylactic mastectomy (CPM)

Increasingly being offered to selected patients with known BRCA mutations, and is increasingly being demanded by breast cancer patients in general. Patients receiving CPM saw no absolute reduction in risk of metachronous contralateral breast cancer (MCBC). In patients with familial genetic risk, both relative and absolute risks of MCBC were significantly decreased among CPM recipients but there was no improvement in overall survival or breast cancer specific mortality. *The American Society of Breast Surgeons consensus group agreed that CPM should be discouraged for an average-risk woman (no genetic/familial predisposition; risk of MCBC is 0.1-0.6% per year) with unilateral breast cancer, women with locally advanced or metastatic disease (18). However, they*

have specified that patient's values, goals and preferences should be included to optimize shared decision making when discussing CPM. The final decision whether or not to proceed with a CPM is a result of the balance between benefits and risks of CPM and patient preference.

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Table 1: SGPGIMS Lucknow Treatment protocol for early breast cancer

Early breast cancer- T1/T2, N0/N1, M0 disease - Stage I, IIA, IIB (T2N1)

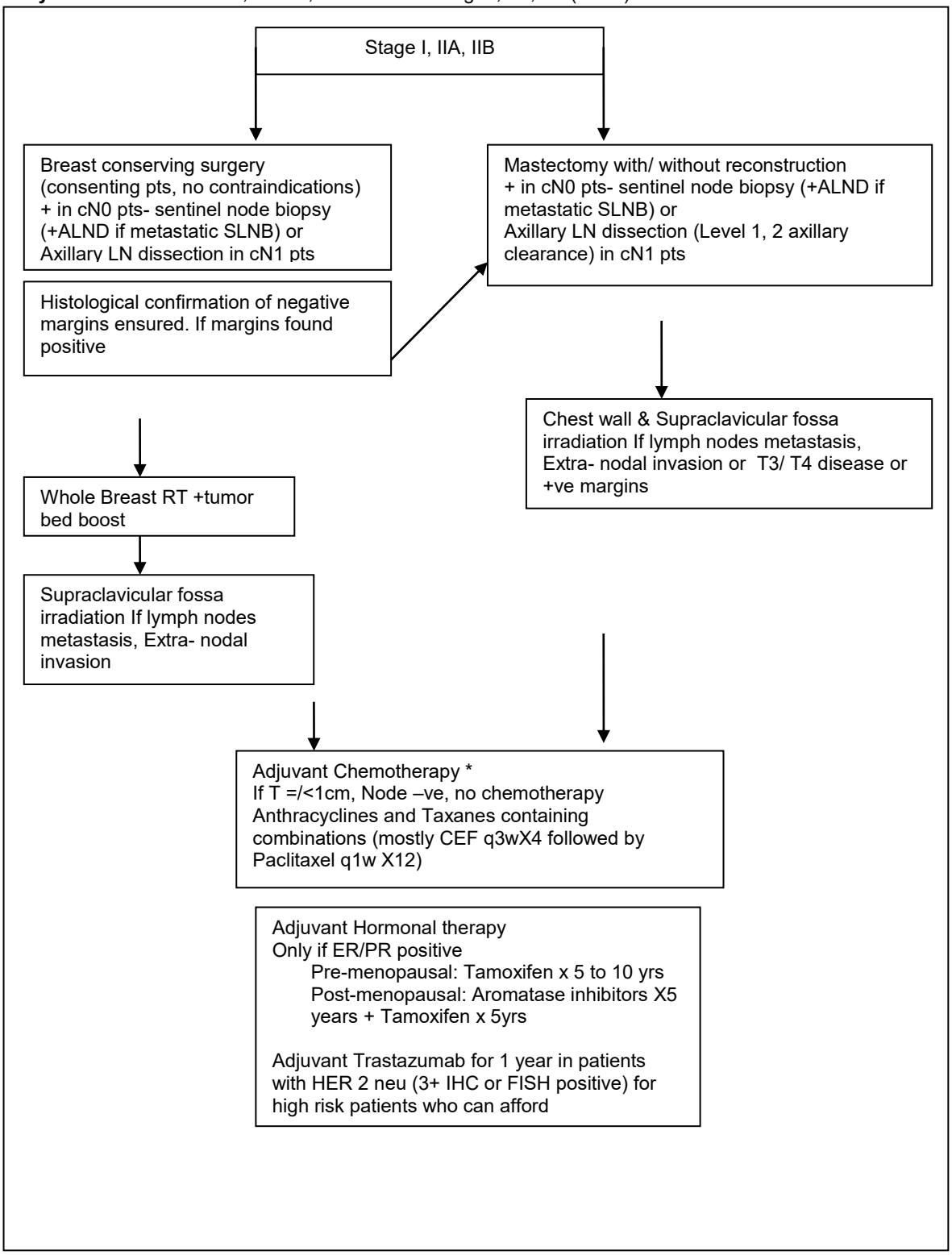
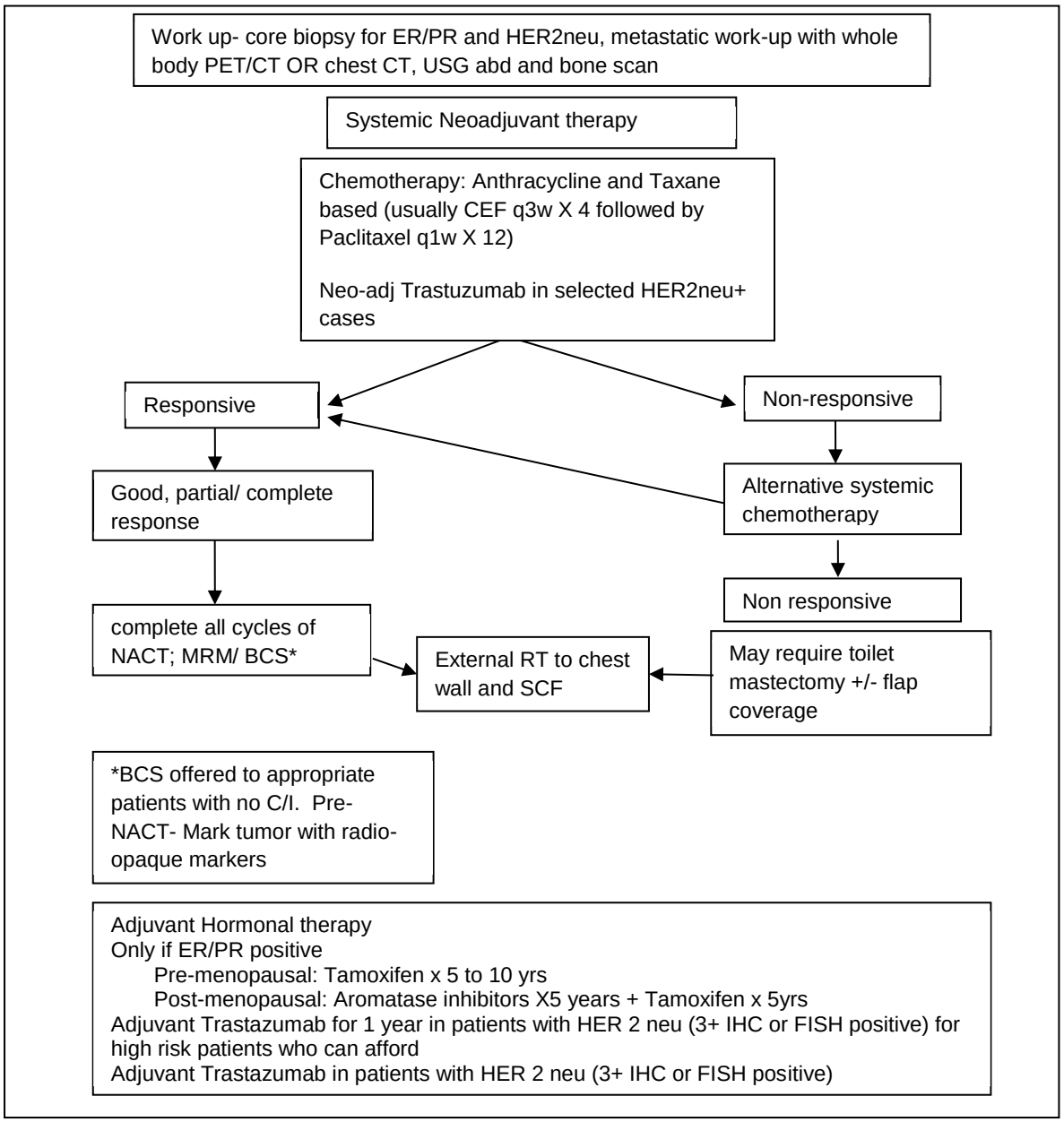


Table 2: **Treatment protocol for locally advanced breast cancer**

Locally advanced (and Large operable) breast cancer- Stage IIIA, IIIB, IIIC, and IIB (T3N0M0)



Oncoplastic breast surgery

Geeta Kadayaprath

It took almost a century before the Halstedian approach to breast cancer was replaced by more conservative methods especially for early breast cancer. Breast conservation therapy was tested in several randomized trials by the NSABP group and the Milan Group and it was concluded that BCT and mastectomy were equivalent in terms of local recurrence as well as distant metastases in suitable cases. Breast conservation became the norm in the West where screen detected cancers and smaller palpable tumors were subjected to wide excision and axillary dissection and subsequently sentinel lymph node biopsy. The essence of this evolution in surgical technique has been to offer less mutilating surgeries without compromising oncological outcome. While the goal of BCS was to achieve complete removal of the tumor with adequate surgical margins, preserving the natural shape and appearance of the breast became a challenge. To address this issue, oncoplastic surgical procedures

were introduced in recent years. This saw an amalgamation of the best principles of oncology along with plastic surgery leading to optimal oncologic outcomes and safety.

History of Oncoplastic surgery (OPS) in Breast Cancer

It all began in the 1990's.This term was first coined by Audretsch to describe the blending of the oncology and plastic surgery techniques. It was slow to pick up but in the last decade, rapid strides have been made in this area, as the acceptance of the various procedures and the dissemination of information has spread.

Classification of Oncoplastic Surgery

Volume Displacement Techniques
The resected defect is reconstructed by moving a range of local glandular or dermoglandular tissue into the defect. Adjacent tissue rearrangement and various mammoplasty techniques are used to achieve this end.

Adjacent tissue rearrangement is frequently used especially if the volume of breast excised is less than 20%. This is the preferred method in large to medium sized breast with reasonable ptosis and dense glandular tissue. It is also known as Type 1 oncoplasty. Adjacent tissue rearrangement involves

a) Accurate placement of skin incision
b) Skin undermining
c) Wide excision from skin to muscle
d) NAC undermining
e) Glandular reapproximation
f) De-epithelialisation and NAC repositioning

These techniques solve 90% of cases requiring oncoplasty. However, this technique may not be desirable in the elderly with fatty breasts where undermining in both the subcutaneous plane and the deep to the gland may compromise the vascularity of the displaced breast tissue. These techniques are simple to perform and do not require specific training. The cosmetic results are good and the re-excision rates are less than 10%.

Mammoplasty techniques makes use of various parenchymal flaps to fill the resection defects. They are indicated when 20-50% of the breast volume is likely to be excised, in large-medium sized breast with significant ptosis.. These are immensely useful for tumors in unfavorable locations like the central quadrant, upper inner quadrant and lower quadrants. Contralateral symmetrisation procedures with a similar procedure may benefit women with symptomatic macromastia.

The commonly used flaps are

1) The superior pedicle flap- allows for resection of tumours in the lower half of the breast.
2) The inferior pedicle flap- allows for resection of tumours located in the upper half of the breast.

Other mammoplasty techniques, which are used in specific clinical situations, are the Round block technique for almost any quadrant, the Grisotti flap for central quadrant tumours, the Batwing approach for upper half tumors located close to the areola etc

Volume Replacement Techniques
Here the resected defect is reconstructed by replacing the excised breast tissue with a similar volume of autologous tissue from an extramammary site. The preferred options include musculocutaneous flaps, pedicled flaps or free flaps

Musculocutaneous flap- The most commonly used flap in this category is the latissimus dorsi musculocutaneous flap. This versatile flap has the ability to reach almost all quadrants of the breast, specifically the superior, inferior and lateral aspects of the breast. If skin is required, a posterolateral incision is designed to harvest the flap. If skin is not required then a Mini LD flap can be harvested through an anterolateral or lateral mammary crease incision, which is also used to resect the tumour.

The other flaps based on perforators are

- The thoracodorsal artery perforator flap (TDAP)- is an adipo-cutaneous flap minus the LD muscle
- The lateral thoracic artery flap – is a fascio-cutaneous flap based on the lateral thoracic artery or the thoracodorsal artery and vein
- The lateral intercostal artery flap(LICAP)- is based on the lateral perforator of the intercostal artery

Indications of OPS

- Breast cancer for which a standard BCS is seemingly impossible without compromising the margins or cosmesis. This includes large tumors, extensive intraductal componenet, multifocal disease, poor response to neoadjuvant chemotherapy or a high tumor to breast ratio with resection of more than 10-20% of breast volume
- Tumors in any location, especially the central, medial and lower pole tumors

Contraindications to OPS

1. Large tumors that require a mastectomy to achieve clear margins
2. Insufficient residual breast after excision
3. Extensive microcalcifications
4. Multicentric disease
5. Inflammatory Carcinoma
6. Previous irradiation
7. Multiple co morbidities and chronic smoking

Why should OPS be offered to patients?

1. OPS allows for bigger resections, wider margins with good oncologic and cosmetic outcomes
2. OPS may avoid the need for mastectomy and circumvent the morbidity associated with mastectomy and immediate reconstruction. Sensory loss associated with reconstruction is also avoided
3. Secondary operations to correct breast deformities are avoided if primary OPS is undertaken
4. OPS reduces the size of the breast allowing the radiation oncologist ease of delivery radiotherapy
5. Bilateral OPS prevents breast asymmetry and allows for histopathological examination of the contralateral breast and incidental discovery of occult carcinoma.

Evaluation of outcomes

The parameters taken in account to measure outcome are

1. Local recurrence rates
2. Cosmesis
3. Patient satisfaction

Based on the limited studies, which have reported outcomes, local recurrence rates and cosmetic failure are within acceptable limits when compared with conventional BCS.

Conclusions

1. OPS has become an integral part of most breast conservation surgeries.
2. Type 1 oncoplasties can be easily mastered and can provide answers for almost 90% of cases
3. Specialised training to pick up plastic surgery techniques are recommended for Type 2 oncoplasties
4. Oncologic and cosmetic outcomes need to be assessed prospectively to establish the safety of this procedure

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Adjuvant therapy in breast cancer

Kishore Singh

Introduction

Globally, breast cancer is the most frequently diagnosed and the leading cause of cancer death in women. For women with newly diagnosed, non-metastatic breast cancer, treatment consists of a multidisciplinary approach that involves input from surgery, radiation oncology, and medical oncology.

Adjuvant treatment is defined as additional cancer treatment given after the primary treatment to lower the risk that the cancer will come back. Adjuvant therapy may include chemotherapy, radiation therapy, hormone therapy, targeted therapy, or biological therapy.

Why adjuvant therapy is important?

It is seen that after mastectomy of early breast cancer cases, recurrence is still very high. Tumor comes back at the scar site is 25-75%, isolated local and without regional recurrence is around 50% and simultaneous distance metastasis is approximately 10-50%.Without use of any adjuvant therapy, the median time to recurrence is 2-3 years, where as the median time to failure in patients receiving adjuvant systemic therapy is 2 - 5years. The addition of chemotherapy and / or radiotherapy not only reduced incidence of relapse but also delays appearance of it.

Role of Adjuvant Chemotherapy

The decision to use adjuvant chemotherapy takes into account tumor histology, expression of estrogen (ER) and/or progesterone (PR) receptors, tumor stage and grade, patient age, as well as high-risk features such as lymphovascular invasion. Chemotherapy reduces the risk of recurrence in women with breast cancer.

Indications of Adjuvant Chemotherapy

- *HER 2 positive* - any tumour >0.5cm and/or node positive.
- *HER 2 negative and ER negative* - Tumour size >1cm, node positive, can be considered in tumours 0.5-1cm if there is presence of LVSI and high grade features.
- *HER 2 negative and ER positive* **-** node positive, high Oncotype Dx recurrence score, can be considered if high risk features are present.

To guide clinical decision-making, gene expression profiles such as the RS, EndoPredict, the Breast Cancer Index (BCI), and the PAM50 intrinsic subtype assay have been developed to identify patients with such a low chance of recurrence that the absolute benefit of chemotherapy may not justify the risk of toxicities. By contrast, patients with higher scores on these assays have a sufficiently high risk of recurrence despite endocrine therapy that the addition of chemotherapy outweighs the risk of toxicities.

In the 2012 EBCTCG meta-analysis, the use of an anthracycline-containing regimen compared with no treatment resulted in the following outcomes

1. Decreased risk of recurrence from 47 to 39 percent (relative risk [RR] 0.73, 95% CI 0.68-0.79)
2. Decreased breast cancer mortality from 36 to 29 percent (RR 0.79, 95% CI 0.72-0.85)
3. Decreased overall mortality from 40 to 35 percent (RR 0.84, 95% CI 0.78-0.91)

Regimen Selection

For most patients in whom chemotherapy is recommended, we prefer doxorubicin and Cyclophosphamide (AC) followed by Paclitaxel (T) 12 weekly cycles or Docetaxel 4 cycles, administered. Patients with history of cardiac diseases should not be given anthracyclin based chemotherapy, in patients with HER 2 positive tumour, we should always add Trastuzumab. Trastuzumab is usually given along with taxanes and continued atleast for one year. In patients for whom anthracyclin is not an appropriate choice, we treat with Docetaxel and Cyclophosphamide (TC)

The rationale for utilizing AC-T regimen is based on evidence demonstrating that an anthracycline-containing regimen is at least equivalent to the historical standard regimen CMF and that the addition of taxane to an anthracycline-based regimen further improves outcomes.

Other regimens are FAC or FEC and TAC. Sometimes Herceptin is combined with Docetaxel and Carboplatin (TC) to avoid Adriamycin induced toxicity.

Timing of Chemotherapy

Optimal duration of adjuvant chemotherapy is 4 to 6 months. Adjuvant chemotherapy is typically started within eight weeks after surgery. Earlier treatment is not necessarily better, but a delay of more than 18 weeks may not be detrimental. For patients who are also going to receive adjuvant radiation therapy, standard clinical practice is to proceed with chemotherapy before radiation therapy. Concomitant chemotherapy and radiation treatment is associated with an increase in acute toxicity without a survival advantage and is therefore not recommended.

Toxicities of Chemotherapy

Risks of chemotherapy include acute toxicities including nausea, vomiting, hair loss, myelosuppression, and amenorrhea. Immunosuppression associated with chemotherapy may also lead to severe infections in some. Taxanes are associated with neuropathy, which generally resolves weeks to months after treatment, but may be

incomplete in severe cases. Longer-term toxicities also include the risks of cardiotoxicity associated with anthracyclin and the rare risk of chemotherapy-related leukemia.

NEOADJUVANT CHEMOTHERAPY

Benefits of NACT

1. Facilitates breast conservation
2. Can render inoperable tumours operable
3. Provides important prognostic information based on response to therapy
4. Allows time for genetic testing
5. Opportunity to modify systemic treatment if no preoperative therapy response or progression of disease

Disadvantages of NACT

1. Possible overtreatment with Systemic therapy if clinical stage is overestimated
2. Possible under treatment loco regionally with radiotherapy if clinical stage is underestimated
3. Possibility of disease progression during preoperative systemic therapy

Ideal Candidates for Preoperative Systemic Therapy

- Patients with inoperable breast cancer
  - Inflammatory breast cancer
  - Bulky or matted N2 axillary nodes
  - N3 nodal disease
  - T4 tumours
- Patients with operable breast cancer
  - Large primary tumour relative to breast size in a patient who desires breast conservation

Prefered Regimens

- Dose dense AC followed by Paclitaxel every 2weeks
- Dose dense AC followed by weekly Paclitaxel
- Docetaxel and Cyclophosphamide

Other regimens

- CMF
- FAC
- FEC
- TAC
- EC

In case of Her-2 positive cases we must add trastuzumab + or - pertuzumab
Currently in inoperable cancers neoadjuvant chemotherapy is standard of care.

Is there an advantage of neoadjuvant chemotherapy in tumors that are operable at diagnosis?

- No, same DFS or OS

NSABP B-18, there was no survival benefit of receiving AC.
NSABP B-27 (PreOp AC Vs PreOp AC→T Vs PreOp AC→Post Op T): Sig ↑ in PCR but there was no significant difference in DFS or OS

ROLE OF ADJUVANT RADIOTHERAPY

Post operative RT

1. Mandatory after BCS, given before Chemotherapy
2. After mastectomy is subtotal removal of primary tumor or $\geq$ 3 LN
3. Also in the presence of unfavorable prognostic features:
   i. Tumour size > 5cm
   ii. Age <35 year
   iii. Gross ECE, grade III, ER negative, LVI, muticentricity
   iv. Four or more nodes positive
   v. Inadequate nodal dissection (less than 10 nodes extracted)
   vi. Controversy regarding patients with 1-3 lymph nodes positive, but after the updated result of EBCTCG meta-analysis, such patients should receive post mastectomy radiotherapy

The objective of adjuvant radiation therapy (RT) is to eradicate any tumor deposits remaining following surgery for patients treated by either breast-conserving surgery or mastectomy. Doing so reduces risk of locoregional recurrence (LRR) and improves breast cancer-specific and overall survivals.

Adjuvant WBRT indicated in all high risk situations to reduce the risks of recurrence and breast cancer death. Whereas in low risk patients with age more than 65years, it can be safely omitted.

Indications for Adjuvant Radiotherapy

WBRT following breast conservation therapy reduces the locoregional recurrence rate and risk of breast cancer death. These benefits of WBRT are demonstrated by the 2011 meta-analysis performed by the Early Breast Cancer Trialists' Collaborative Group (EBCTCG), which included over 10,000 women (known to be either pathologically node-negative or positive) in 17 trials. The main results of the meta-analysis were that WBRT resulted in:

1. A nearly 50 percent reduction in the 10-year risk of any first recurrence compared with breast-conserving surgery alone (19 versus 35 percent, respectively, relative risk [RR] 0.52, 95% CI 0.48-0.56). The reduction in recurrence rate associated with RT was due to a decrease in locoregional rather than distant recurrences.

2. A reduction in the 15-year risk of breast cancer death (21 versus 25 percent, RR 0.82, 95% CI 0.75-0.90).

Dosing and Schedule

Most women receive conventionally dosed WBRT, which is delivered to the entire breast in 1.8 to 2 Gy daily fractions over 4.5 to 5 weeks to a total dose of 45 to 50 Gy. Another option is a shorter fractionation ("hypofractionated") schedule, which has been associated with less toxicity, and is a reasonable choice for many patients. In general, a hypofractionated regimen delivers more radiation per dose, but the overall treatment duration is shorter (40 to 42.5 Gy in approximately three to five weeks with or without a boost). Cosmetic and disease outcomes have been equivalent between hypofractionated and conventional schedules. If an RT boost is administered, 10 to 14 Gy in either 2 Gy or 2.5 Gy fractions is usually administered.

ASTRO recommends that use of hypofractionated RT should be strongly encouraged in women who meet all of the following criteria

- Aged 50 years or older
- With pT1-2N0 breast cancer
- With estrogen receptor (ER)-positive disease treated primarily with adjuvant hormonal therapy systemically

Accelerated Partial Breast Irradiation

APBI refers to the use of limited, focused RT as a more convenient alternative to conventional WBRT for women following breast-conserving surgery. Compared with WBRT, APBI delivers a higher dose of RT per day to a limited volume of tissue, encompassing the lumpectomy bed with margin over a shorter period of time.

Selection Criteria

American Society for Radiation Oncology (ASTRO), American Society of Breast Surgeons (ASBS), and American Brachytherapy Society (ABS) that properly selected patients who meet all of the following criteria are potential candidates for APBI, although WBRT remains the accepted standard option.

- ≥45 years of age
- Diagnosed with a small (≤3 cm), node-negative breast cancer
- Tumor excised to negative surgical margins

Timing of RT

For patients in whom adjuvant chemotherapy is indicated, RT is generally administered after its completion. For patients in whom adjuvant endocrine therapy is indicated, RT can be given concurrently or prior to its initiation. For patients in whom trastuzumab is indicated, RT is given concurrently.

ROLE OF ADJUVANT HORMONE THERAPY

Hormone receptor-positive (ie, estrogen [ER] and/or progesterone [PR] receptor-positive) breast cancers comprise the most common types of breast cancer, accounting for 75 percent of all cases. Several meta-analyses have demonstrated that endocrine therapy consistently improves survival outcomes for women with non-metastatic, hormone receptor-positive breast cancer and has a generally favorable toxicity profile.

The agents used in this setting are

1. The selective estrogen receptor modulator (SERM), tamoxifen.
2. Aromatase inhibitors, which block the peripheral conversion of androgens to estrogens.ie letrozole, anastrozole and exemestane.

3. Ovarian suppression or ablation

In **premenopausal women** with non-metastatic, hormone receptor-positive breast cancer the treatment preferred is tamoxifen or ovarian suppression along with exemestane. In post menopausal women the preferred hormonal agent in adjuvant setting is Aromatase inhibitor rather than tamoxifen.

Duration of Hormone Therapy
When Tamoxifen alone is used, it should be used for minimum duration of 10years. Whenever possible we should start the treatment with Aromatase inhibitor because the risk of recurrence is high within the first two years of therapy and Aromatase inhibitors give better results than tamoxifen.
When Aromatase inhibitors are used without tamoxifen, then the duration of treatment should not exceed 5years.if we switch over to Aromatase inhibitor from tamoxifen then it should be given to an additional period of 5years.

Toxicities of Hormone Therapy
There is risk of endometrial carcinoma, increased risk of thromboembolic episodes, hot flushes, sexual dysfunction and cognitive impairments with use of hormonal therapy.

Chemotherapy Regimen

AC / EC
Doxorubicin 60 mg / m2 i.v. bolus or Epirubicine 100 mg / m2 i.v. bolus
Cyclophosphamide 600 mg / m^2 i.v. bolus
Cycles repeated after 21 days
Total 4 cycles

TC
Docetaxel 75 mg / m^2 i.v.
Cyclophosphamide 600 mg / m^2 i.v. bolus
Cycles repeated after 21 days
Total 4 cycles

FAC
5 Fluorouracil 500 mg / m^2 i.v. bolus
Doxorubicin 50 mg / m^2 i.v. bolus
Cyclophosphamide 500 mg / m^2 i.v. bolus
Cycles repeated after 21 days
Total 6 cycles

CMF
Cyclophosphamide 600 mg / m^2 i.v. bolus Day 1 and Day 8
Methotrexate 40 mg/ m^2 i.v. bolus Day 1 and Day 8
5 Fluorouracil 600 mg / m^2 i.v. bolus Day 1 and Day 8
Cycles repeated after 28 days
Total 6 cycles

Paclitaxel
Paclitaxel 80 mg / m^2 i.v. in N Saline glass bottle over 1 hour via codan set
Pre medication with Dexamethasone 8 mg, Pheniramine 50 mg, Ranitidine 50 mg given i.v. 30 minute before Paclitaxel
Weekly for 12 cycles

TAC
Docetaxel 75 mg / m^2 i.v. 250ml 0.9% sodium chloride over 60 minutes
Doxorubicin 50 mg / m2 i.v. bolus
Cyclophosphamide 500 mg / m^2 i.v. bolus
Cycles repeated after 21 days
Maximum 6 cycles

TCH
Docetaxel 75 mg / m^2 i.v. 250ml 0.9% sodium chloride over 60 minutes
Carboplatin AUC 6 i.v. in 250 ml 5% Dextrose infusion for 1 hour
Trastuzumab (Herceptin)
Loading dose 8 mg/kg in 250ml sodium chloride 0.9% i.v. infusion over 90 minutes
Maintenance dose 6 mg/kg in 250ml sodium chloride 0.9% i.v. infusion over 30 minutes
Total one year

Approach to a patient with breast lump

P N Agarwal, Anurag Mishra

A new breast mass/lump is the most common presentation of breast disease for which patients seek medical attention, other presentation being an abnormal mammogram, pain and tenderness without a mass, nipple discharge, or skin changes. Such are best evaluated by using what is known as Triple assessment which takes into account

1. Clinical Evaluation
2. Imaging
3. Histological assessment

Clinical Evaluation

A thorough history and physical examination are essential components of the diagnostic evaluation of a breast abnormality.

- History:
  - Key features of the history include details about the presenting symptom, history of previous breast disease, and risk factors for breast cancer including a menstrual history and other contributing past medical history.

  - Patient history should include questions regarding the duration of the symptoms or mass, change in size, associated pain or skin changes, relationship to pregnancy or the menstrual cycle, and previous trauma. Nipple discharge should be characterized according to its color and whether it is spontaneous, unilateral, or emanating from a single duct. Any skin changes in the nipple or areola should be noted.

  - The hormonal history includes age of menarche, date of last menstrual period, regularity of menstrual cycle, number of pregnancies, age at first-term pregnancy, lactational history, and age at menopause or surgical menopause (note if oophorectomy performed).

  - A history of previous breast biopsies, breast cancer, or cyst aspiration should be ascertained, including any known pathology results and treatment regimens. A history of previous oral contraceptive use and hormonal replacement therapy should be elicited. The patient should provide dates of previous mammograms and location of the films. A detailed family history of breast and gynecologic cancer should be recorded, including the age at diagnosis and the location. This history should include at least two generations as well as any associated cancers, such as ovary, colon, or prostate (in men).

  - Assessment of breast cancer risk: Breast cancer is the most common malignancy among women worldwide (Int J Cancer 1999;80:827). Hormonal exposure, or pathologic factors or genetics may be correlated to a risk for breast cancer.
    - *Hormonal*: Factors that increase a patient's risk by 1.5- to 4.0-fold include increased exposure to estrogen or progesterone due to early menarche (before age 12 years) and late menopause (age >55 years), high body-mass index after menopause, presence of hyperplastic breast tissue with atypia, and exposure to ionizing radiation. A late age at first full-term pregnancy is an important determinant of breast cancer risk. Women with a first birth after age 30 years were shown to have twice the risk of those with a first birth before age 18 years. Breast-feeding may exert a protective effect against the development of breast cancer. Lifetime and 5-year breast cancer risk can be estimated using the Gail model, which is based on age, onset of menses, onset of menopause, age at first birth, and prior breast biopsies. This model is used for entering women in chemopreventive trials.
    - *Pathology*: Certain pathologic features observed on breast biopsy are associated with increased breast cancer risk. No increased risk is associated with adenosis, cysts, duct ectasia, or apocrine metaplasia. There is a slightly increased risk with moderate or florid hyperplasia, papillomatosis, and complex fibroadenomas. Atypical ductal or lobular hyperplasia carries a 4- to 5-fold increased risk of developing cancer; the risk increases to 10-fold if there is a positive family history. Patients with increased risk should be counseled appropriately. Those with atypia or lobular carcinoma in situ (LCIS) should be followed with semiannual physical examinations and yearly mammograms.
    - *Genetics*: A family history of breast cancer in a first-degree relative is associated with an approximate doubling of risk. If two first-degree relatives have a history of breast cancer (e.g., a mother and a sister have had breast cancer), the risk is even higher. These familial effects are enhanced if the relative had either early-onset cancer or bilateral disease.

- *BRCA*. BRCA1 and BRCA2 are breast cancer susceptibility genes associated with 80% of hereditary breast cancers, and they account for approximately 5% to 10% of all breast cancers. Women with BRCA1 mutations have an estimated risk of 85% for breast cancer by age 70 years, a 50% chance of developing a second primary breast cancer, and a 20% chance of developing ovarian cancer. BRCA2 mutations carry a lower risk for breast cancer and account for 4% to 6% of all male breast cancers. Surveillance should include a monthly breast self-examination, semiannual clinical examination, and annual mammography beginning at age 25 to 35 years. Screening for BRCA1 and BRCA2 gene mutations should be reserved for women who have a strong family history and have undergone a multidisciplinary evaluation, including genetic counseling. Prophylactic bilateral mastectomy provides a cancer risk reduction of 90% to 100% and is an option for some patients.
- *ErbB2* (Her2/neu) oncogene overexpression is seen in approximately 30% of breast adenocarcinomas, and its presence in a tumor specimen is a negative prognostic factor. Current research is investigating methods of targeting this oncogene for future therapies.

Table 1: Risk Factors for Breast Cancer

Female Gender
Increasing age
Genetic risk factors
BRCA1 or 2
Ataxia-telangiectasia
Li-Fraumeni
Cowden syndrome
Family history of breast cancer
Personal history of breast cancer
Previous breast biopsy
Proliferative breast disease without atypia
Atypical hyperplasia
Lobular carcinoma in situ
Previous thoracic radiation
Endocrine risk factors
Early menarche
Late menopause
Late parity
Nulliparity
Long-term hormone replacement with estrogen and progesterone
Lifestyle factors
Alcohol
Obesity

- Physical examination
  - The physical examination should be performed with respect for patient privacy and comfort without compromising the complete evaluation.

  - Inspect the breasts with the patient in the upright position, initially with the arms and pectoral muscles relaxed. Look for symmetry; deformity; skin changes, such as erythema or edema; and prior biopsy scars. The nipples are inspected for retraction, discoloration, inversion, ulceration, and eczematous changes. The patient is then asked to lift her arms for a more careful inspection of the lower half of the breasts. This maneuver also highlights any subtle retraction/ dimpling that is not readily visible with the arms relaxed.

  - The regional nodes should be palpated with the patient in the upright position, pectoral muscles relaxed. Axillary and supraclavicular nodal regions are evaluated. Size, number, and fixation of nodes should be noted.

  - The patient's breasts should be palpated in the upright and supine positions. In the supine position, the patient's breast is examined with the ipsilateral arm raised above and behind the head. The flat surface of the examiner's fingers should be used to palpate the entire breast systematically. The examination should extend to the clavicle, sternum, lower rib cage, and midaxillary line. If a dominant mass (defined as being three-dimensional, distinct from surrounding tissues, and asymmetric relative to the other breast) is palpated, its size, shape, texture, tenderness, fixation to skin or deep tissues, location, and relationship to the areola should be noted. A diagram in the chart noting these features is helpful. If uncertainty remains regarding the significance of an area of nodularity in the absence of a dominant mass in a premenopausal woman, a repeat examination at a different point in the menstrual cycle may clarify the issue.

  - In patients who present with nipple discharge, the nipple discharge is often elicited during palpation of the breast. The character, color, and location of the discharging duct or ducts should be documented.

Breast imaging

- ***Mammography***
  - A screening mammogram is performed in the asymptomatic patient and consists of two standard views, mediolateral and cranio-caudal. Studies have shown that screening mammography reduces mortality by 24% to 44%, depending on the age group. The current recommendation from the National Cancer Institute and American College of Surgeons is annual screening mammography for women aged 40 years and older. In the presence of hereditary breast cancer with known BRCA mutations, annual mammograms should begin at age 25 to 30 years, along with semiannual physical examinations. In patients with a strong family history of undocumented genetic mutation, annual mammograms and semiannual physical examinations should begin 10 years earlier than the age of the youngest affected relative and no later than age 40 years.

  - Diagnostic mammograms are performed in the symptomatic patient or to follow up on an abnormality noted on a screening mammogram. Additional views, such as spot-compression views or magnification views, are performed to further characterize any lesions noted. Spot compression may be used to differentiate an area of summated breast tissue from an abnormal lesion. Magnification views may be used to more clearly evaluate microcalcifications. A normal mammogram in the presence of a palpable mass does not exclude malignancy, and either further workup with a different imaging modality (ultrasound) or a biopsy should be performed. Mammography is not generally performed in lactating women or patients younger than age 30 years unless the degree of clinical suspicion is high. In the augmented breast, displacement views should be ordered to maximize the amount of parenchyma that can be visualized.

  - These views demonstrate the fibroglandular breast tissue. Right and left views are examined side by side so that asymmetries can be observed. The images are also examined for areas of microcalcifications.

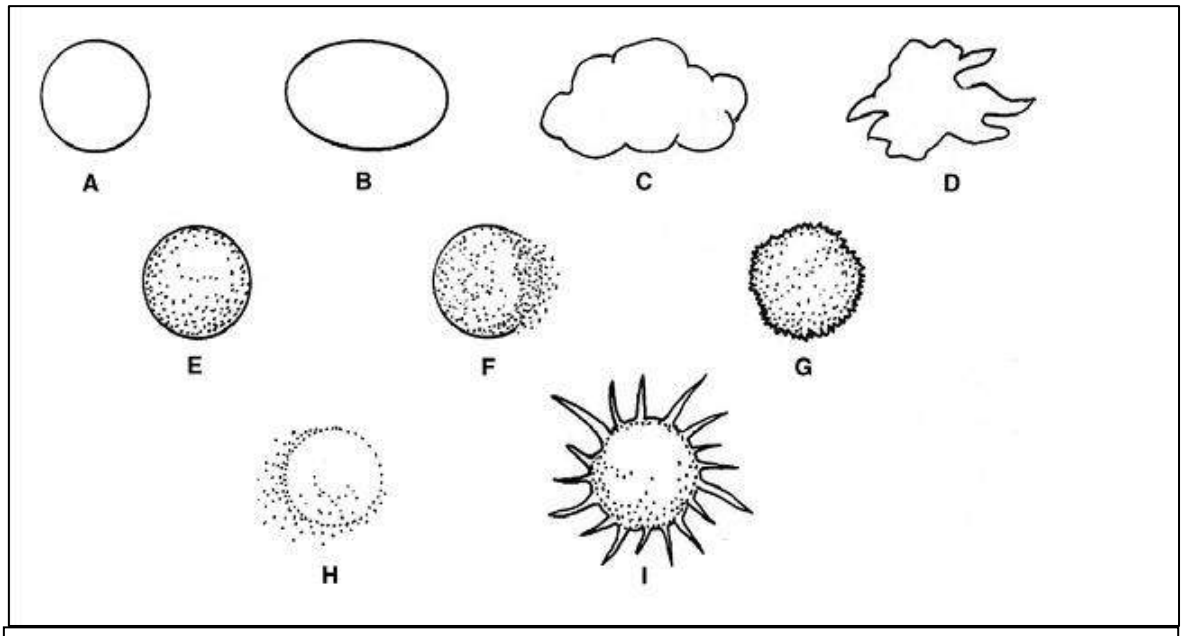

Fig. 1. Masses. Shape: (A) round; (B) oval; (C) lobular; (D) irregular. Margin: (E) circumscribed; (F) obscured; (G) microlobulated; (H) indistinct; (I) spiculated.
(Reproduced from Baker RJ, Fischer JE. Mastery of surgery: diagnostic approach to breast problems, 4th ed. Philadelphia: Lippincott Williams & Wilkins, 2001.)

  - Most mammographically visible cancers present as masses, calcifications, or architectural distortion, or a combination of the three. A mass is a space-occupying lesion that can be detected in two projections. If a finding is only seen on one projection, it is referred to as a density. A density may or may not prove to be a real finding after directed diagnostic imaging. Masses are characterized by their shape, margin, density, and associated microcalcifications to determine the probability of malignancy. The shape of a mass can be described as round, oval, lobulated, or irregular. Round or oval masses are usually benign. Masses that are irregular imply a greater probability of malignancy. Lobulated masses suggest an infiltrative growth pattern that may be suggestive of malignancy. Similarly, margin assessment is important because of the infiltrative nature of most breast cancers. Margins can be described as circumscribed, microlobulated, obscured, indistinct, or spiculated. A circumscribed margin that sharply delineates a mass

from the surrounding tissue is commonly a benign finding, such as a fibroadenoma or a cyst. A mass with spiculated or stellate margins is suspicious for malignancy

- Calcifications are a common mammographic finding. Most calcifications are not associated with malignancy. When found, the shape or morphology, location, number, and distribution of the calcifications should be noted. Malignant-appearing calcifications are usually less than 0.5 mm, pleomorphic or heterogeneous, and grouped. They can also be fine, linear, and branching, indicating an intraductal process

- After analyzing the mammographic images, radiologists classify findings into a final assessment category. The Breast Imaging Reporting and Data System (BIRADS) final assessment classification was developed by the American College of Radiology to standardize mammographic reporting. The BIRADS classification is listed in Table 2.

Table 2: Breast Imaging Reporting and Data System Classification

Assessment	Category	Recommendation
0	Need additional imaging evaluation	Add views or ultrasound
1	Negative	Annual mammography
2	Benign finding	Annual mammography
3	Probably benign finding- short interval follow-up suggested	Unilateral mammography 6 mo follow-up suggested and bilateral examinations 12 and 24 mo after initial examination
4	Suspicious abnormality	Biopsy should be considered
5	Highly suggestive of malignancy- appropriate action should be taken	Biopsy
6	Known carcinoma	

- ***Digital mammography-*** Recent evidence indicates that digital mammography is more sensitive than film mammography in screening women who have dense breasts and women who are younger than 50 years or are premenopausal or perimenopausal. Potential advantages of DM include the use of computer-aided detection (algorithm-based computer programs that alert the radiologist to possible abnormalities on the mammogram), and allowing centralized film reading.

- ***Ultrasonography***
  Ultrasonography is used to further characterize a lesion identified by either physical examination or mammography. Ultrasound can be used to determine whether a lesion is solid or cystic or to better define its size, contour, or internal texture. Although not a useful screening modality by itself due to significant false-positive and false-negative rates, when used as an adjunct with mammography, ultrasonography may improve diagnostic sensitivity of benign findings to >90%, especially among younger patients, for whom mammographic sensitivity is lower. Solid masses may have benign or malignant features. Malignant features of a solid mass on ultrasound are irregular margins, hypoechoic to the surrounding tissue, with posterior acoustical shadowing. Malignant-appearing masses usually have a vertical growth appearance (taller than wider). Benign features include ellipsoid shape, hyperechogenicity or hypoechogenicity, and smooth, well-circumscribed margins.

- ***Magnetic Resonance Imaging***
-
  Magnetic Resonance Imaging (MRI) is being used with increasing frequency for the screening and diagnosis of breast cancer. MRI has several advantages. There is no ionizing radiation to the patient with MRI. MRI is not limited by breast density and is an excellent tool for the screening of young women with increased risk for inherited breast cancer. In patients with indeterminate mammographic or ultrasonographic findings, MRI may be used for clarifying the imaging but should not replace biopsy for clinically suspicious lesions. Disadvantages of MRI are cost, limited availability, and decreased sensitivity for premalignant lesions. Images are obtained before and after the administration of gadolinium, an MRI contrast agent. The images are then evaluated for areas of enhancement and the morphology of the enhancement curve is noted. Lesions suspicious for cancer will display postcontrast enhancement with malignant morphologic features. MRI may be useful in patients who have axiliary or other adenopathy and no obvious primary tumor and in evaluation of the integrity of the breast prosthesis.

- ***PET scanning*** –Although positron imaging is very useful in identifying recurrent metastatic disease, its use for diagnosis of primary breast tumor is not recommended. The tumor size and cell type are factors that affect PET scan accuracy. Accuracy in detecting tumors larger than 2 cm is high, PET may miss approximately one third of the invasive cancers smaller than 1 cm. PET and combined PET/CT scanners are also being used to direct radiation therapy in patients who have localized metastatic disease in areas such as the chest wall or in bone.

Breast biopsy for palpable masses

- Fine-needle aspiration biopsy (FNAB) is a reliable and accurate office technique with sensitivity greater than 90%. A 22- to 25-gauge needle on a 10-mL syringe is advanced into the mass, and suction is applied. The needle is moved back and forth within the tumor with quick short strokes in nearly the same line as the original puncture. Cells are collected in the hub of the needle. The suction is released and the needle withdrawn. The contents of the needle are expelled onto a glass slide. A second glass slide is inverted over the first, and the two are pulled apart. One slide is fixed immediately, and the second is allowed to air dry. Two to three passes are performed for a total of four to six slides. False-negative findings are caused by inadequate sampling or improper specimen processing. FNAB results should be concordant with clinical impression and mammographic findings of the lesion (triple assessment). Fine-needle aspiration diagnoses the presence of malignant cells; however, it does not give information on tumor grade or the presence of invasion. Fewer than 5% of malignant masses are comprised of ductal carcinoma in situ (DCIS). Nondiagnostic or indeterminate aspirates do not exclude malignancy and require a surgical biopsy (Am J Surg 1997;174:372).

- Core biopsy, with either a Tru-Cut device, can be used to obtain more tissue. The skin is infiltrated with lidocaine and a nick made in the skin. The needle is inserted into the mass and fired. Three to five cores are taken and placed in formalin. Invasion, grade, and receptor status can be determined. For indeterminate specimens, an open surgical biopsy is necessary.

- Excisional biopsy is performed in the operating room using local anesthesia and intravenous sedation. Incisions should be oriented along Langer lines for optimal cosmesis (curvilinear, parallel to the areola). All incisions should be planned so that they can be incorporated into a mastectomy incision. Masses should be excised as a single specimen, the specimen should be oriented so that a short suture is placed superiorly and a long suture laterally, and the margins should be inked. Improper specimen handling may obscure margin status.

- Incisional biopsy removes a wedge of tissue from a fungating/ ulcerated breast mass. It is indicated for the evaluation of a large breast mass suspicious for malignancy but for which a definitive diagnosis cannot be made by FNAB or core biopsy.

- Punch Biopsy: While the diagnosis of inflammatory breast cancer is made largely clinically, histologic confirmation of cancer cells within the dermal lymphatics is pathognomonic for inflammatory breast cancer. In patients who present with skin changes, including erythema and/or peau d'orange, a 3- to 5-mm punch biopsy can be performed in the office using local anesthesia. The biopsy should be full thickness through the most suspicious area. Most inflammatory breast cancers do not present with a palpable mass, but if present, a core biopsy can then be obtained through the punch biopsy site to provide more tissue for receptor assays.

Nonpalpable lesions

- Stereotactic core biopsy is a minimally invasive method of obtaining core samples of nonpalpable, mammographically suspicious lesions under radiographic control. This technique is ideally suited to establish tissue diagnoses of several foci in disparate quadrants of the breast. Using a computer-driven stereotactic unit, two mammographic images, each at a 15-degree angle from the center, are taken to triangulate the position of the site to be biopsied in three-dimensional space. A computer determines the depth of the lesion and the alignment of the needle, which can be positioned within 1 mm of the intended target. Biopsies are taken, and postfire images are obtained of the breast and specimen. Contraindications include lesions close to the chest wall or in the axillary tail and thin or ptotic breasts that would allow needle strike-through. For indeterminate specimens, an open surgical biopsy is necessary. Nondiagnostic and insufficient specimens should also undergo NLB.

- Vacuum-assisted biopsy has been developed as a response to the difficulties that FNAB and core biopsy have with evaluating microcalcifications and DCIS. The Mammotome uses an 11-gauge biopsy probe to contiguously acquire tissue, which is pulled into the probe by vacuum suction. The advantage of this tool is that it can pull back several larger volume samples of tissue into the probe while the device remains in the breast. This technique allows removal of all of the tissue around a cluster of calcifications during a single insertion of the probe. This device also has the ability to place a marking clip through the probe to allow for future identification of the biopsy site.

- Needle localization biopsy is performed by placing a needle and hookwire into the patient's breast adjacent to the lesion under mammographic guidance. The patient is then brought to the operating room. With the localization mammograms as a map, an excisional biopsy is performed, encompassing the tissue around the wire and lesion. The specimen is oriented and a radiograph obtained to confirm the presence of the lesion in the specimen. It is not necessary to remove skin around the needle insertion site.

- *Emerging techniques*. Iodine-125 seed localization biopsy is a new technique that avoids needle placement for localization and allows for greater flexibility in operative planning. A titanium seed containing 0.05 to 0.3 mCi ^{125}I is inserted into the breast lesion or area of microcalcifications by the nuclear medicine radiologist under radiographic guidance, and a skin marker is placed. The titanium seed is localized by dissection with the aid of a handheld gamma detector, and the tissue around the seed is excised. The remaining cavity can be probed for residual activity to ensure adequate circumferential dissection, and the biopsy specimen is examined radiographically to confirm removal of the seed and the lesion. Seeds can be inserted the day before a scheduled biopsy to allow for more flexibility in operative planning.

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Adrenalectomy by minimal access surgery

Arun Prasad

Currently these are the methods to do an adrenalectomy

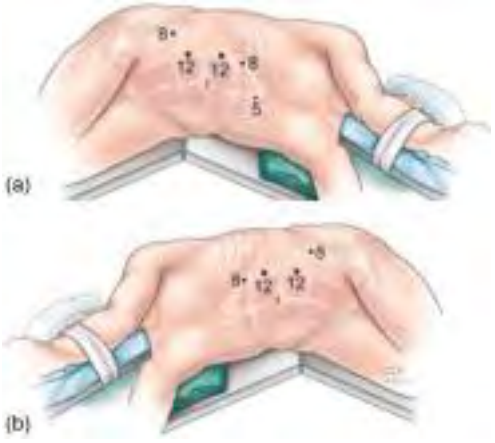
1. Open transperitoneal surgery
2. Open retroperitoneal surgery
3. Laparoscopic transperitoneal adrenalectomy (LTA)
4. SILS / LESS adrenalectomy
5. Posterior retroperitoneal adrenalectomy (PRA)
6. Robotic Adrenalectomy (RA)

Since the first adrenalectomy performed by the English surgeon Thornton in 1889, only in these last decades thanks to improvement of endocrinology knowledge, a better diagnostic support, and especially to minimally invasive techniques, the adrenal surgery has seen an important step forward. The first successful laparoscopic transperitoneal adrenalectomy (LTA) was performed by Michel Gagner in 1992 [1] .

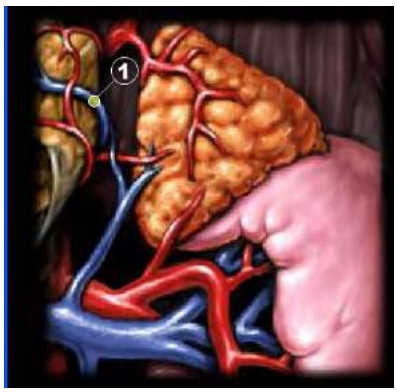
Initially adopted to treat small benign tumors, nowadays it is considered the “gold standard” technique to treat a broad spectrum of functioning and non-functioning adrenal diseases with described cases of resection of masses up to 12–15 cm 2 3 4 5 6 . Currently indications to LTA for lesions >6 cm is still a matter of debate and experienced endocrine surgeons are divided between supporters 7 8 9 10 11 and detractors [12 13] . This safe and effective approach offers all the benefits of minimally invasive technique such as low morbidity rate, short hospitalization, improved cosmesis and a rapid recovery in addition to increasing patients’ satisfaction and comfort [14] .

Shortly after Gagner, Gaur et al. described an alternative minimally invasive technique, the retroperitoneoscopic adrenalectomy (RA) [15 16] . This approach consists of two surgical variants, either a posterolateral or a true posterior approach 17 18 19 . Posterior retroperitoneoscopic adrenalectomy (PRA), was first popularized by Waltz et al., in 1996, and since the beginning appeared resulting in less postoperative pain and a faster recovery than LTA [20 21 22 23 24].

Laparoscopic transperitoneal adrenalectomy



According to Gagner, LTA is performed with patient in lateral decubitus position with the affected side facing upward and the operative table flexed just above the level of the iliac crest [1] . Can be used 3 ports for left-sided tumors, with one additional port if required, and 4 ports for right-sided tumors. The ports are commonly made at the umbilicus and the subcostal area in the anterior axillary and midclavicular lines, port sites could be modified at the discretion of the surgeon. The intra-abdominal pressure is kept at 12 mmHg. For left adrenalectomy, the left colonic flexure is mobilized along to Gerota fascia. Dissecting through the avascular plain between the pancreatic tail and the kidney, the spleen and the pancreatic tail are moved medially. In right adrenalectomy, the liver is mobilized along the lateral border of the inferior vena cava to control potential bleeding. Subsequently, the adrenal vein is identified and divided. The adrenal gland and the surrounding fat tissue are removed en bloc with a retrieval bag.

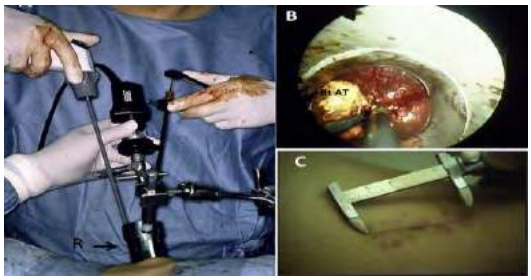


Identification of vascular structures represents the most crucial and technically demanding step during adrenal surgery. The dissection of the adrenal vein can be challenging because of the unique anatomic location of the adrenal gland. Understanding variant adrenal venous anatomy is important to avoid bleeding, particularly in patients with large tumors or pheochromocytomas [20] . In this regard, extra attention to the venous anatomy is advised during right adrenalectomy. The left adrenal vein is easier to divide because it is longer and narrower; conversely, the right adrenal vein is easier to identify but shorter and more difficult to control. Adrenal arteries tend to be small and indistinct, and they usually can be easily cauterized [21] .

Recognizing the main anatomic landmarks during both right- and left-side procedures is the best way to prevent inadvertent intraoperative complications. On the left side, the left renal vein, the tail of the pancreas, the superior pole of the kidney, and the psoas muscle can be very helpful to have a better exposure of the surgical field. On the right side, it is important to visualize the edge of the IVC, the right renal vein in addition with the superior pole of the kidney, and, not less important, the psoas muscle. During our adrenal dissection, the psoas muscle can be seen when mobilizing the gland circumferentially.

Retroperitoneoscopic adrenalectomy

According to Waltz, RA is performed with the patient in a prone jack-knife position, the back prepped and dropped, or in lateral decubitus position (flexed through the torso at a 45° angle), with the surgeon and assistant stand on the side of the operating adrenal gland [20] . The retroperitoneal space is entered posteriorly through a 12 mm transverse incision near to the tip of the 12th rib. A medial 10 mm trocar is placed along the border of the paraspinal muscle at a 45-degree angle pointing directly at the adrenal gland. A lateral 5 mm trocar is placed at the tip of the 11th rib. A 12 mm blunt balloon trocar is then introduced through the initial incision and CO 2 insufflation is established at a pressure of 25 mmHg.



The dissection of the retroperitoneal fat tissue from the capsule at the upper renal pole is performed. After visualization of the inferior vena cava at the right side and the identification of the renal vein at the left side, the adrenal vein is divided. Subsequently, dorsal, lateral and cranial mobilization of the tumor is performed. The adrenal gland and the surrounding fat tissue are removed en bloc with a retrieval bag.

Robotic adrenalectomy

Laparoscopic adrenalectomy was first reported in 1992. Since then it has largely replaced the open approach as the standard of care for adrenal removal, given well-known advantages such as less postoperative pain, minor blood loss, and better cosmetic appearance. Nevertheless, laparoscopy is recognized as associated with a steep learning curve. In 1999, Piazza et al. and Hubens et al. described the first robotic adrenalectomy cases using the AESOP 2000, which was the commercially available robotic platform in Europe at that time.

With the introduction of the da Vinci system (Intuitive Surgical, Sunnyvale, CA, USA), several series of robotic adrenalectomy have been reported, showing the safety and feasibility of the procedure as well as potential

advantages over laparoscopy, given the unique features of the currently available robotic system, such as three-dimensional vision and the EndoWrist technique.

To date, robotic surgery in urology remains mainly used for extirpative procedures including significant reconstructive components such as radical prostatectomy and partial nephrectomy, whereas its use for purely extirpative procedures such as nephrectomy and adrenalectomy is more limited mainly because of cost issues [25].

Since the report of initial cases in 2002 [26] , da Vinci robot-assisted laparoscopic adrenalectomy (RA) has been shown to be safe and feasible [27] . Recent evidence supports the use of robotic surgery for minimally invasive surgical management of adrenal masses and suggests that RA can be effectively performed with operative time and complication rates similar to laparoscopy, but with potential shorter hospital stay and less blood loss [28].

As for any other robotic procedure, careful case selection is of utmost importance for RA, especially during a surgeon's early experience. Indications include hormone-secreting tumors, adrenal masses >5 cm, smaller lesions suspicious for malignancy, and lesions increasing in size on serial imaging [27] . Contraindications include infiltrative adrenal masses and tumors of extremely large size because size of adrenal lesions correlates with the potential for adrenal carcinoma [28] . A known (or suspected) diagnosis of adrenocortical carcinoma is better managed with open surgery because there might be an increased risk of recurrence and death compared with laparoscopy [29]. However, authors have advocated the feasibility of RA for adrenocortical carcinoma [30].

Morbidly obese patients have been considered at higher risk of complications when undergoing LA [31] . Aksoy et al. did not found any difference in perioperative outcomes between RA and LA in obese patients, suggesting that difficulties in maintaining exposure and dissection in obese patients nullify the advantages of robotic articulating versus rigid laparoscopic instruments in adrenal surgery [32] . Notably, our RA population included obese and morbidly obese patients with a high median BMI of 29.5 kg/m 2, which reflects the referral pattern for our tertiary care institution.

In laparoscopy, both the transperitoneal and retroperitoneal approach can be used effectively [33]. According to a recent meta-analysis, the transperitoneal approach is the preferred one for RA [34]. The larger operative field of this approach aids in a better orientation and visualization of familiar anatomic landmarks, which is particularly helpful during the early learning curve. A larger working space is useful for removal of larger adrenal masses.

Systematic review and a meta-analysis of current evidence show that robot-assisted adrenalectomy can be performed safely and effectively with operative time and complication rates similar to laparoscopic adrenalectomy. In addition it can provide the potential advantage of a shorter hospital stay and less blood loss. These findings seem to support the use of robotic surgery for the minimally invasive surgical management of adrenal masses.

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Video Assisted Thoracoscopic (VATS) Thymectomy

Rajinder Parshad, Bharath V, Eshan Verma

Thymus gland is situated in the anterior mediastinum with finger like extensions into the neck. It consists of multiple lobes (2 to 5 or more) with varying amounts of thymic tissue in the fat surrounding the lobes, both in the neck and chest.

Historical Milestones

- First thymectomy for the treatment of myasthenia gravis was performed by Sauerbruch in 1913 using transcervical approach.
- Blalock in 1937 used transsternal approach, which remained gold standard for years.

- With the observation that thymic tissue can be found in various other locations like mediastinal fat, peritracheal, cervical fat aortopulmonary window etc. Masaoka and Monden described extended transsternal thymectomy. (2,3)
- With accumulating experience there was a realization that more the thymic tissue resected better would be the results (Maggi, et al., 1989) therefore a maximal thymectomy was described by Jaretzki et al. in 1987, which is combined extended transsternal and transcervical technique to remove as much thymic tissue as possible.
- More recently thoracoscopic thymectomy(VATS,unilateral) as described by Sugarbaker in 1993(jaretzki, et al., 1987) and its modifications like bilateral thoracoscopic and VATET (bilateral videothoracoscopic and transcervical)(Novellino, Longoni, & Spinelli, 1994) , have been used to improve the outcome following thymectomy.
- In 2001, Yoshino described the first robotic thymectomy in the treatment of small thymoma. In 2003, Ashton and Rea published a case report on robotic thymectomy in MG using two different approaches: the former surgeon from Columbia University adopted a right-sided approach with completion of the operation through a left-sided approach, the latter from the University in Padua used a left-sided approach only.

INDICATIONS:

- In the treatment of Myasthenia gravis
  1. With moderate to severe weakness
  2. With mild weakness having trouble breathing or swallowing
- Thymomas
- Thymic Carcinoma.
- Thymic cysts
- Thymic hyperplasia.

Thymectomy classification of the Myasthenia Gravis Foundation of America	
T-1	Transcervical thymectomy • Basic • Extended
T-2	Videoscopic thymectomy • Classic • Extended
T-3	Transsternal thymectomy • Standard • Extended
T-4	Transcervical and transsternal

SURGICAL APPROACHES for thymectomy includes:

- **Transcervical approach.**The first thymectomy performed for a patient with myasthenia gravis done by Sauerbruch,was done using transcervical approach.A curved transverse skin incision is given 2 cm above the sternal notch and extended laterally, then skin flaps are elevated and a retractor is placed to separate strap muscles in the midline. Superior poles of thymus are then identified and a cephalocaudal blunt dissection of thymus is performed.
  Transcervical approach though a minimally invasive approach offering lower post-operative morbidity,is quicker, obviates the need for double lumen tube intubation and can be done as an outpatient procedure but has many limitations like it has only one incision , which may be more prone to crowding of instruments and secondly if a technical complication like bleeding occurs it would be difficult to control it using this approach and a higher chance of recurrent laryngeal nerve injury. This approach has potential risk of leaving residual thymic tissue (Ng, Wan, & Yim, 2010) which is confirmed by the findings of residual thymic tissue following transcervical resection.Henze and colleagues reported the largest series of failed transcervical thymectomies due to incomplete resection.(Sonett & Jaretzki iii, 2009)

- **Extended transcervical approach** was describedby Cooper et al.(Cooper, 1988), includes addition of a partial median sternotomy and the associated use of mediastinoscopy. It was claimed that the extent of thymic resection is comparable to the more invasive procedureslike transsternal thymectomy. But Shrager et al.(Shrager, 2006) reported that the cervical and mediastinal perithymic fat may not be removed completely thus leaving a considerable amount of thymic tissue.

- **Standard Transsternal approach.** In 1937, Alfred Blalock did a thymectomy through transsetrnal approach of a young woman who had Myasthenia gravis, the patient improved postoperatively. Later, Blalock reported other myasthenic patients who improved after thymus removal, establishing thymectomy as an adjunctive treatment for Myasthenia gravis.(Blalock , Mason, Morgan, & Riven, 1939)(Pascuzzi, 1994)

This approach consists of a vertical skin incision over the sternum,followed by splitting of sternum by a sternal saw then a small retractor is inserted and sternum is opened slowly and removal of thymic and perithymic tissue done starting at the lower pole and moving caudally with gentle manipulation to avoid injury to important structures in the operative field.
However with the findings of residual thymic tissue in the neck as well as mediastinum following standard approach, it has been considered inadequate.

- **Extended thymectomy** as described by Masaoka and Monden(Ruckert, 2004) is removal of thymus and surrounding adipose tissue in the anterior mediastinum by sternal splitting. The extent of resection is between bilateral phrenic nerve and cephalo-caudally between lower poles of thyroid and diaphragm. No effort is made to clear cervical adipose tissue as well as the fat in the middle or posterior mediastinum such as the aorticopulmonary window.

- **Maximal thymectomy**(jaretzki, et al., 1987)i.e**.** combinedtranssternal and transcervical approach, consists of removal of gland plus excision of all mediastinal fat and tissue from the diaphragm to the horns of the thyroid and laterally to each phrenic nerve including the fat lateral to phrenic nerve, as well as the mediastinal pleural envelopes and aortopulmonary window.
Cooper et al.(Sonett & Jaretzki iii, 2009), has described this approach as a benchmark against which other techniques should be measured.

Studies assessing Transsternal approach have found it to be a radical procedure but this approach has higher post-operative morbidity such as more pain , higher incidence of pulmonary compromise, wound complications, sternal dehiscence and delayed return to normal activity (Jurado, 2012)thus making it less acceptable to the neurologists and the patients.

- **Thoracoscopic(Video assisted or Robot assisted)**: The thoracoscopic approach to thymectomy was first reported by Sugarbaker from Boston and also the Belgium group in 1993 . Subsequently, it has evolved to form several variants including:
    1. Unilateral (right or left)
    2. Bilateral
    3. VATET,which is combined bilateral VATS and transcervical.
    4. Sx VATET which is combined bilateral VATS with subxiphoid Incision.
    5. Robot assisted.

  Closed port trocars are placed in the intercostal spaces for the 30 degree scope and other dissecting instruments. After identifying the important landmarks like phrenic nerve, superior vena cava,internal mammary vessels and the thymus within surrounding mediastinal fat dissection is done starting from the caudal end.
  Studies examining thymectomy through VATS have shown that this procedure is associated with less pain, shorter drainage time, shorter hospital stay, and improved cosmesis when compared to upper sternotomies.

  Even though VATS is associated with reduced blood loss, operative times and earlier hospital discharge compared with robotic thymectomy as depicted in Mayo clinic study(2015), several studies have established safety and efficacy of Robotic thymectomy in patients with Myasthenia gravis (Jens C. R€uckert, Comparison of robotic and nonrobotic thoracoscopic thymectomy:, 2011)

AUTHOR , DATE & COUNTRY	STUDY DESIGN (LEVEL OF EVIDENCE)	NUMBER OF PATIENTS and APPROACHES USED	COMMENTS
Shiono et al, 2009 , Japan	Retrospective cohort Study (level 2b)(Shiono, Kadota, Hayashi, & Okumura, 2009)	median sternotomy (n = 26) bilateral VATET (n = 32)	VATET is equally effective as sternotomy at thymic tissue resection.
Lin et al., 2005 Taiwan	Retrospective cohort Study(level 2b)(Lin, Chang, Huang, & Lee, 2010)	VATS n=51 Transsternal n=31 .	VATS approach is not a compromise on operative efficacy.
Zu-Yang Yuan et al., 2013 , China	Retrospective cohort study(Yuan, Cheng, Sun, Mao, & Li, 2014)	VATS n=38 Open thymectomy N=91	36 thymic masses resected (accounting for 95%) in VATS thymectomy group confirmed by

			pathology had complete covering membrane that was applied to prove that thymus was entirely removed, comparable to 80 open thymectomies (accounting for 88%).
Julissa jurado et al, 2012, USA	Retrospective cohort Study(Jurado, 2012)	N=263 Bilateral VATS (n=77) Open thymectomy (n=186)	Minimally invasive technique is safe and achieves a comparable resection and postoperative complication profile when used selectively for all indications.
Tomulescu et al, 2006, Romania	Retrospective cohort study(tomulescu, 2006)	*VATS(n=107)*	VATS provides similar benefits to those of the "standard extended transsternal thymectomy.
Meyer et al, 2009,USA	Retrospective cohort study(Meyer, Herbert, Sobhani, Tavakolian, & Duncan, 2009)	VATS(n=48) Transsternal(n=47)	Equivalent clinical outcomes obtained by either VATS or transsternal approach.
Wright et al, 2002,Australia	Prospective study(Wright , Barnett, & Clarke, 2002)	VATS (N=26)	VATS thymectomy is a safe, effective method.

PREOPERATIVE PREPARATION

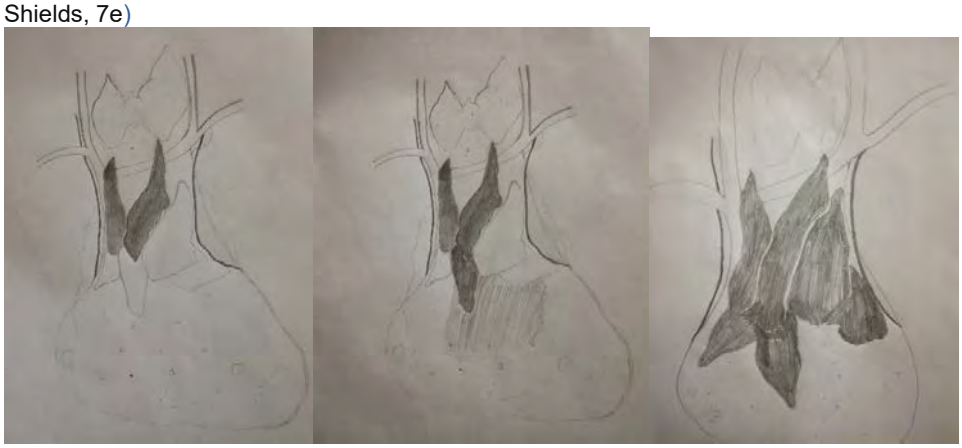
- Patients with Myasthenia are ***optimized*** under ***neurologist care*** before taking up for surgery.

POSITION AND PORT PLACEMENT

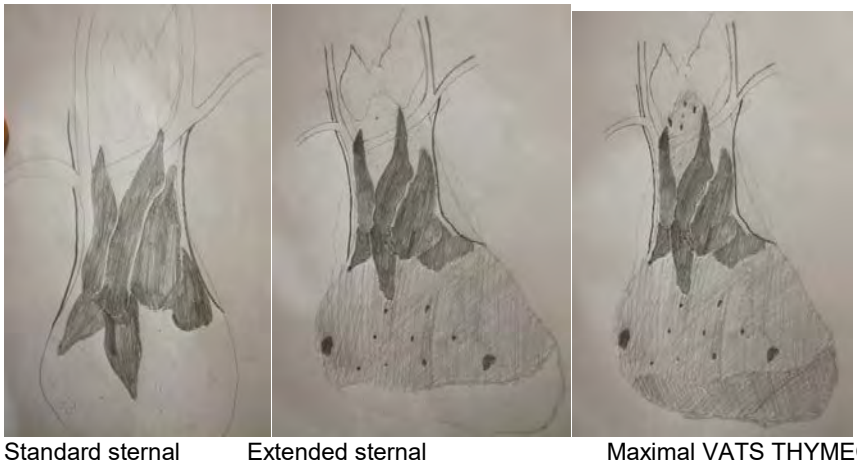
- Patient is placed in supine position with arm hyperextended.
- Lung isolation is obtained using Double Lumen Endotracheal tube.

A recent RCT – MGTX trial (Aug 2016,NEJM) comparing thymectomy with medical management in myasthenia gravis concluded that thymectomy improves clinical outcomes in nonthymomatous myasthenia gravis.

EXTENT OF RESECTION ACHIEVED THROUGH VARIOUS APPROACHES (General Thoracic Surgery by Shields, 7e)



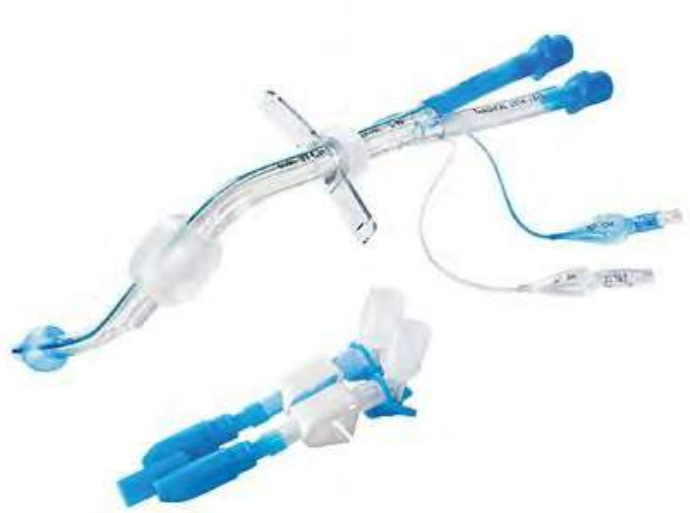
Basic cervical Extended cervical VATS

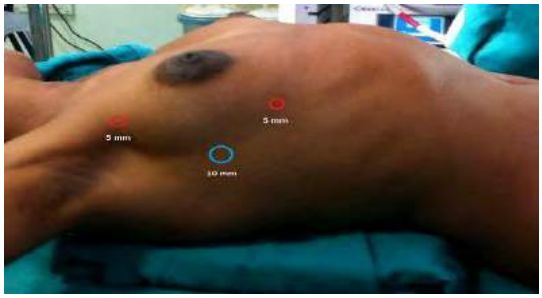


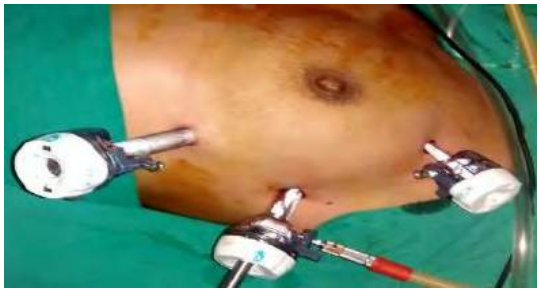
Standard sternal Extended sternal Maximal VATS THYMECTOMY

Double Lumen Endotracheal Tube

- Classic 3 port technique is used , but if the need arise 4th port can be inserted.

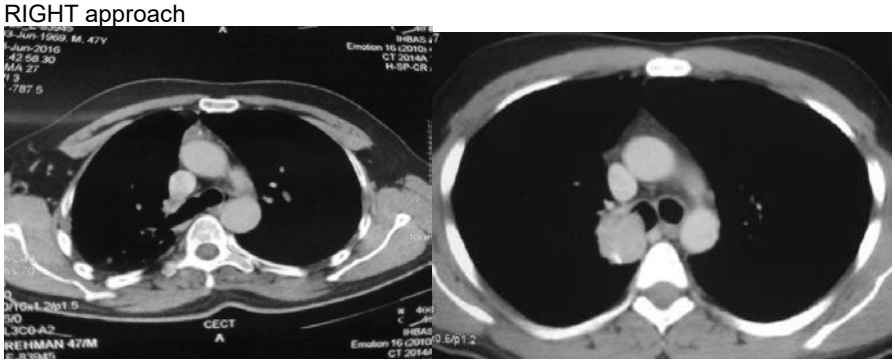




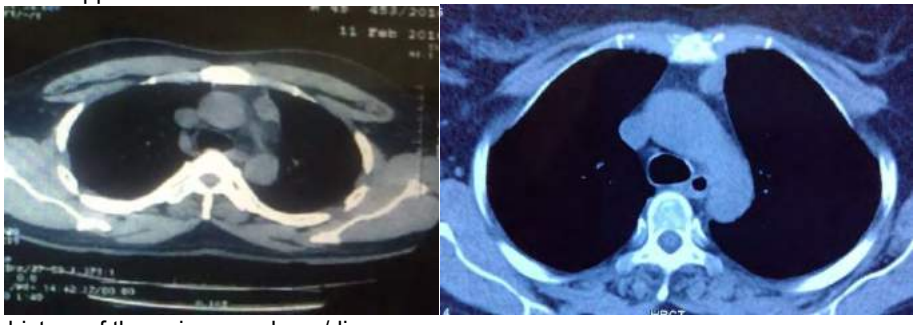


APPROACH – Mediastinum canbe approached from Right or Left thoracic cavity or in a few cases where deemed necessary a bilateralapproach is undertaken.
We decide approach based on

- Pre - operative imaging (CT/MRI)
  - RIGHT approach



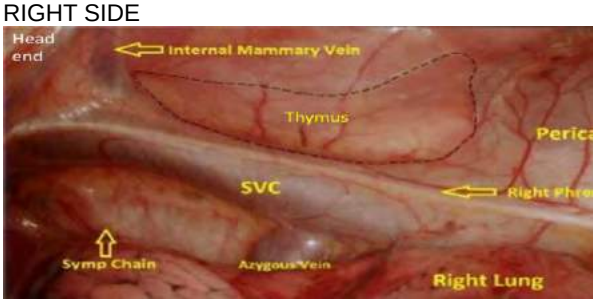
  - LEFT approach



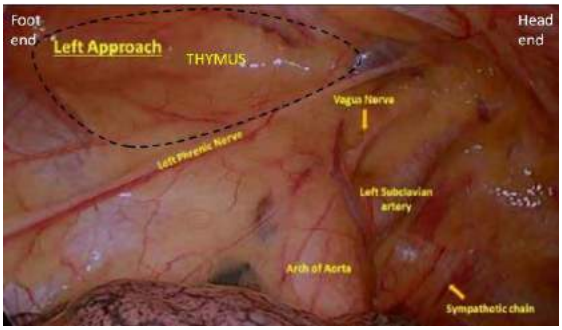
- Previous history of thoracic procedures/disease

INTRAOPERATIVE VIEW

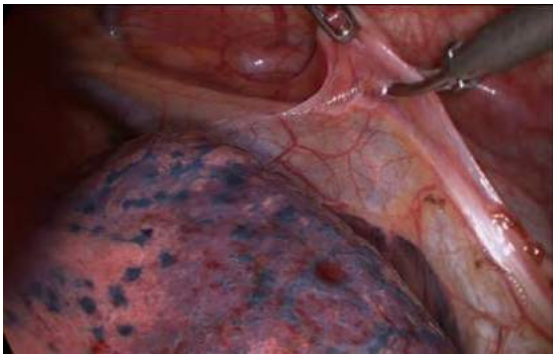
- RIGHT SIDE



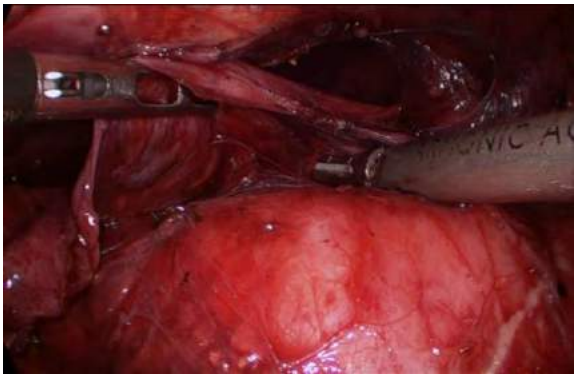
- LEFT SIDE



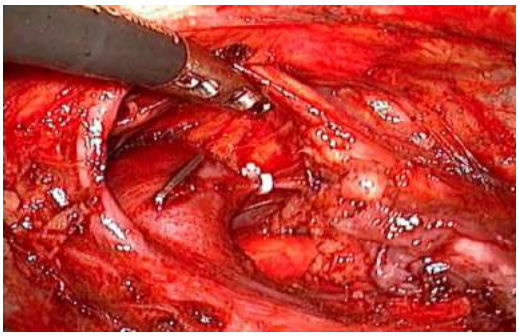
DIVISION OF MEDIASTINAL PLEURA



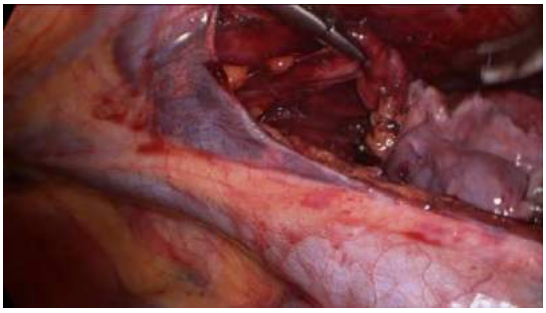
DISSECTING THYMUS OFF PERICARDIUM



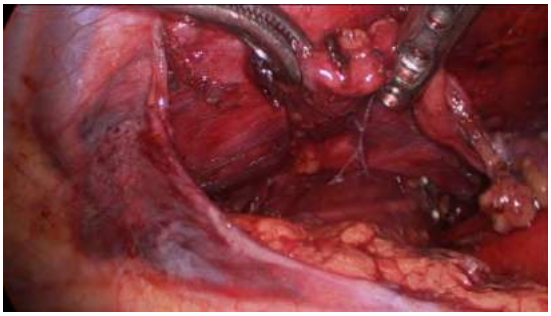
CLIPPING THYMIC VEIN



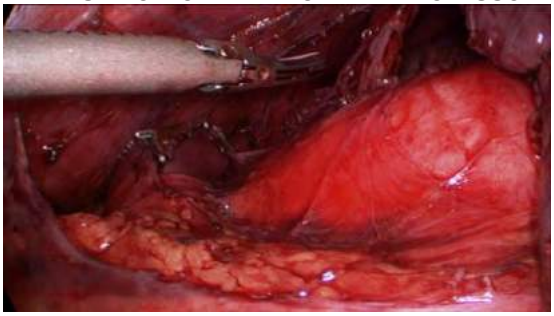
MOBILISATION OF RIGHT SUPERIOR HORN



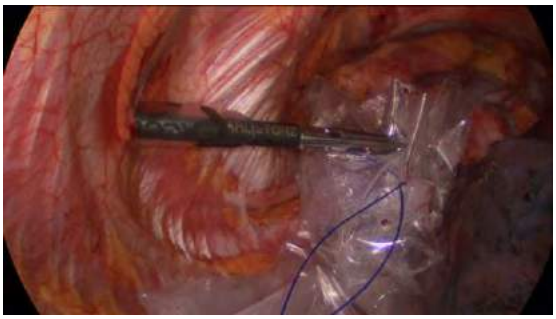
MOBILISATION OF LEFT SUPERIOR HORN



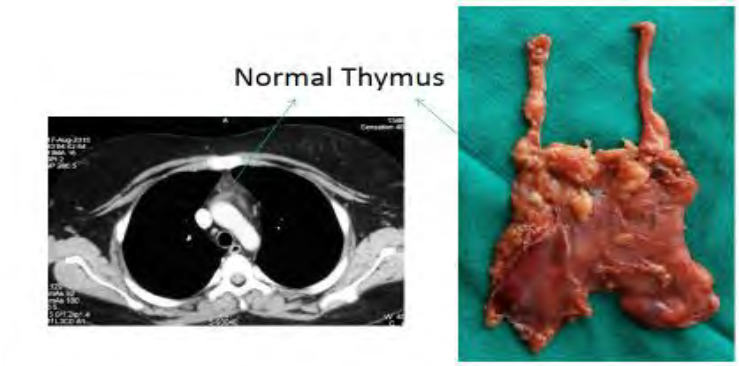
MEDIASTINUM CLEARED OFF THYMIC TISSUE

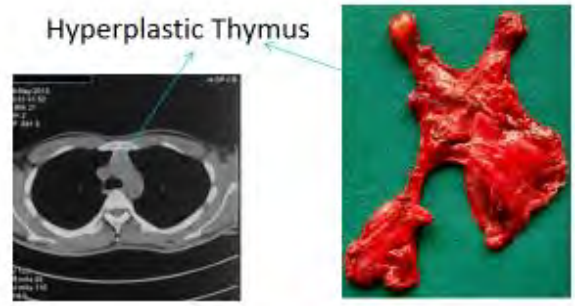


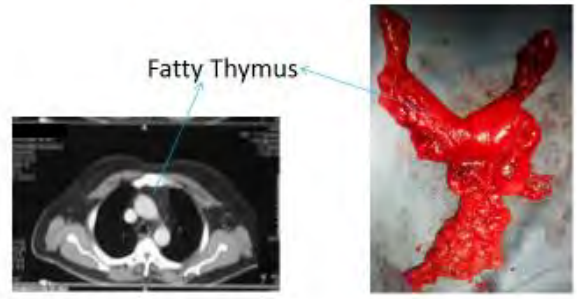
SPECIMEN REMOVAL BY ENDOBAG

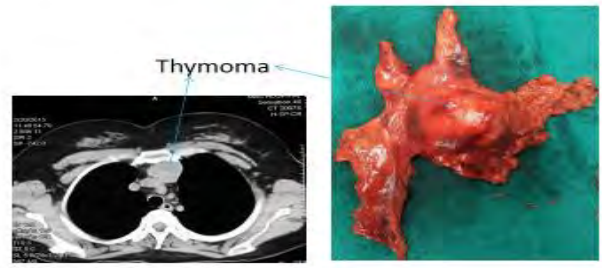


Representative specimen pictures





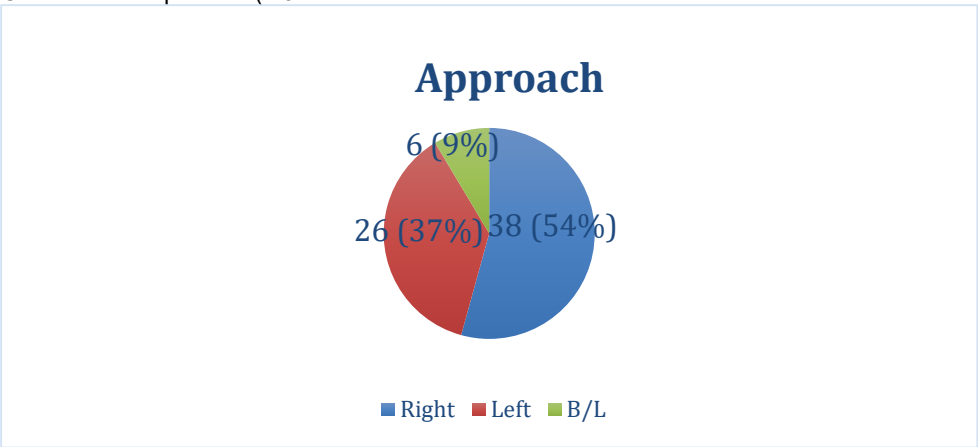




OurVATS Thymectomy Results
Operative Details

- Success rate - 97.1% (68/70) patients

- Conversion - 2 patients (2.9% - dense adhesions



- NO PERIOPERATIVE MORTALITY

Operative time (in minutes)	146.3 (90 - 240 mins)
Blood loss (in ml)	176.6 (25 - 700 ml)
Intra-op complications	2 (2.86%) (Pericardium opened)
Post-op ICD indwelling time (in days)	Median 2 (1 - 5 days)
Post-op ICD drainage (in ml)	Median 300 (50 - 1500 ml)
Post-op complications	8 (11.4 %)
Postoperative hospital stay (in days)	Median 4 (2 - 18 days)

- CONCLUSIONS
  - VATS thymectomy is a safe procedure.
  - Can be accomplished with minimal morbidity.
  - It is associated with less pain shorter drainage time, shorter hospital stay, and improved cosmesis when compared to sternotomy.

TURP : Indications, modifications, complications & alternative modalities

Anil Varshney

Transurethral resection of the prostate (TURP) developed in US in 1920s & 1930s. Cystoscope developed independently by Nitze & Lieter (1887) paved way for endoscopic urological surgeries. Several significant factors were important in its development.

- Development of fenestrated tube by Hugh Hampton-Young, which allowed obstructing tissue to be sheared off blindly
- Invention of vacuum tube in 1908 by De Forest, which allowed constant production of high-frequency electrical current that could be used in resecting tissue
- 1926: Bumpus combined cystoscope & tubular punch. Also, at that time, Stearns developed tungsten loop that could be used for resection. This was put together by McCarthy in 1932, using oblique lens so that he could resect tissue under direct vision using a wire loop
- 1970s: Development of fiberoptic lighting system, together with Hopkins (1976) rod lens wide-angle system, significantly improved visualization for endoscopic surgery

Optical system was a series of small lenses placed in rigid tube. In Hopkins rod lens wide-angle system, Air spaces were replaced by solid glass rods. Spacer tubes were shorter, resulting in minimal obstruction & increased admission of light. For most of 20th century premier treatment for symptomatic benign prostatic hypertrophy (BPH) was TURP. It is first successful, minimally invasive surgical

procedure of modern era. It remains standard therapy for obstructive prostatic hypertrophy & is both surgical treatment of choice and standard of care [1].

- **INDICATIONS**
  - Most frequent indication (50–60%): LUTS refractory to medical therapy
  - Following BPE/BPO complications are considered strong indications for TURP:
  - Recurrent urinary retention
  - BPH- or BPE-related macrohaematuria refractory to medical therapy with 5α-reductase inhibitors (5-ARI)
  - Renal insufficiency or upper urinary tract dilatation
  - Bladder stones
  - Recurrent urinary tract infection (UTI)
  - Only contraindications for TURP: Untreated UTI & bleeding disorders[2]
- **ACUTE URINARY RETENTION**

  Several short-term randomised studies have shown that in men with acute urinary retention (AUR), a trial without catheter (TWOC) after blockade for 3–5 day reveals increased likelihood of spontaneous voiding. Although a substantial number of patients will eventually require surgery within 6–12 months even under a blockade, about 20% will avoid surgery in long term. Therefore, a TWOC should be offered to all patients presenting with acute urinary retention
- **HAEMATURIA**

  Randomised controlled trials (RCT) demonstrated that because of their impact on prostatic angiogenesis, 5-ARIs have positive effect on BPE-related haematuria. Although long-term randomised data are not available, this possibility needs to be discussed with patient. Positive effect of 5-ARIs on natural history of disease (reduction of risk of AUR or risk of surgery) renders this therapeutic approach particularly attractive for men with BPE-related haematuria & prostate volumes >30–40 ml.

- **BLADDER STONES**

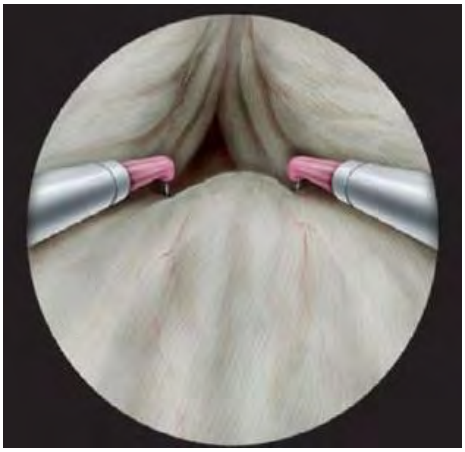
Traditionally, bladder stones have been considered a strong indication for surgery.These patients usually underwent TURP & lithotripsy in same anaesthesia session.One study showed that these patients can be managed without TURP (ie, that bladder lithotripsy combined with a blockade is feasible & safe in those with spontaneous voiding). This approach is particularly warranted in those with high perioperative risk & limited life expectancy.

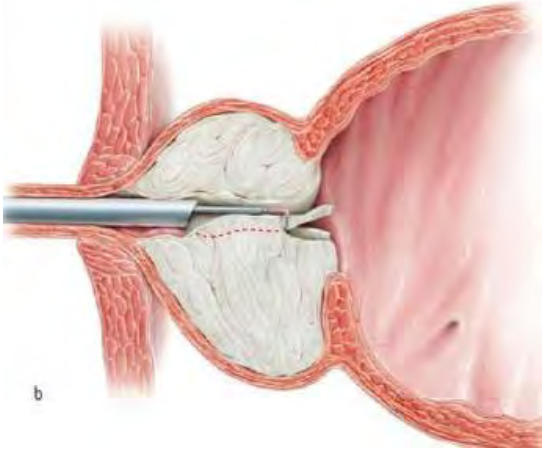
- **TECHNIQUE**

  Various techniques have been suggested for systematic removal of adenomatous tissue, all based on principle that resection should be done stepwise.As bleeding is surgeon's major problem, leading to loss of visual field & disorientation, it is imperative that resection and haemostasis should both be completed in one area of fossa before next area is tackled.

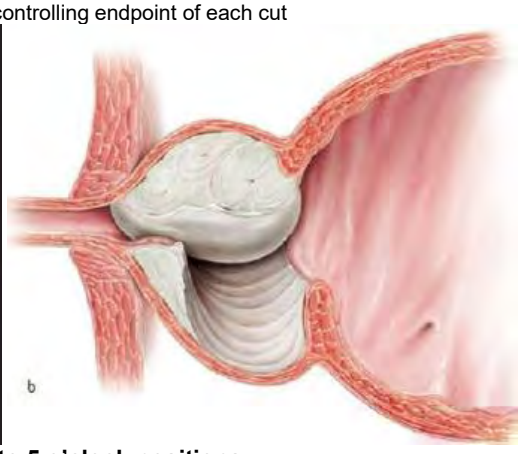
  TURP is traditionally divided into 4 steps:
  - Midlobe resection
  - Paracollicular resection
  - Resection of lateral lobes & ventral parts
  - Apical resection
  - From these recent developments are suprapubic trocar systems & continuous-flow resectoscopes, which both have improved irrigation pressure
  - Another main development: Video-assisted resection[3]

- **MAUERMAYER'S STANDARD TECHNIQUE**
  - Resection in lobes (middle lobe & tissues lat. to veru → lt lobe → Rt → Lobe apical tissues)
  - Apical tissues last

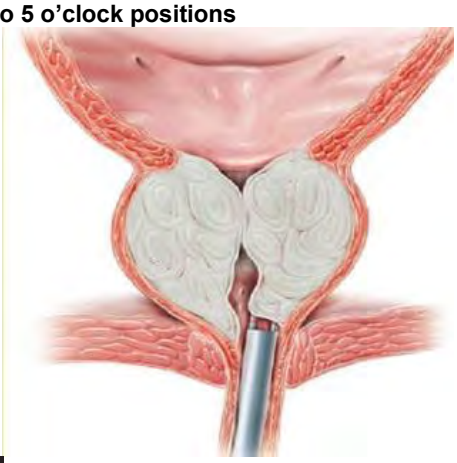
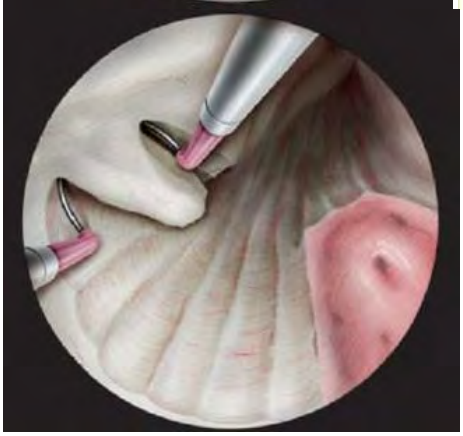
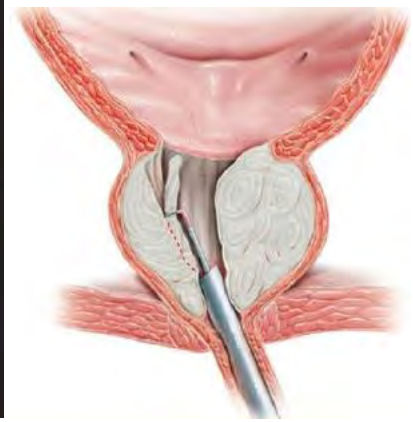




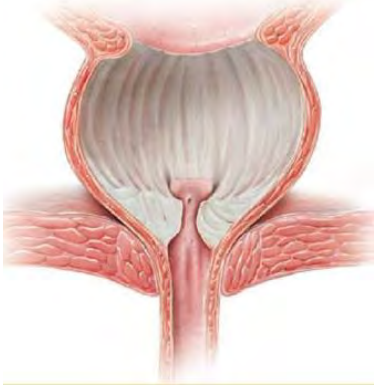
- Resection begins at proximal portion of middle lobe at 6 o'clock position. Resectoscope is placed just proximal to verumontanum & resection carried out always controlling endpoint of each cut

- **Continue resecting middle lobe from 7 to 5 o'clock positions**

- **Resection of right lateral lobe (proximal part) in long cuts next to each other to achieve smooth surface (fossa).Which lobe first depends on preference of surgeon.**



Shape of surface (fossa) after resection of proximal part of both lateral lobes .

Table 2 – Main perioperative complications after TUR—comparison of three periods

Authors	N	Transfusion (%)	Revision (%)	Infection (%)	TUR-syndrome (%)
Early					
Zwergel 1979	232	21.2	n.a.	n.a.	1.6
Mebust 1989	3885	6.4	n.a.	2.3	2.0
Doll 1992	388	22.0	3.0	14.0	n.a.
Intermediate					
Zwergel 1995	214	14.6	n.a.	n.a.	0.8
Horninger 1996	1211	7.6	n.a.	n.a.	2.8
Haupt 1997	934	2.2	n.a.	n.a.	0.3
Gallucci 1998	80	0.0	n.a.	5.0	0.0
Gilling 1999	59	6.6	3.3	8.2	0.0
Borboroglu 1999	520	0.4	n.a.	2.1	0.8
Recent					
Heilbronn 2003[a]	126	4.8	4.2	1.7	0.8
Baden-Württemb. 2003	7707	3.0	5.0	3.5	0.8
Kuntz 2004	100	2.0	3.0	4.0	0.0
Muzzonigro 2004	113	7.1	n.a.	n.a.	0.0
Berger 2004[b]	271	2.6	n.a.	n.a.	1.1

n.a. = not available.
[a] Present study.
[b] With coagulating intermittent cutting.

Table 1 – Incidence and type of intra- and perioperative complications after TUR—detailed comparison of selected studies during three periods

Type of complication	Early		Intermediate		Recent
	Mebust 1989	Doll 1992	Haupt 1997	Borboroglu 1999	Kuntz 2004
Technical complication (%)					
Clot retention	3.3	11.0	1.9	1.3	5.0
Bleeding & transfusion	6.4	22.0	2.2	0.4	2.0
TUR-syndrome	2.0	n.a.	0.3	0.8	0.0
Capsular perforation	0.9	10.0	n.a.	n.a.	4.0
Hydronephrosis	0.3	n.a.	0.0	0.0	0.0
Epididymitis/UTI	3.9	25.0	1.6	4.0	4.0
Urosepsis	0.2	3.0	0.2	0.0	0.0
Failure to void	6.5	3.0	n.a.	7.1	5.0
Incontinence	n.a.	38.0	0.3	n.a.	1.0
Associated morbidity					
Cardiac arrhythmia	1.1	n.a.	0.4	1.3	n.a.
Myocardial infarction	0.05	0.5	0.2	0.2	0.0
Pulmonary embolism	n.a.	n.a.	0.1	n.a.	0.0
Pneumonitis	n.a.	n.a.	0.2	n.a.	0.0
COPD	0.5	n.a.	0.1	n.a.	n.a.
Deep vein thrombosis	n.a.	n.a.	n.a.	0.0	0.0
Mortality	0.23	0.8	0.1	0.0	0.0

n.a. = not available.

New techniques in BPH management

Resurgence in minimally invasive therapies is now following different strategies informed by new understanding of multifactorial cause of LUTS & based on unique features of novel mechanism of ablation and methods of monitoring and imaging. When examining & comparing these new technologies, it is useful to consider following framework

Coagulating intermittent cutting was developed to realize blood-sparing TURP by modifying standard high-frequency generator: Phases with predominant cutting effect alternate with coagulating phases of constant pulses under control of pulse intervals. Other instrumental alternatives to decrease TURP morbidity:

- Modified electrode shapes (thick loop)
- Generator modifications that enable tissue vaporization (TUVP)
- Additional mechanical ablative effects such as rotoresection

Manufacturers such as Gyrus, Vista-ACMI, Olympus & Karl Storz introduced bipolar devices that differ with respect to loop shape & technical solution of bipolar TURP (active & return electrode).High-frequency (HF) energy up to 160 watts passes through conductive irrigation solution of 0.9% sodium chloride. This results in vapour layer of plasma that contains energy-charged particles that induce tissue disintegration through molecular dissociation. This results in lower resection temperature than conventional monopolar systems, which theoretically reduces thermal damage to surrounding tissue. Use of physiological sodium chloride for irrigation nearly eliminates risk of TUR syndrome

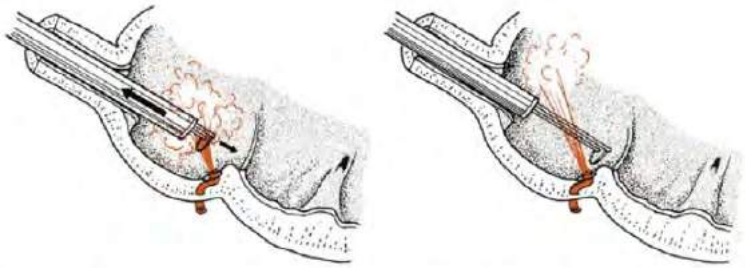


Fig. 1 – Retraction of resectoscope with advancement of the loop to achieve a better angle for visualization of a bleeding artery.

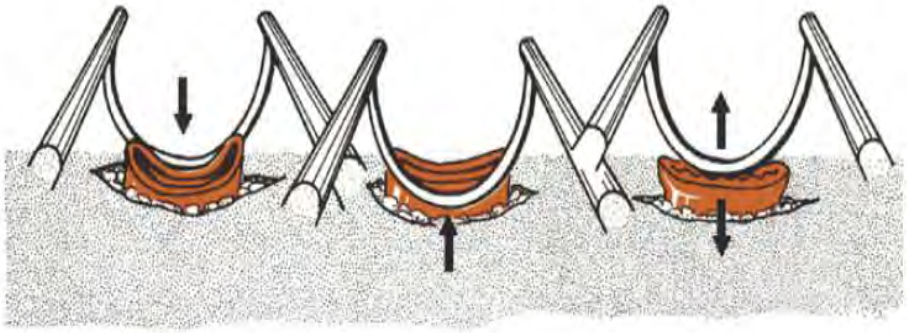


Fig. 2 – Effective coagulation of a large vessel by sealing of the lumen using slow circumferential movements of the loop.

Through improvements in endoscopic instruments & new high-frequency technology, TURP has become increasingly safe procedure Modified optical devices & video cameras enable experts and residents to teach and learn this technique like any open procedure.Innovative technological approaches include 'coagulating intermittent cutting' (Storz Medical AG, Tägerwilen, Switzerland), 'Instant Response' (Valleylab, Boulder, CO), as well as 'Dry-Cut technology' (ERBE Elektromedizin GmbH, Tübingen, Germany) that combine cutting & coagulating effects, allowing blood-sparing cut and significantly lowering blood loss and morbidity.Several prospective, randomized studies have demonstrated that bipolar resection is associated with less blood loss, fewer transfusions, shorter length of catheterization, fewer instances of clot retention, and shorter hospital stay as compared with standard TURP.

M-TURP procedure by leaving anterior segment of prostate was superior regarding perioperative morbidity, with reduced bladder irrigation and catheter times and reduced hospital stay. M-TURP procedure can be a valid alternative in medium size BPH by leaving anterior segment of prostate (< 100g), while other advanced methods as laser techniques in medium-sized prostate have no advantages over TURP

LASER PROSTATECTOMY

- Alternative ablative technologies include Holmium-YAG laser resection , ablation or enucleation and KTP-laser photoselective vaporization of prostate.These techniques are reported to be virtually bloodless & to provide short catheter times with comparable functional outcomes like TURP

- **SUMMARY**

  Choice of technique should be based on size of prostate, risk factors of patient, as well as availability of surgical armamentarium & expertise of surgeon. M-TURP, which can be regarded as reference comparator, is currently challenged by different transurethral techniques. Available evidence suggests that B-TURP is an attractive alternative to M-TURP as both techniques lead to a long-lasting & comparable efficacy. Laser techniques, such as HoLEP, thulium laser applications & PVP are treatment alternatives to TURP. HoLEP appears as durable alternative to TURP & open prostatectomy with comparable long-term results. For PVP, various laser generators are available & 180W model is currently the only one actively sold. Current evidence is only available for the 80 and 120W laser. With

the lower powered 80W laser the reoperation rate reported from studies was higher than those reported from other surgical techniques. Thus, future studies have to show whether the higher powered laser systems will generate improved results. Concerning data on thulium laser, currently, only 1 study reported 5-year results. These data are encouraging but need to be further confirmed in future trials

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1 Campbell-Walsh Urology, 10th edition, Section XVI. Prostate. Pg. 2580.
2. MARZALEK M, ET AL. EUR UROL SUPPL. 2009; 8: 504-512
3. Ketabchi AA, et al. Nephro-Urol Mon. 2013; 5(2): 758-61.

Laparoscopic cholecystectomy

Lovenish Bains, A K Sarda

INTRODUCTION
The laparoscopic revolution in general surgery began between 1985 and 1987, whenlaparoscopic cholecystectomy was introduced. The development of the technique toperform a cholecystectomy by laparoscopy was the beginning of a radical changethat, in a few years, involved general surgeons all over the world.Laparoscopic cholecystectomy (LC) has become the standard of care for patients requiring the removal of the gallbladder.A National Institutes of Health consensus statement in 1992 stated that laparoscopic cholecystectomy provides a safe and effective treatment for most patients with symptomatic gallstones and has become the treatment of choice for many patients.

LC is now the gold standard treatment of symptomatic gallstones and is the commonest operation performed laparoscopically world-wide.The initial driving force behind the rapid development of laparoscopic cholecystectomy was patient demand. Laparoscopic cholecystectomy has been more instrumental in ushering in the laparoscopic age far more than any other procedure.Laparoscopic cholecystectomy decreases postoperative pain, decreases the need for postoperative analgesia, shortens the hospital stay from 1 week to less than 24 hours, and returns the patient to full activity within 1 week. Laparoscopic cholecystectomy also provides improved cosmesis and improved patient satisfaction as compared with open cholecystectomy.

However, a significant increase in the incidence of bile duct injury was noted more than that occurring in the era of open cholecystectomy reaching up to 0.5% and injuries were more commonly reported early in each surgeon's experience. Issues like poor surgical technique, lack of understanding of how injuries occur, surgeon resistance to convert to open surgery, inadequate visualization, inflammation, aberrant anatomy, and misidentification of the ducts or other technical errors are key risk factors for the development of injuries and a debilitating sequelae of bile duct injury leading to significant morbidity and cost. Bile duct injury rates have increased since the introduction of laparoscopic cholecystectomy, occurring in about 3 per 1,000 procedures performed.Population-based studies have reported a significant increase of iatrogenic bile duct injury incidence following LC, compared to open technique, ranging from 0.3 % to 1%.

Henceforth it is essential to understand the technique for a 'safe cholecystectomy'

SAGES (Society of American Gastrointestinal and Endoscopic Surgeons) has also launched 'The SAGES Safety in Cholecystectomy Task Force', aiming to establish a universal culture of safety in laparoscopic cholecystectomy. The SAGES Safe Cholecystectomy Program has identified 6 strategies that a surgeons can employ to adopt a universal culture of safety for cholecystectomy and to minimize the risk of bile duct injury.

INDICATIONS
The indications for laparoscopic operations on the gallbladder and biliary tree have not changedsince the 1992 National Institutes of Health Consensus Development Conference Statement onGallstones and Laparoscopic Cholecystectomy.Most patients with symptomatic gallstones are candidates for laparoscopic cholecystectomy, ifthey are able to tolerate general anaesthesia and have no serious cardiopulmonary diseases or other co-morbid conditions that preclude operation.Symptomatic gall stones causing biliary colic, acute cholecystitis, mucocoele, gallstone pancreatitis, cholecystitis and its complications like empyema gall bladder, gall bladder perforation, gangrenous cholecystitis.

Cholecystectomy is not indicated in most patients with asymptomatic (silent) gallstones, because only 2-3% of these patients go on to become symptomatic each year.In 2012 Duncan and Riall reviewed the evidence-based current surgical practice for calculous gallbladder diseases and concluded that prophylactic laparoscopic cholecystectomy for asymptomatic gallstone patients is still not recommended. Nevertheless, according to the conclusion of 2009 Cochrane Review on LC in silent stones, there is no RCT or high-level studies which offer scientific evidence to refuse LC to asymptomatic gallbladder stone patients. Till such data and evidence are available, surgeons and patients together would take a decision depending on their assessment of individual

risks and choices. There MAY be a case for suggesting preventive cholecystectomy in a young (20s or 30s) patient with large gall stones in northern India but, as of today, there is no data or evidence to support it.Patients who are immunocompromised, are awaiting organ transplantation, or have chronic hemolytic conditions (sickle cell anemia) are at higher risk for the development of complications and should be treated irrespective of the presence or absence of symptoms.

Additional reasons to consider laparoscopic cholecystectomy include the following:

- Calculi greater than 3 cm in diameter, particularly in individuals in geographic regions with a high prevalence of gallbladder cancer
- Non-functioning gallbladder; biliary dyskinesia
- Calcified (porcelain) gallbladder
- Gallbladder polyp larger than 10 mm or showing a rapid increase in size
- Gallbladder trauma
- Anomalous junction of the pancreatic and biliary duct
- Life expectancy >20 years
- Questionable Indication**-** Patient living in an area remote from medical facilities

  - Indications include but are not limited to symptomatic cholelithiasis, biliary dyskinesia, acute cholecystitis, and complications related to common bile duct stones including pancreatitis with few relative or absolute contraindications.(Level II, Grade A).
  - Relative contra-indications are untreated coagulopathy, lack of equipment, lack of surgeon expertise, hostile abdomen,advanced cirrhosis/liver failure, and suspected gallbladder cancer.(Level II, Grade A).

PRE OPERATIVE ANTIBIOTIC PROPHYLLAXIS

A recent meta-analysis of randomizedcontrolled trials concluded prophylactic antibiotics do not prevent infections in low risk patientsundergoing laparoscopic cholecystectomy, while the usefulness of prophylaxis in high riskpatients (age > 60 years, the presence of diabetes, acute colic within 30 days of operation,jaundice, acute cholecystitis, or cholangitis) remains uncertain. The latestrandomized, prospective study included in the above mentioned meta-analysis showed no difference in thepostoperative wound infection rate, although the control group had a 1.5% infection rate and theantibiotic group had a 0.7% infection rate.

The current status is:

- Antibiotics are not required in low risk patients undergoing laparoscopiccholecystectomy. (Level I, Grade A).
- Antibiotics may reduce the incidence of wound infection in high risk patients (age > 60years, the presence of diabetes, acute colic within 30 days of operation, jaundice, acutecholecystitis, or cholangitis). (Level I, Grade B).
- If given, they should be limited to a single preoperative dose given within one hour ofskin incision. (Level II, Grade A).

PATIENT POSTIONING

There are two basic room set-ups for performinglaparoscopic biliary tract surgery. The first is the standard supine position with the surgeonstanding at the patient's left and monitors at the head of the table (American approach). The second iswith the patient in stirrups the surgeon standing between the legs (European Approach).Some surgeons tuck the left arm to improve theworking space of the operating surgeon. The patient is generally placed in a reverseTrendelenburg position and rotated right side up once the pneumoperitoneum has been established. A nasogastric tube is inserted and the stomach aspirated. The tube is kept in the stomach during the operation but removed at the end of the procedure. The surgeon operates from the left side of the patient with the camera person by his side and the assistant and scrub nurse on the other side of the operating table.

- With no data to guide choices, surgeon preference should dictate room set-up. (Level III, Grade A).

Ensure that the instruments and necessary equipment like light source, telescope, CO2 insufflator, electro cautery or other energy sources, cables and connections are adequately functioning before the start of procedure.

STEPS

1. Creation of pneumoperitoneum and ports placement

The creation of pneumoperitoneum is the foremost step for any laparoscopic procedure. Both open and closed methods for gaining peritoneal access are in use and are reportedly safe. A recent meta-analysis of 17 randomized controlled trials comparing a variety of open and closed access techniques found no difference in complication rates; potentially life threatening injuries to blood vessels occurred in 0.9 per 1000 procedures and to the bowel in 1.8 per 1000 procedures. As of now, there are no demonstrable differences in the safety of open

versus closed techniques for establishing access and creating the initial pneumoperitoneum, therefore decisions regarding choice of technique are left to the surgeon and should be based on individual training, skill, and case assessment. The patient is asked to empty the bladder before the procedure and stomach should be aspirated especially when the closed technique or Verres needle is used. The various techniques are:

i) Verres needle.
ii) The open Hasson technique.
iii) Directtrocar placement without prior pneumoperitoneum.
iv) The optical view technique, in which thelaparoscope is placed within the trocar so that the layers of the abdominal wall are visualized asthey are being traversed.

- Open technique

The technique entails a small sub-umbilical incision that is taken down to the linea alba. The skin edges are retracted with small Langenbeck retractors and the fat separated from the umbilical scar. The umbilical pillar is lifted with a towel clip and the junction between the umbilical pillar and the linea alba is defined, this site all the layers of linea alba and umbilical cicatrix are fused and the thinnest. An incision is made in the umbilical scar in a vertical direction to incise only the fascia and rectus sheath. The peritoneum is entered gently with the little finger or closed artery forceps, the little finger is used to sweep the peritoneal surface of the incision to remove any adhesions. The trocar is introduced without its introducer and is done under vision, therefore it is said to be safer in preventing bowel or vascular injury during the first port insertion. This is especially true for patients where previous surgery has been done and adhesions are expected.

- Closed technique or Verres Needle

The Verres needle is introduced in the peritoneal cavity directly in the infraumblical or supraumblical site. Care is taken to lift the infraumblical abdominal wall (this makes the intestinal loops fall back in the cavity) and direct the needle towards the pelvis. These two steps prevent the needle inadvertently entering bowel wall or major vessel.Grasp the shaft of the Verres needle with the dominant hand like a dart and enter into the incision- at 45 degrees caudal angle (in asthenic patients) or 90 degrees vertical (in obese patients). There will be sensation of initial resistance followed by a give at two points- traversing of fascia and peritoneum. Confirm position of needle in peritoneal cavity and begin insufflation. The trocar is placed blindly once the abdomen has been distended.
The telescope is introduced into this first port and rest of the ports are placed under vision to ensure that no abdominal structure is injured while penetrating. The four port technique of laparoscopic cholecystectomy as described by Reddick is the most widely adopted technique.

A 10mm port [a] in the epigastrium at the junction ofupper 1/3rd and lower 2/3rd of the line joining xiphisternum and umbilicus., a 5mm port [b] at the midclavicular line about 2cm below the costal margin, and a 5mm port [c] at the anterior axillary line at the 5-8 cm below the costal margin. The epigastric port is placed just right of the falciform ligament. A primary intra abdominal survey is done and patient moved into position.

2. Dissection of hepato-cystic triangle.

The fundus of the gall bladder is held with a ratcheted grasper and retracted by the assistant in a cranial direction towards patient‘s right shoulder. Adhesions are separated from the gall bladder and surrounding structures with care to always remain close to gall bladder. The subcostal port grasper is used to grasp the gall bladder at the infundibulum and retract it laterally and caudally to widen the peritoneal fold containing the cystic artery and duct and to place on a stretch.Dissection commences in the safest area by division of the peritoneal fold between the Hartman’s pouch and the liver using a curved dissector or hook dissector. The dissection is blunt or using short bursts of electrocautery. The key to safe dissection is by remaining close to the gall bladder. This space is cleared till the junction between the gall bladder and cystic duct is seen and cystic artery identified. The infundibular grasper is retracted antero-medially and the posterior aspect of Calots triangle is exposed. Again the dissection is started from the junction of the liver and the Hartman‘s pouch. This is continued to separate the cystic duct and cystic artery and to completely skeletonise these structures. Both structure should be identified from anterior and posterior view ()

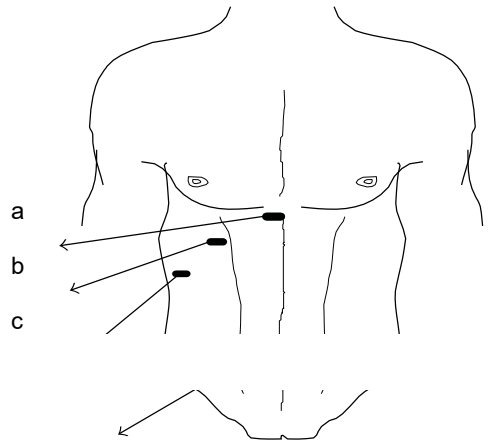

Fig. 1: Port placements

It is essential to use the Critical View of Safety (CVS) method defined by Strasberg et al and endorsed by SAGES for identification of the cystic duct and cystic artery during laparoscopic cholecystectomy which emphasizes three criteria-

- The hepatocystic triangle is cleared of fat and fibrous tissue. The hepatocystic triangle is defined as the triangle formed by the cystic duct, the common hepatic duct, and inferior edge of the liver. The common bile duct and common hepatic duct do *not* have to be exposed.
- The lower one third of the gallbladder is separated from the liver to expose the cystic plate or liver bed. .
- Two and only two structures should be seen entering the gallbladder.

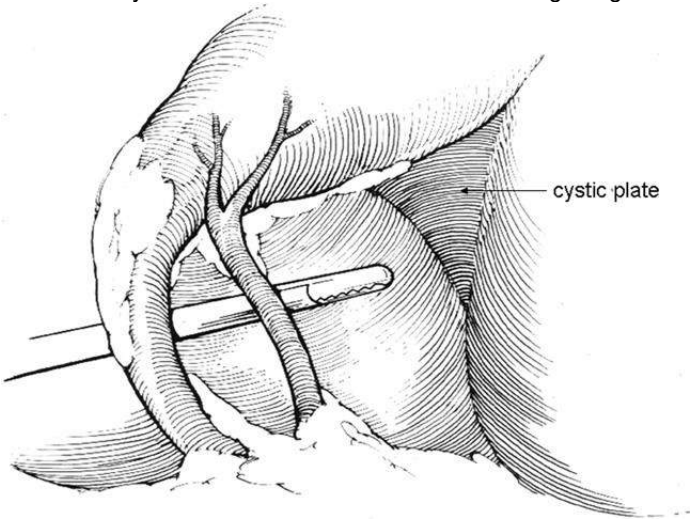

Fig. 2: Critical view of safety (anterior view)

Both structures and lower 1/3rd of cystic plate should be identified from anterior and posterior views i.e. “Doublet view”.

3. Ligation and division of cystic artery and duct

Once the structures have been confirmed, the cystic duct is clipped preferably with two clips onthe proximal end and single clip on the distal end and is divided between these clips.During clip application, traction of the Hartman‘s pouch is laterally so that the cystic duct is at rightangle to the Common Hepatic Duct (CHD) and Common Bile Duct (CBD) junction. This ensures thatclip is applied only on the cystic duct and does not take a bite of the CHD or CBD. The clip is onlyapplied only after both the limbs of the clip applicator are completely visualized. This ensures that noother structure is taken in the clip.Cystic artery is also clipped in similar way and divided. It is desirable to divide artery before the duct, however in certain situations duct needs to be divided to expose the artery. Care is taken not to retract the cystic duct so forcefully that the clip impinges onto common hepatic duct. One should be aware of various anatomical aberrations of duct and artery before clipping and dividing them. Ensure use of proper sized clips. Too large clips can slip out later and too small clips can lead to incomplete closure of the duct leading to leakage.Commonly used clips 200 (medium) has aperture of 4 mm and closed length of 5.39 mm, 300 (medium/large) has aperture of 6.4 mm and closed length of 8.99 mm, whereas 400 (large) has aperture of 7.5 mm and closed length of 12.26 mm.

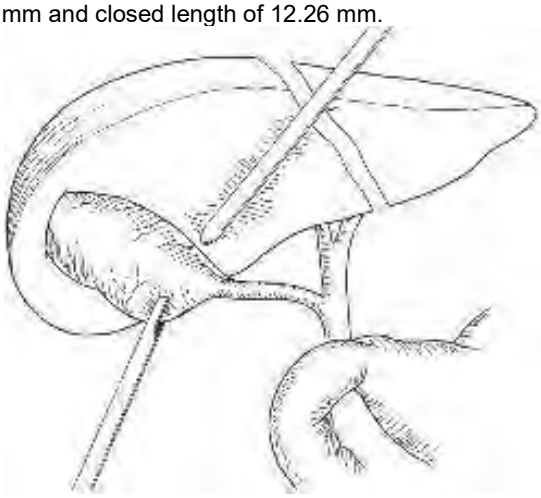

Fig. 3: Traction on Hartman’s pouch before clipping.

4. Separation of gall bladder from liver bed & Extraction of specimen

The separation of gall bladder from the liver bed is usually a combination of blunt and sharp dissection aided significantly by the traction of gall bladder. The peritoneal folds are made taut, first medially and then laterally, the gall bladder is separated from the fossa using a diathermy hook, spatula, scissors or Harmonic Scalpel. This allows maximum tension on the folds and also gives upward traction on the liver so that bleeding points can be visualized and coagulated during dissection of the gall bladder. Prior to complete detachment, the liver bed is inspected for adequate hemostasis or bile leak. The table is positioned in the normal position.

The extraction of gall bladder can be carried out through the umbilicus or the epigastric port.
A 10 mm extractor is introduced and gall bladder is grasped at the neck. It is withdrawn in the 11 mm port and delivered out along with the port. However if the gall bladder is too distended to come out of the port, then holding the gall bladder with theextractor, the complete port is withdrawn out of the abdomen to bring the mouth of the gall bladder outof the abdominal opening. The ends are held with artery forceps and bile can be aspirated, before itsremoval, to decrease the size of the gall bladder. If the gall bladder is still too large, stones can beextracted to allow its removal or else the fascial incision can be extended to expedite removal of gall bladder.Any such anticipation can be dealt by placing the gall bladder in indigenously made glove bag or commercially available Endobag.This prevents rupture of the gall bladder inside the abdomen, spill of stones or bile andconsequent chances of contamination.

5. Final inspection and port closure

The gall bladder fossa is examined again for hemostasis, through wash with saline is given in cases of bile or stone spill. A drain if required can be placed through the lateral most port. The instruments and ports are withdrawn under vision to check that no bleeding occurs from trocar sites. Pneumoperitoneum is evacuated. The fascia of the 10 mm ports is closed with polyglactin suture. Skin closure is done with sutures, clips or glue.

TIPS & COMMENTS

1. Use the Critical View of Safety (CVS) method of identification of the cystic duct and cystic artery during laparoscopic cholecystectomy.
2. Perform an Intra-operative Time-Out during laparoscopic cholecystectomy prior to clipping, cutting or transecting any ductal structures.
3. Understand the potential for aberrant anatomy in all cases.
4. Make liberal use of cholangiography or other methods to image the biliary tree intraoperatively.
5. Recognize when the dissection is approaching a zone of great danger and halt the dissection before entering the zone. Finish the operation by a safe method other than cholecystectomy if conditions around the gallbladder are too dangerous.
6. Get help from another surgeon when the dissection or conditions are difficult.

   The above mentioned are the 6 strategies surgeons can employ to adopt a universal culture of safety for cholecystectomy to and minimize the risk of bile duct injury. (Adapted from 'The SAGES Safe Cholecystectomy Program')

7. Stay close to the gall bladder at all times or hug the gall bladder. The dissection should always start at the infundibulum of the gallbladder, enabling an easy location of the cystic duct.
8. Mucocoele of gall bladder should be aspirated before starting the procedure. If the gall bladder gets open while dissection, the rent can be closed with a large clip or Endoloop.
9. Do not apply clips blindly in case of bleeding as this might lead to panic reaction. This only spells disaster. The immediate response to bleeding should be compression.
10. Gall bladder may be used to give direct compression on the bleeding site if this is in the gallbladder bed. In case of bleeding from the cystic artery, gauze can be used to compress the area and once the bleeding is controlled, careful diathermy of the bleeding point can be done. Clips are rarely required.
11. In case of difficult anatomy, where the Calot's triangle cannot be isolated properly, a fundus first approach may be used to reach the junction of gall bladder and cystic duct.
12. Clips on the artery should always be double for extra safety.
13. A short cystic duct can be lengthened after dissecting and dividing the cystic artery flush with the gall bladder and teasing out fibrous bands which kink and shorten the duct.
14. Laparoscopic cholangiography is no substitute for careful dissection. Its main indication is to exclude or confirm presence of CBD calculi.
15. Over-confident surgeon and the easy case may spell danger.
16. Patient's outcome from complications is best if detected during first surgery and correctivemeasures taken during the same sitting.
17. Conversion to open cholecystectomy is not a failure but very judicious and wise decision of the surgeon to prevent iatrogenic injuries to bile ducts and surrounding viscera, thus minimising the morbidity of the patient.

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Current management of CBD stones

Anubhav Vindal, Jagdish Chander

During the era of open cholecystectomy the management of common bile duct stones (CBDS) was relatively straightforward, but with the advent of laparoscopic cholecystectomy (LC) in 1980s, the treatment of CBDS, whether recognized preoperatively or peroperatively remains controversial. Treatment options include selective preoperative endoscopic retrograde cholangiopancreatography (ERCP), open choledochotomy, intraoperative ERCP with endoscopic sphincterotomy (ES), postoperative ERCP with ES, and single stage laparoscopic clearance of CBD stones.

History

In first part of the 19th century, surgery of the biliary system consisted of attempts to duplicate what nature had shown to be effective treatment: creation of cutaneous fistulas and delayed enteric fistulas. The introduction of ether anaesthesia in 1846 ushered in the era of modern biliary surgery and the first successful removal of a gallbladder. It was not until 1890 that the first surgical exploration of the common bile duct (CBD) was performed by a Swiss Surgeon, Ludwig Courvoisier, who removed a gallstone via an incision in the CBD, 8 years after Langenbuch reported the first cholecystectomy.[1]

Then Thorton and Abbe reported their experiences with direct incision into the CBD to remove calculi.[2] The next important milestone was the introduction of intraoperative cholangiography in 1932 by Mirizzi.[1] This procedure resulted in two effects. First, it reduced unnecessary bile duct explorations. Second, it reduced the incidence of retained stones, which was associated with high reoperative mortality.

The introduction of endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic sphincterotomy (ES) by gastroenterologists from Germany and Japan in the 1970s, led to a revolution in the treatment of CBDS. This method soon became the treatment of choice for managing choledocholithiasis.[2]

Berci was pivotal in the development and dissemination of first the rigid, and later the flexible, choledochoscopy.[1] By the 1980s, the use of intraoperative choledochoscopy was widely disseminated and proven to reduce retained stones in an additional 10% to 15% of patients that otherwise would have been missed.[3,4]

All was well in the world of biliary surgery until 1989, and the treatment of CBD calculi was relatively straightforward. Patients suspected of harbouring CBD stones underwent intraoperative cholangiography. If CBD calculi were discovered, the bile duct was opened and the stones retrieved. If there were too many or they could not all be retrieved, a biliary enteric anastomosis was performed.

The biliary world turned upside down with the introduction of therapeutic laparoscopy. Preoperative diagnostic endoscopic retrograde cholangiography (ERC)/endoscopic sphincterotomy (ES) became the standard for patients suspected of having choledocholithiasis to avoid conversion to open CBD exploration (CBDE). Postoperative ES became the preferred approach for the treatment of common duct stones encountered at surgery or discovered afterward.[5,6]

Efforts to treat patients with common duct stones in one session and avoid the potential complications of ES (especially in younger patients with small-diameter CBDs) resulted in several laparoscopic techniques of trans cystic CBD exploration (LTCBDE) including lavage, trolling with wire baskets or biliary balloon catheters, cystic duct dilation, ampullary balloon dilation, biliary endoscopy, and stone retrieval with wire baskets under direct vision, even antegrade sphincterotomy and lithotripsy. Almost concurrently in 1990s, the technique of laparoscopic CBD exploration using a choledochotomy was also described.[6] This technique was the laparoscopic replica of the open procedure that many surgeons were well versed with. The trans choledochotomy approach was especially useful in cases where the stone size was too large, or the stones were too many or the cystic duct morphology was unfavourable for the trans-cystic route.

Incidence
Common bile duct stones are a fairly common entity. Between 3% to 18 % of patients undergoing Laparoscopic Cholecystectomy (LC) for gallbladder stones have synchronous CBD stones.[7,8]

Clinical presentation
The symptoms and signs of CBDS are highly variable and can range from patients being completely asymptomatic, to complications such as cholangitis or pancreatitis.[9]

The prevalence of asymptomatic CBDS has been found to be between 5.2% and 12%.[10] A common presentation of CBDS is the biliary colic. Pain is often situated in the right hypochondrium or epigastrium and can last from 30 minutes to several hours, with associated symptoms such as nausea and vomiting. Other common symptoms include jaundice along with pale stools and dark-coloured urine.[9]

Two serious complications of CBDS are cholangitis and gallstone pancreatitis. Acute obstructive cholangitis is a life-threatening complication caused by an infection of the biliary ductal system secondary to biliary obstruction.[9] In cholangitis, the classic symptoms of Charcot's triad may be encountered, and the less common Reynold's pentad adds to the diagnosis.[9] Despite the advancement in treatment, acute obstructive cholangitis still carries a mortality rate of 10–20% .[11]

Diagnostic investigations
The preoperative evaluation for CBD stones should include a careful history, biochemical tests and abdominal ultrasonography. It seems reasonable to avoid further diagnostic preoperative investigations and routine intraoperative cholangiography in patients with absence of jaundice, normal liver function tests, and ultrasonographic evidence of a normal biliary tree (CBD diameter <9 mm).[12]

However, investigation of the group at risk is necessary. If there is any suspicion that preoperative choledocholithiasis is present, magnetic resonance cholagio pancreatography (MRCP) or endoscopic retrograde cholangio pancreatography (ERCP) is performed. ERCP should be performed only in patients who are expected to require an intervention; it is not recommended for use solely as a diagnostic test.[12]

Laboratory Tests
Patients exhibiting the symptoms described above require diagnostic investigations to assess for the presence of CBDS.[13] Liver function tests (LFTs) can be used to screen for CBDS. Elevated serum bilirubin and alkaline phosphatase typically reflect biliary obstruction, but these are neither highly sensitive nor specific for CBDS.[14] Various studies have proven elevated serum gamma glutamyl transpeptidase (GGT) and alkaline phosphatase (ALP) to be the most frequent abnormalities in laboratory values of patients with symptomatic CBDS.[9] Most of the

studies have shown that laboratory studies must be used in addition to imaging modalities to predict the likelihood of CBDS.[14]

Imaging Modalities

Transabdominal Ultrasonography (TAS)
It is the first line investigation in patients with suspected CBDS.[9] Its sensitivity for detecting CBDS is between 25% to 63%, with a specificity of approximately 95% depending on the degree of dilation of the CBD and investigator's experience.[9,13]

Endoscopic Retrograde Cholangio Pancreatography (ERCP)
ERCP is often described as the gold standard test to for the detection of CBDS. This procedure was initially used primarily in diagnosis, but today is more commonly used as a therapeutic modality.[13] ERCP has sensitivity between 90% to 95% in detecting CBD stones and a specificity of 92% to 98%.[13,15] Christensen et al. demonstrated that the ERCP has a morbidity rate of 15.9% and a mortality rate of 1%.[16]

Percutaneous Transhepatic Cholangiography (PTC)
It is an invasive procedure where the intra hepatic biliary system is cannulated under radiological guidance followed by instillation of dye through a percutaneously placed needle. It is not a routine initial diagnostic test in patients with CBD stones but is the modality of choice in patients with previous gastric surgery, distal obstructing CBDS that failed ERCP or in patients with cholangio hepatitis and extensive intrahepatic stone disease.[17]

Endoscopic Ultrasound (EUS)
It involves the endoscopic insertion of an ultrasound probe through the stomach and up to the second half of the duodenum, allowing for ultrasound images of the CBD without the interference of subcutaneous fat and bowel gas.[18] It allows application of the ultrasound transducer directly against the luminal surface, thereby enhancing image quality. The proximity of the transducer to the target tissue also permits the use of higher frequency ultrasound, which further contributes to the enhanced image resolution. Sensitivity of EUS varies from 95 – 97%, while specificity is between 95 – 98%.[18,19] EUS is significantly more sensitive than TAS in detecting CBD stones. Its sensitivity is comparable to the diagnostic ERCP, while its major advantage is a significantly decreased morbidity compared to ERCP.[18]

Magnetic Resonance Cholangio Pancreatography (MRCP)

It has emerged as an accurate, non-invasive diagnostic modality for investigating the biliary ducts.[20] It may be especially beneficial in identifying patients who would benefit from early intervention.[12] A meta-analysis of 67 published controlled trials shows that MRCP has an excellent overall sensitivity of 95% and a specificity of 97% for demonstrating CBDS.[21] Some major disadvantages of MRCP, as compared to ERCP, are the lower spatial resolution, potential for claustrophobia, and the inability to evaluate patients with pacemakers or ferromagnetic implants.[20,21]

Intra Operative Cholangiography (IOC)

This technique involves instillation of contrast into the biliary tree through the cystic duct, and the visualization is done using fluoroscopy. The routine use of IOC is still controversial. Some authors supporting routine IOC, while others favour selective IOC, and others report no advantages in IOC with respect to missed CBD stones.[12] However, it can be an useful tool to identify choledochal stones.[12] This procedure can be performed during open or laparoscopic cholecystectomy. IOC has a sensitivity of 98% and specificity of 94% to detection of CBDS.[22] IOC can fail primarily due to inability to cannulate the cystic duct, leakage of contrast fluid during the injection, air bubbles mimicking stones, failure to fill the biliary tree because of too rapid contrast injection into the duodenum, and spasm of the sphincter of Oddi. Reports have shown that this procedure ensures fewer retained stones, fewer postoperative ERCPs, and a reduction in the number of CBD injuries.[9,12,22] One drawback is lengthening of the operative time by approximately 15 minutes.[12,22]

Intra Ductal Ultrasonography (IDUS)

The technical evolution of EUS has lead to the development of small calibre intra ductal ultrasound (IDUS) mini probes (about 2 mm), which can be passed through standard endoscopes directly into the bile or pancreatic duct. The small calibre, flexibility, and excellent image quality produced by these catheters makes them ideal for evaluating a variety of biliary disorders. IDUS is capable of producing better image resolution than standard endoscopic ultrasound. Acoustic coupling is optimized by the tubular anatomy of the bile duct, which is fluid filled and only slightly larger in calibre than the probe itself. In addition, the probes operate at higher frequencies (12 to 30 MHz) than standard EUS, which leads to higher image resolution. Although the utility of intra ductal ultrasonography (IDUS) for common bile duct stones has been reported, the clinical significance of this procedure in making therapeutic decisions has not been well clarified.[23] IDUS is a valuable method for residual small stones in the common bile duct after endoscopic lithotripsy.[23,24] IDUS increases sensitivity and specificity in the diagnosis of choledocholithiasis, and these gains are not translated into a notable increase in procedure time

(7–15 minutes).[24] IDUS is especially recommended in patients who have a dilated bile duct with suspected small bile duct stones when ERCP is not diagnostic.[24]

Management options

No consensus exists regarding the ideal management of gallbladder and CBD stones. CBD stones can be detected preoperatively, intra operatively or postoperatively. Consequently the management options are quite varied especially in the present era of advanced laparo endoscopic techniques.

The following management strategies are available:

- Endoscopic Sphincterotomy (ES) with stone extraction followed by laparoscopic cholecystectomy.
- Simultaneous endoscopic stone extraction with laparoscopic cholecystectomy
- Combined laparoscopic cholecystectomy and CBD exploration (LCBDE)
- Open CBD exploration
- ES post cholecystectomy

Other methods include electrohydraulic lithotripsy (EHL), extracorporeal shockwave lithotripsy (ESWL), laser lithotripsy, and dissolving solutions that are indicated only in special situations.

Every procedure has its advantages and disadvantages and there is a broad overlap between the indications for an ideal management option in a particular clinical scenario. Therapeutic decision making is based on the local availability of expertise. Two groups of interventions have significant roles in management of CBD stones:

(1) Pre or post operative ERCP with endoscopic biliary sphincterotomy (ES) in a two-stage procedure,
(2) Surgical bile duct clearance and cholecystectomy as one stage procedure – open or laparoscopic.

Several randomized controlled trials showed similar effectiveness for both methods of treatment.[25,26] It has been reported that one-stage management of symptomatic CBDS is associated with less morbidity and mortality (7% and 0.19%) than two-stage management (13.5% and 0.5%).[26]

Open CBDE

Open exploration for CBD stones was the traditional treatment for management of this disorder. However, with the advent of laparoscopic surgery in general, and laparoscopic CBD exploration in particular, fewer than ever procedures are being done through the open approach worldwide.[27] The advantages offered by the laparoscopic approach over the open approach include, among many others, lesser postoperative pain and discomfort for the patient, faster postoperative recovery and significantly shorter hospital stay. The patients are able to return to the activities of daily living much faster compared to the open technique. However, there still remain few situations in which the open route is preferable over the laparoscopic approach, and these include non availability of the expertise/equipment, unfavourable biliary anatomy, large impacted stones in the CBD and other general contraindications to laparoscopic surgery.[12,27]

Pre operative ERCP

The success rate for stone clearance is 87% to 97% but up to 25% of patients require two or more ERCP treatment.[28] The associated morbidity and mortality rates are 5% to 11% and 0.7% to 1.2% respectively. Moreover, ERCP is not possible in 3% to 10% of all patients.[26] Complications of ERCP include bleeding, duodenal perforation, cholangitis, pancreatitis and bile duct injury.[26,28] Schreurs et al. showed 75%–84% patients undergoing ERCP/EST had no symptoms with up to 70-month follow up.[29]

Intraoperative ERCP

It is another option for removal of CBDS, particularly stones in the common hepatic duct or intrahepatic system. The use of intraoperative ERCP is effective but is associated with logistic and technical difficulties. It requires additional equipment and additional personnel availability in the OT during the procedure. The patient's position may be suboptimal for the endoscopist to perform endoscopy, identify the papilla and cannulate it.[26,28]

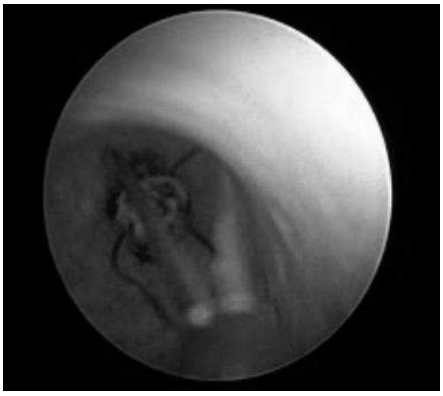
Postoperative ERCP

Postoperative ERCP is done for intra operatively diagnosed CBD stones during laparoscopic cholecystectomy when the expertise to perform laparoscopic CBD exploration is not available. The patients are usually taken up for ERCP in the same admission and the success rates of removal of stones vary from 55 to 80%.[28] However, the dangers include all the complications of ERCP and the dilemma of managing CBD stones in ERCP failure because a third procedure would then be needed.[26,28]

Laparoscopic CBD exploration

Laparoscopic exploration of the CBD via the trans cystic route was first reported in 1991.[1,2] Laparoscopic choledochotomy and CBD exploration also was first reported in 1991 but has been less widely documented.[2] Berci and Morgenstern, in the multi-institutional SAGES study, documented the procedure for laparoscopic extraction of CBDS in 1994.[30] In 1999, Cuschieri et al. in the EAES study concluded that the laparoscopic single-stage approach for management of gallstone disease and choledocholithiasis is the preferable option in fit patients[31]. However, the dissemination of this procedure has been limited.

For the trans cystic exploration, a balloon angioplasty catheter (8 Fr) is used to dilate the cystic duct and CBD stones are visualized using either IOC and fluoroscopy or direct visualization using a choledochoscope. CBD stones are removed using trolling with wire baskets or balloon catheters or flushed into duodenum by saline lavage.[30]



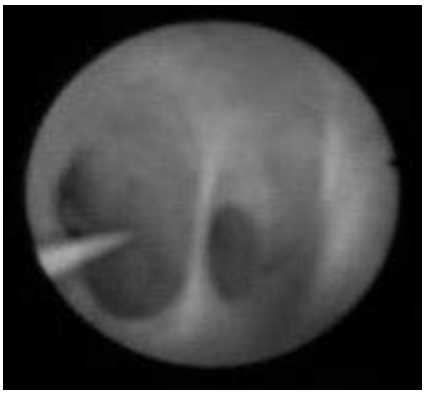
For the trans choledochal route, a choledochotomy is made in the supra-duodenal part of the CBD. Intraoperative choledochoscopy is usually performed to visualize and remove the CBDS under vision and to check for the completion of removal at the end of the procedure. An additional 5-mm port inserted at the highest point in the epigastrium in the right paramedian position for choledochoscopy of the lower CBD.[32] The calculi are extracted by using a Dormia basket under choledochoscopic vision. Impacted stones can be broken under direct vision using intracorporeal lithotripsy with Holmium laser, and the fragments can be flushed through the ampulla into the duodenum with hydrostatic pressure.[32]

Closure of the CBD can be done in several ways depending on the merits of each case. In case of concern of residual debris, extensive inflammation, or manipulation or spasm of the ampulla, closure over a drainage tube is preferred. This can either be in the form of an external drainage (T-tube), or internal drainage (endo-biliary stent).[32] In cases with no residual debris or any inflammation of the CBD primary closure of the duct without any drainage is preferred. Choledochotomy is generally closed using continuous sutures of 4-0 polygalactin, although some surgeons may prefer an interrupted closure.[32] For CBDs > 20 mm in size and/or impacted CBD stones, laparoscopic choledochoduodenostomy is preferred creating a stoma of at least 20 mm, using single layer of interrupted sutures of 3-0 polygalactin.[32,33]

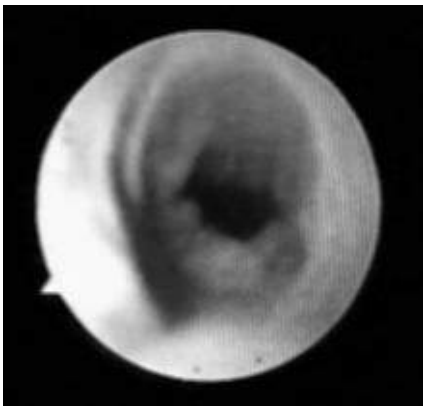
The successful laparoscopic management of CBDS is dependent on several factors including surgical expertise, adequate equipment, the biliary anatomy and the number and size of CBD stones. Successful stone clearance rates for LCBDE range from 85% to 95% with a morbidity rate of 4% to 16% and mortality of 0% to 2%.[32,34] A metanalysis of 1762 patients who underwent LCBDE from 19 studies worldwide showed a mean duct clearance of 80% with average morbidity of <10% (4–16%) and mortality of <1% (0–2.7%).[35] Also, trans cystic stone clearance may have a recovery very similar to laparoscopic cholecystectomy alone as it is a more anatomical approach.[34,35]

Laparoscopic trans cystic common bile duct exploration (LTCBDE) vs laparoscopic choledochotomy[32]

	LTCBDE	**Lap choledochotomy**
Skill	Endoscopy	Lap suturing
Stones (number)	<8	Any number
Stone Size (mm)	<9	Any size
Stone Location	Distal to cystic duct	Entire duct
CBD diameter (mm)	Any	>9
Drain	Optional	Suggested
Contraindication	Friable cystic duct	Small-diameter CBD
	Intrahepatic stones	
	Multiple, large stones	
Advantages	No T-tube	T-tube for postop access
	Shorter hospital stay	
	Quick	
Disadvantages	Equipment	Lap suturing
	Intensive new skills required	T-tube



In our series of laparoscopic CBD exploration, which is the largest such series published from south east Asia, the majority of patients had stones between 5 to 15 mm.[32] As a result of the large average stone size and number trans choledochal route was used in the majority of patients. The average duration of surgery was 139.9 ± 26.3 (range, 90–205) min and the conversion rate is 4% which is one of the lowest reported in the published literature.[32] Fifteen percent of our patients had nonfatal postoperative complications ranging from wound infection, transient hyper-amylasemia, bile leakage, intra-abdominal collection, and upper gastrointestinal hemorrhage. There were three cases of retained stones (2%), all of which were managed effectively with postoperative ERCP. Postoperative stay ranged from 2 to 33 days with an average of 4.6 ± 4.1 days. Eighty-one percent of the patients had a stay of 5 days or less.[32]



The ideal method of CBDS removal is the one that does not cause injury to the sphincter of Oddi, because it is desirable to preserve the sphincter in patients younger than aged 60 years.[32,36] One-stage management of CBDS with LC and LCBDE has lowest morbidity and mortality and is cost-effective with a short hospital stay.[27] It treats both gallstones and CBDS in single stage compared with staged procedures, and can be performed as a day care procedure.[27,35] LCBDE also preserves the function of sphincter of Oddi and hence reflux-related complications, such as cholangitis and recurrent stones associated with sphincter damage, are not seen.[32,36] The mean number of procedures needed per patient for complete clearance of CBDS has been reported as 1.46 with ERCP ± ES and 1.23 with LCBDE.[26,31]

Extra corporeal Shock Wave Lithotripsy (ESWL)

ESWL was first used for treating gallstones in 1980s following its successful use in fragmenting renal calculi.[9] ESWL involves the percutaneous administration of sound waves directed at the liver and bile duct. It is not performed during endoscopy, but rather before an ERCP in hopes of shattering large stones into smaller, more manageable fragments. European studies evaluating ESWL report duct clearance rates of 83% to 90%, but its acceptance elsewhere has been slow.[9,12]

Dissolution techniques

These solutions are instilled either directly into the biliary tree or are administered orally, absorbed by GIT and then secreted in the bile. They do not cause irritation of the biliary tree and are not toxic. Every dissolution therapy will last for several weeks, therefore the ideal solvent has not yet been produced.[37] The use of urso-deoxy-cholic acid (UDCA) and cheno-deoxy-cholic acid has only been shown to dissolve cholesterol-containing stones. Approximately 85– 95% of patients in the west will have cholesterol stones. Continuing therapy with UDCA appeared to prevent recurrence of gallbladder microlithiasis.[9] Methyl-Tert-butyl-Ether (MTBE) is an excellent cholesterol solvent that has been shown to work faster, but it is toxic to liver and duodenal mucosa. It has been proposed by several studies that using dissolution in combination with endoscopic retrieval or lithotripsy has better outcomes.[9,12,37]

Percutaneous extraction

This technique is used for non operative extraction of CBD stones when ERCP has failed or has not been possible due to an altered anatomy and an inaccessible papilla. As a preliminary procedure, a percutaneous trans-hepatic cholangiography is performed and stones are visualized. Percutaneous trans-hepatic balloon dilation of the papilla of Vater is then performed and the stones are pushed out into the duodenum using a Fogarty balloon catheter.[38] If the stone diameter is larger than 15 mm, then basket lithotripsy is performed before balloon dilation. The procedure has a success rate of 80 - 96% in CBD stones and in 55 - 61.5% in intra hepatic stones.[38] Complications described for this procedure include cholangitis, subcapsular biloma, subcapsular hematoma, subcapsular abscess, bile peritonitis, duodenal perforation and CBD perforation.[38]

Endoscopic versus laparoscopic removal

Endoscopic methods, such as ERCP ± ES, need an experienced and skilled endoscopist to be successful.[26] Even after ERCP, ES is not always possible, and when ES is successful the duct is not always cleared of stones.[25,26]

Although useful, the endoscopic procedures are not without cost, morbidity, mortality, and significant lifestyle disruption. It has been seen that ERCP increases total cost to twice that of LCBDE.[26] For ERCP ± ES, the stone clearance rates are 65–75% after one session and increase to 85–92.5% after three sessions.[39] The success rates decrease in patients with altered anatomy, such as intra-diverticular papilla, abnormal localization of papilla, retropancreatic stenosis of bile duct, Billroth II bypass, and Mirizzi syndrome.[26,39]

ERCP ± ES has a morbidity of 7.6–13.5% and includes the risk of pancreatitis, bleeding, perforation, cholangitis, delayed stricture of sphincter, residual/recurrent stones, papillary stenosis, and mortality of 0.4–0.55%.[25,26]

Preoperative ERCP also causes bacterial contamination of CBD.[12,26] It has been seen that all recurrent stones after ES are bilirubinate type regardless of the type of initial stones, indicating a role of reflux with infection due to ablation of the sphincter.[12,25,26] Post-ES stricture of the sphincter with proximal residual dilatation of CBD also has been postulated to cause stasis of bile and recurrent stone formation.[26,39] Late papillary stenosis is observed between 10 and 33%, with recurrent stone formation and subsequent cholangitis.[9,26]

With advancing technology, laparoscopic biliary surgery has become safe, efficient, and cost-effective.[40] Randomized trials, comparing two-stage (pre- or postoperative ERCP/ES and laparoscopic cholecystectomy) versus single stage (laparoscopic cholecystectomy with LCBDE) reported similar success rates.[30,31,39] Laparoscopic CBD exploration was associated with successful stone clearance rates ranging from 75 to 95%, morbidity of around 10%, and mortality of approximately 1.5%.[30,32,40] Patients treated by LCBDE had a

significantly shorter hospital stay and lower hospital cost compared with those who underwent a two-stage procedure.[30,31,39] Cuschieri et al. concluded that laparoscopic treatment was preferable for ASA II and ASA III patients, whereas ERCP/ES was indicated for high-risk patients.[31]

The morbidity rate after ES followed by LC ranged from 3 to 16% (mean 13%), whereas after laparoscopy it ranged from 7 to 19% (mean 8%). The mortality rate after ES ± LC ranged from 0 to 6% (mean 2%) and was twice higher the rate after laparoscopy, which was 1%.[12,30,39]

Current scenario

Stones Diagnosed Preoperatively

The general trend of management of preoperatively diagnosed CBD stones has been by ERCP with stone extraction with stenting if indicated, followed by laparoscopic cholecystectomy. However single stage LCBDE is emerging as a primary and cost effective treatment modality with less morbidity.[30,31,39]

In elderly and unfit patients, ERCP and stone extraction from the CBD is the initial and probably the definitive treatment. It is also the initial treatment in patients presenting with jaundice, cholangitis or severe pancreatitis. Laparoscopic cholecystectomy is undertaken once the condition of the patient has improved. Biliary stenting is advocated for patients with large dilated CBD, multiple impacted stones or stones not completely removed by ERCP.[12]

For patients who are fit for surgery, the choice is between single stage operative exploration of CBD or a sequential approach i.e. preoperative or postoperative ERCP with ES along with laparoscopic cholecystectomy. ERCP has a morbidity rate of 5 to 9.8 % and a mortality rate of 0.3 to 2.3 %, mostly due to post procedural acute pancreatitis, duodenal perforation and bleeding.[31] Moreover it causes injury to the sphincter of Oddi which should be avoided in patients younger than 60 years.[26,32,36]

Recent studies indicate that one-stage management of CBD stones with LCBDE has less morbidity and mortality and is cost effective with a short hospital stay.[26,39] It treats both gallstones and CBD stones in single stage compared with sequential procedures, and can also be performed as a day care procedure.[40] LCBDE also preserves the function of sphincter of Oddi and hence prevents reflux-related complications, such as cholangitis and recurrent stones associated with sphincter damage.[26,32,36]

Performing ERCP along with LC implies organizational problems concerning the availability of an endoscopist in the operating theatre whenever needed. Finally, performing ERCP after surgery would raise the dilemma of managing CBD stones whenever ERCP fails to retrieve them because a third procedure would then be needed.[36]

Reference centres for laparoscopic surgery currently propose treating both gallbladder and CBD stones during the same laparoscopic procedure.[30-32,36] No consensus has been achieved concerning the best approach (laparoscopic or endoscopic) because the laparoscopic management of CBD stones has not had a wide diffusion till now. In situations where there are difficulties in performing a combined laparoendoscopic procedure or the laparoscopic experience is limited, it is safer to perform an ERCP followed by cholecystectomy.[36]

A number of studies have reported about the mid-long-term results of laparoscopic CBD exploration, with excellent results reported up to 15 years post surgery.[27,41-44] These studies have also pointed out the advantage of the laparoscopic approach over the endoscopic approach in maintaining an intact sphincter of Oddi, thus obviating the drawbacks of bile reflux in the lower end of the surgery in the long term. This is especially more important in case of young patients, where the incidence of post procedural bacteriobilia and recurrent stones has been linked to loss of the function of sphincter and the accompanying reflux into the lower end of the CBD.[27,44]

Stones Discovered Intra operatively

The available options are; (a) total laparoscopic clearance, (b) combined laparoendoscopic treatment, (c) conversion to open CBD exploration, and (d) post cholecystectomy ERCP.

If the surgeon is experienced the most appropriate treatment would be a total laparoscopic approach. Several cohort studies have shown that two thirds of the stones detected by intraoperative cholangiography can be removed via the trans-cystic approach.[45] However this may not be true in Asian population where the CBDS are often large, multiple and densely impacted in the CBD. For patients in whom trans-cystic extraction of CBD stones fails, laparoscopic choledochotomy and stone extraction may be performed. However, this approach requires experience in laparoscopic suturing and a CBD of adequate diameter.

A Cochrane systematic review by Martin et al. concluded that a single-stage treatment of bile duct stones via the cystic duct approach was recommended for intra-operatively discovered CBD stones.[26] In patients where it is not possible to clear the duct by this approach, a delayed postoperative ES should be the preferred option in most centres.

The other alternative to immediate treatment of CBD stones discovered at surgery is delayed treatment. Surgeons can insert a biliary stent through the cystic duct into the CBD and through the sphincter of Oddi.[26] This procedure ensures access to the bile duct for postoperative ES.

Stones Discovered Postoperatively

These patients are best managed by endoscopic clearance, which is considered as the least morbid procedure. Failure rates of upto 10 % have been reported.[26,31] In these situations the treatment options are either laparoscopic or open exploration depending on the surgical expertise and resources at disposal.

LESS

Laparoendoscopic single-site (LESS) surgery has emerged as an alternative to conventional laparoscopic surgery with some proven benefits.[46] Many clinical applications of LESS surgeries have been reported in the fields of gynaecology, urology, and general surgery. Although laparoscopic CBD exploration has a high rate of stone clearance rate and low morbidity and mortality, this technique requires the acquisition of suturing and knot tying skills.[46] Suturing and ligation are more difficult in LESS surgery, compared to conventional laparoscopic surgery due to the angle limitations.

Robotic

Recent developments in laparoscopic CBD exploration have focused mainly on implementation of robotically assisted surgery and new imaging methods.[47] Since FDA approval of the da Vinci robotic system (Intuitive Surgical, Sunnyvale, CA, USA) for general surgical procedures, several reports have addressed their application for biliary surgery. Most surgeons gain their first clinical experience with surgical robots when performing cholecystectomies. The da Vinci system currently is the most widely used robotic system.

Conclusion

The best treatment for choledocholithiasis is the one that is simple, reliable, readily available, and cost-effective for most patients. With advances in technology and an increasing experience in laparoscopic techniques making LCBDE feasible and safe, this has emerged as the favourable choice in the hands of experienced laparoscopic surgeon. The benefit of avoiding a preoperative ERCP, in an otherwise healthy patient with choledocholithiasis, is that it excludes the hazards associated with ERCP and keeps the ampulla anatomically intact. Moreover, the benefits of minimally invasive surgery can be extended to the subset of patients with large and/or multiple CBDS which are otherwise unfit for ERCP and ES and have to undergo open procedures for stone removal.

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Laparoscopic hernia repair

Randeep Wadhawan, Hemanth Kumar

GROIN HERNIA

INTRODUCTION:

A **hernia**, by definition, is the protrusion of tissue or part of an organ through the bone, muscular tissue, or the membrane by which it is normally contained. The lifetime risk of developing an inguinal hernia is 3% for women and 27% for men[1]. The incidence rises with age and is eight times higher in persons with a family history. Indirect hernias are twice as common as direct ones and femoral hernias account for only 5% of all inguinal hernias. Inguinal hernias are more often on the right side than the left[2].

The following risk factors have been described :

- chronic obstructive pulmonary disease,
- cigarette smoking,
- low body-mass index,
- and collagen diseases.

CLINICAL FEATURES AND DIAGNOSTIC EVALUATION:

A reducible protrusion in the inguinal region is definitive evidence of an inguinal hernia and needs no further diagnostic evaluation beyond physical examination. Non-reducible inguinal masses always need further diagnostic evaluation. Meta analysis confirmed the utility of ultrasonography for this purpose, with a 96.6% sensitivity, 84.8% specificity, and a positive predictive value of 92.6%[3]. For the diagnosis of occult hernias, magnetic resonance imaging was found to be superior to both ultrasonography and computerized tomography.

INDICATIONS FOR GROIN HERNIA REPAIR:

The goal of treatment is to improve symptoms and the quality of life , prevent adverse events such as incarceration, while keeping the rate of surgical complications low. Treatment with a truss does not achieve any of these goals therefore surgery is recommended for all symptomatic inguinal hernias as it can improve the quality of life of patients. In men with asymptomatic , non-progressive inguinal hernia, surgery is not recommended(Level 1 evidence) although women should be operated in all cases of primary inguinal hernias because of the possibility of a femoral hernia. In recurrent inguinal hernia the decision to operate must be made individually, in consideration with the initial technique that is with or without a mesh, symptoms, and accompanying morbidity. Recurrences subsequent to a mesh, that have a palpable well-defined hernia borders may have a greater tendency to be incarcerated than recurrences after suture-based techniques. The indication for a second operation in such cases may, therefore, be stronger.

METHODS OF INGUINAL HERNIA REPAIR:

Inguinal hernias can be repaired by either suture or mesh based techniques, through an anterior or a posterior approach, and by either open surgery or laparoscopy/endoscopy. Minimally invasive procedures are always done through a posterior approach and with the use of a mesh while the open, suture-based operations are performed through the classic anterior approach. The well-known suturing techniques are those of Bassini and Shouldice. The standard mesh-based technique through an anterior approach is that of Lichtenstein. Shouldice repair is associated with a lower recurrence rate than other popular suture-based techniques, such as that of Bassini (7% vs. 4.3%) , but the recurrence rate of suture-based techniques in general is four times higher than that of mesh-based techniques (4% vs. 0.9%). In the guidelines of the European Hernia Society (EHS) mesh based techniques have a lower recurrence rate than suture based techniques (level 1evidence) therefore the recommendation for the adult patients is either the Lichtenstein procedure or an endoscopic/laparoscopic technique (if the surgeon has the necessary expertise) as the standard for hernia repair (recommendation grade A).Adults aged 18 to 30 also benefit from mesh-based techniques, and studies have shown that such techniques have no effect on male fertility[5].Unilateral primary inguinal hernia can be treated either by open surgery or by endoscopy/laparoscopy, the latter seems preferable because of the lower frequency of chronic postoperative pain.

LAPAROSCOPIC GROIN HERNIA REPAIR:

ADVANTAGES:

Numerous studies have shown that laparoscopic repair of inguinal hernias has advantages over conventional repair, including:

-Reduced postoperative pain
-Earlier return to work
-Less wound infection/hematoma
- Faster recovery

DISADVANTAGES:

- Higher learning curve
- Chances of injury to bladder and vascular structures.

INDICATIONS:
The classic indications for endoscopy/laparoscopy are inguinal hernia in a woman, bilateral inguinal hernia, and recurrent hernia after a prior anterior approach.

CONTRAINDICATIONS :
There is no absolute contra-indication to laparoscopic repair of groin hernia repair. Patient not fit for general/regional anaesthesia in view of medical illnesses. Some relative contra-indication like a lower midline incision, previous preperitoneal surgery (eg, prostatectomy). Medical illness including coagulopathies and intra-abdominal infections,ascites, irreducible/strangulated hernia and giant scrotal hernia are also relative contraindiactions for laparoscopic groin hernia repair.

LAPAROSCOPIC ANATOMY GROIN HERNIA:
For a safe and successful surgical treatment, the actual obvious knowledge of this surgical structure, from the relevant region, is very important. Laparoscopic repair is essentially ***a rear strategy view***, requiring anatomical understanding from peritoneal surface outwards. The inguinal region is a unique practical amalgamation of musculo-skeletal, visceral and neuro-vascular components, maintaining physiological integrity of the region.

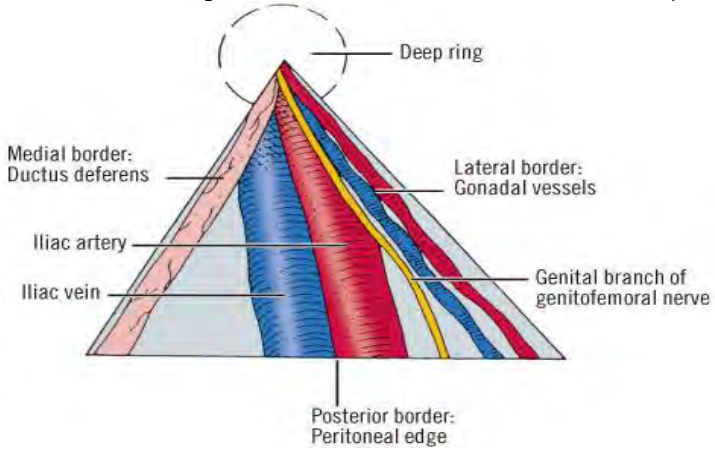
MYOPECTINEAL ORIFICE OF FRUCHAUD- In 1956 , **Henry Fruchaud** proposed that all groin hernia originate in a single weak area called the **myopectineal orfice** .He described this as **oval, funnel** like, potential orifice which is divided through the iliopubic tract and the inguinal ligament into an 'inguinal outlet' above and a 'femoral outlet' below**.** Proper exposure of the area is essential during a pre-peritoneal(posterior) repair and also for the adequate fixation of the mesh.

THE EXTRAPERITONEAL SPACE:
Space Of Bogros - Space between the peritoneum and the posterior lamina of transversalis fascia.
Vascular space- Space between the posterior and anterior laminae of the transversalis fascia. This includes the aponeurosis of the transversus abdominis muscle. Contents include inferior epigastric vessels.
Space Of Retzius- Preperitoneal space, medial to space of bogros, lies deep to supra vesical and medial umbilcal fossa. contains loose connective tissue and fat. Contents include obturator vessels and accessary pudendal vessels(10%).

PERITONEAL FOLDS:
Median Umbilical Ligament-Represents obliterated urachus and extends from apex of bladder towards umbilicus
Medial Umbilical Ligament-Represents obliterated umbilical artery and can be traced down to internal iliac artery.
Lateral Umbilical Ligament-Ridge of peritoneum, raised by the inferior epigastric vessels and course from the internal inguinal ring to the posterior rectus sheath.
FOSSAE: The order of the fossae, from periphery to midline :
Lateral-Lateral to lateral umbilical ligament. Site for indirect hernia.
Medial-Between lateral and medial umbilical fold. Site for direct hernia
Supravesical-Between medial and median umbilical fold. Site for external supravesical hernia

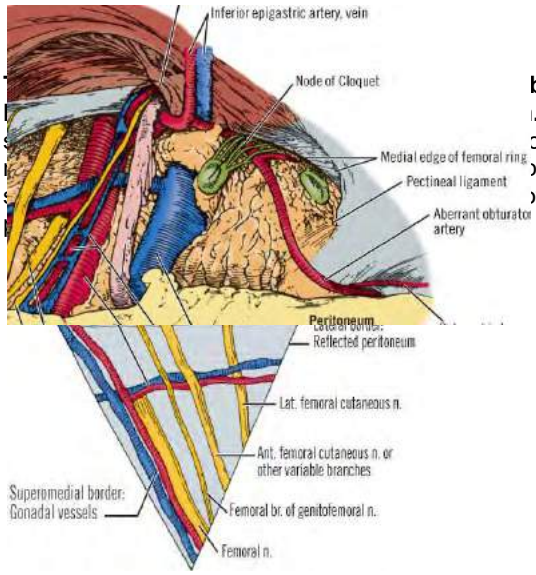
HASSELBACH'S TRIANGLE It is the site Most **direct inguinal hernias** and **external supravesical inguinal hernias** occur in this area and is bounded by lateral edge of the rectus abdominis muscle medially , inferior epigastric vessels laterally and inguinal ligament inferiorly.

TRIANGLE OF DOOM
It is formed through the meeting from the vas deferens(medial border) and the testicular vessels(lateral border) at the internal ring, which forms the apex of the triangle.Within this triangle are external iliac vessels,deep circumflex iliac vein**,** genital branch of the genitofemoral nerve, and the femoral nerve (deep).



CORONA MORTIS

The pubic branch from the Inferior epigastric artery in 25-30% of people is big and can replace the obturator artery (abberant). It can encircle the neck of a hernia sac and be injured in a femoral hernia repair. It might also be injured while exposing the Cooper's ligament by clearing it of areolar-adipose ligament.



bic tracts superiorly and the **gonadal vessels medially and** .The contents of this imaginary triangle include several nerves, oral cutaneous, femoral branch of genitofemoral, and femoral paroscopic inguinal hernia repair is that no tacks /fixation device f the mesh as it may result in intractable postoperative groin

COMPARISON OF LAPAROSCOPIC/ENDOSCOPIC TECHNIQUES (TAPP VERSUS TEP)

TAPP: "Transabdominal preperitoneal endoscopic inguinal hernia operation in which the approach to the inguinofemoral region is transabdominal, and the final placing of the prosthesis is extraperitoneal".

TEP: "Total extraperitoneal endoscopic inguinal hernia operation in which both the approach to the inguinofemoral region as well as the placing of the prosthesis is completely extraperitoneal". According to the guidelines of the International Endohernia Society (IEHS) , the two approaches have similar rates of severe complications and recurrences (evidence level 1) and can thus be considered clinically equivalent (recommendation grade A). The learning curve for laparoscopic/endoscopic hernia repair is longer than that for open repair by the Lichtenstein technique (evidence level 3–4).

TECHNIQUE:

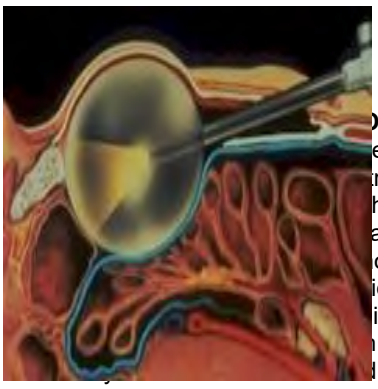
TOTALLY EXTRAPERITONEAL REPAIR OF HERNIA(TEP):General anesthesia is preferable. It can be done under regional anesthesia also if the patient is not fit for general anesthesia. Bladder catheterization can be considered. Prophylactic antibiotic is given at the time of induction.

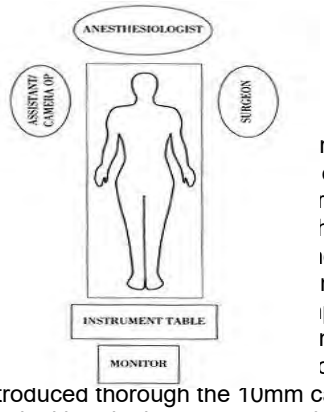
The position of the surgeon is to the opposite side of the hernia. The head end is kept at a lower level (about 15^0).The contents of the hernia if need be is reduced.

An Incision is made below the umbilicus and the subcutaneous fat is retracted. A transverse incision made on the anterior rectus. Rectus muscle is retracted and extraperitoneal space approached by placing a 10mm cannula. Insufflation of the space is done with carbon dioxide.

CREATION OF EXTRAPERITONEAL SPACE:

This can be done by balloon dissection or by using the telescope (0 degree). Two 5mm ports are inserted in the midline-one 2-3 cm above pubic symphysis and the second in between the two ports –both in midline.





ONEAL SI ed with a ructure (t h. The di and the a oeuvres a ion alway igated us can res be upto rp dissection. The coopers ligament extended 2-3 cms into the retropubic rally towards the hernia. The hernia he hernia sac dissection is performed e injuries to the ductus deferens and mplete hernia , the sac should ideally pt to completely reduce the sac with n and seroma formation. The lateral c spine. Desired polypropylene mesh with size not less than 15cms X 12 cms is introduced thorough the 10mm cannula and fixed to coopers ligament after proper placement.In cases of bilateral inguinal hernia the process can be repeated using the same ports.

TRANS ABDOMINAL PREPERITONEAL REPAIR OF GROIN HERNIA(TAPP):

General anesthesia is the preferred method. Foleys catheterization can be considered. Prophylactic antibiotic is given at the time of induction. Contents of the hernia if present are reduced manually. Both arms are preferably tucked by the side of the patient. The operating surgeon stands on the opposite side of the hernia, while assistant can be on the same side or to the opposite side of the surgeon (preferable). The laparoscopic unit is placed at the foot end of the patient.

After painting and draping with adequate exposure, pneumoperitoneum is done with standard laparoscopic practice (veres needle, open Hassan or optical trocar).The port placement are generally 10mm supraumbilical, 5mm on either side in the mid-axillary line, lateral to the rectus muscle forming a triangulation to enable easier suturing. Peritoneum is incised 2cms above the anterior superior iliac spine upto the medial umbilical ligament using a monoplar hook or scissors. The preperitoneal space is entered and the anatomy delineated. The sac (direct &indirect) is reduced along with contents if any. A 15cms X 12cms mesh is placed in the preperitoneal space and fixed to coopers ligament with suture or tack. The peritoneum is subsequently closed with a running suture using a 2-0 monofilament non absorbable suture. The contralateral hernia is treated in the same manner.

POSTOPERATIVE CARE:

The patient may be considered for discharge on the same day (short stay surgery) or the following day. Urinary retention may be a common complaint requiring catherterisation. Diet can be resumed 6 hours after the procedure and the convalescent period is at a 1-2 day minimum with full activity resumed at 7 days.

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VENTRAL HERNIA

INTRODUCTION:

Ventral and incisional hernia repair is one of the most common operations performed in everyday clinical practice. Incisional hernia is a common long-term complication of abdominal surgery and is estimated to occur in 11–20% of laparotomy incisions. Almost 50% of incisional hernias develop within the first 2 years after the primary surgery, and 74% develop after 3 years.[1,2] Leblanc and Booth[3] described the first laparoscopic ventral hernia repair (LVHR) in 1991. It is based on the same physical and surgical principles as the open underlay procedure described by Stoppa, Rives et al, and Wantz. LVHR is now being used with increasing frequency, even for the management of complex incisional hernias. It offers earlier recovery, decreased hospital stay, and low recurrence rates, moreover, it is well accepted that the primary advantage of the laparoscopic approach is that wound infections are less frequent compared with the open approach.

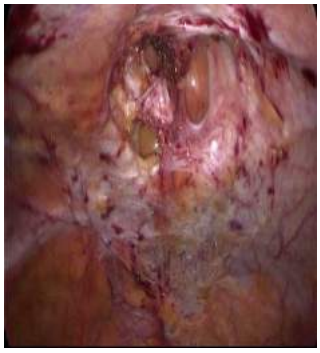
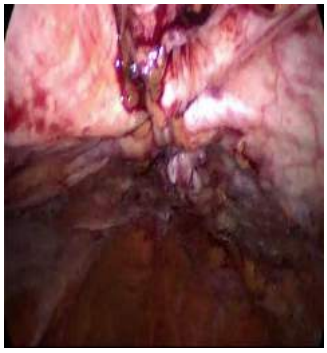
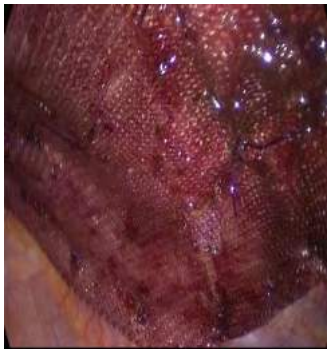
CONTRAINDICATIONS:

The laparoscopic approach is not indicated in emergency situations, especially in cases with hemodynamic instability or incarcerated hernia, with or without gangrenous bowel. Severe coagulopathy is an absolute contraindication for laparoscopy. An open approach also may be indicated for patients with a hostile abdomen eg. enterocutaneous fistulae, history of an open abdomen, severe abdominal injuries, or previous extensive operations may be associated with diffuse adhesions and may render the laparoscopic approach very tedious or impossible.

PREOPERATIVE PREPARATION:
Smoking and obesity are known risk factors for the development of infectious complications and recurrence. Therefore cessation of smoking for at least 2 weeks before surgery is desirable. Obese patients should try to lose weight on a dietary program for 2 months before surgery. Abdominal imaging with computed tomography (CT) is necessary in patients with large or recurrent hernias, as well as those with strangulated hernias. For complex hernias or those along the abdominal border, knowing the proximity of the edges of the hernia defect to the bony landmarks is useful in preoperative planning for mesh fixation.[4]

PROCEDURE: The procedure starts with entry into the peritoneal cavity with a Veres needle, an open Hasson method, or an optical trocar. Three trocars are used, one 10-mm and two 5-mm trocars, which are placed as laterally as possible on the abdominal wall, so they are at an adequate distance from the hernia orifice. Most operations can be completed with 3 trocars. The next step of the operation is the most tedious one: adhesiolysis. The adhesions in the abdomen are lysed with electrocautery or an ultrasonic scalpel. The abdominal contents of the hernia sac are reduced into the peritoneal cavity .No cauterization should be done that may injure the bowel wall. Perforation of the intestine is the most serious injury associated with LVHR. In this case, there should be a low threshold to conversion to an open procedure. If an open approach is used, the hernia should be repaired primarily or by implanting a biological mesh otherwise the injury can be repaired laparoscopically, the adhesiolysis can be completed, and the hernia repair can be completed after 1 week. After adhesiolysis, the sac contents are gently reduced into the peritoneal cavity with atraumatic graspers, while the hernia sac is left in situ. However, it may be necessary to excise a portion of the sac if the bowel is closely adherent. If the hernia content cannot be reduced, conversion to an open procedure is necessary.[4] Primary fascial closure of the defect has been developed in an effort to reduce postoperative bulging and formation of seroma after laparoscopic ventral hernia repair. Given

Fig 1- Defect, Fig 2- Tranfascial closure of the defect, Fig 3- The repair covered with a composite Mesh.

Fig 1  Fig 2  Fig 3 

LaPlace's law, a central nonfunctional portion of the abdominal wall acts like a “sail in the wind” and is prone to bulging. Primary fascial closure restores normal anatomy by reapproximating the abdominal wall under physiologic tension, which may restore its function.[5]

The techniques for closure include intracorporeal closure, extracorporeal closure, or a mixed technique. The most commonly used technique is extracorporeal suturing, according to which small skin incisions are made after which a suture passer is used to close the defect. By eliminating the dead space, this technique decreases the incidence of seromas and wound complications. Moreover, it allows wider lateral mesh overlap that reduces the possibility of recurrence.[6]

MESHES:
The peritoneal surface is cleared extensively, by lysing adhesions well away from the defect. For hernias located in the upper midline, the falciform ligament should be dissected from the abdominal wall by using an energy source. The pneumoperitoneum is then reduced to 5 to 8 mm Hg, so that the abdominal wall is minimally stretched revealing the true size of the hernia defect. The periphery of the hernia defect is evaluated by direct vision and palpation and is marked on the abdominal wall skin with a marker. The craniocaudal and lateral measurements are taken, to define the size of the prosthetic mesh. Because most meshes are associated with significant postoperative shrinkage, a 5-cm overlap is suggested[4]. It is very important to identify all hernia defects and include all of them within the measured distances by the mesh. Polypropylene prosthesis has been abandoned in the laparoscopic approach, because it may create adhesions with bowel loops.Tissue separating, synthetic meshes are preferred prosthetic material used in LVHR.

After the selection of the appropriate sized prosthesis, 4 sutures are placed on the axial edges of the mesh. Permanent sutures are most widely used. The mesh is rolled tightly and is inserted in the peritoneal cavity through the 12 mm trocar. It is unrolled inside the abdomen and spread under the defect. Assisted by a suture passer, the 4 transfascial sutures are used to fix the mesh to the interior of the abdominal wall, avoiding postoperative migration of the mesh. The mesh is further secured with 5-mm fixation devices with absorbable or non absorbable tacks. The tacks are placed circumferentially at the margins of the mesh at 1-cm intervals, to

prevent the bowel from becoming incarcerated between the mesh and the abdominal wall (single-crown technique). A second row of tacks is recommended at approximately 2-cm intervals and 2 cm from the edge, to provide a more robust mesh fixation to the peritoneal surface (double-crown technique).[7] COMPLICATIONS:

HEMORRHAGE:
Intraoperative bleeding may occur initially during the insertion of trocars, usually from branches of the inferior epigastric vessels. If the bleeding is persistent, cauterization or suture placement may be necessary.
During adhesiolysis, bleeding may occur from the cut omentum or adhesive bands. The source of bleeding can be controlled by electrocautery or ultrasonic shears or by suturing or clipping if the bleeding site is on the bowel or mesentery.

INCIDENTAL ENTEROTOMY:
Iatrogenic enterotomy is a serious complication during LVHR with an incidence from 0 to 14%. Dense bowel adhesions, recurrent hernias, and use of external energy devices for adhesiolysis contribute to the risk of this serious complication.A recognized enterotomy is repaired by conversion to an open method , the bowel is returned to the abdominal cavity, and the hernia repair can be accomplished laparoscopically after an interval of 1 week. The enterotomy is recognized after surgery in approximately 18% of cases and is best managed by re-exploration in an open or laparoscopic procedure.

SEROMA:
Seroma can be detected by ultrasonography in up to 100% of patients after LVHR. Formation of a seroma most often occurs at postoperative day 7 and it is resolved usually by day 90. Seromas are usually asymptomatic; however, 30–35% of patients experience symptoms, such as pain, pressure, and erythema. Risk factors for development of seroma are nonreducible hernia, multiple incisions, recurrent hernia, and suture placement through the hernia sac during the repair. For prevention, cauterizing the hernia sac may afford a lower risk of seroma. In addition, compression dressing for 1 week after surgery reduces the occurrence of seroma.[8] As for treatment, expectant management is reasonable, since most seromas resolve spontaneously. Aspiration is justified in large symptomatic seromas, but there is always a risk of mesh infection, especially if it is repeated several times.

CHRONIC PAIN:
The LVHR procedure may lead to residual pain in almost 26% of patients. Non midline LVHR is more often associated with chronic pain. The evidence on whether the type of suture, tack, glue, or mesh used alters the incidence of chronic pain is not conclusive. Absorbable fixation tacks are associated with few cases of chronic pain at 1 year after surgery. Suture fixation at 2- to 3-cm intervals results in a higher number of patients with pain at 6 months after surgery, compared with tacks-only fixation.[8] Prolonged intractable pain is usually due to nerve entrapment by a suture or tack. Injection of a local anesthetic at the suture sites or intercostal nerve block is a helpful method in the treatment of chronic pain. In persistent cases, removal of a suture or tack will usually resolve the pain.

INFECTIOUS COMPLICATIONS:
The incidence of infectious complications in LVHR is lower than in the open approach (range from 16–18% to 2–3%) due to the length of the incision is shorter, reducing the risk that bacteria will enter the subcutaneous tissue. Infectious complications are significantly associated with larger hernias, previous herniorrhaphy, longer operating times, and extended hospital stays.[8]Patient characteristics that increase the risk of SSI include smoking, old age, steroid use, obesity, diabetes, malnutrition, and remote site infection.

RECURRENCE:
The mechanisms of recurrence in decreasing order of frequency are: infection, lateral detachment of the mesh, inadequate mesh fixation, inadequate size of mesh, inadequate overlap, missed hernias, increased intra-abdominal pressure, and trauma. Recurrence may be a 2-step process, beginning first with an intraoperative shift of the mesh, followed by contraction, which may accentuate the shift.[8] The recurrence rate reported in the literature after LVHR is not greater than 7%. The general opinion of most surgeons is that a dual method of fixation with tacks and sutures is necessary for a more robust repair. A mesh overlap of at least 5 cm and fixation of the lower margin of the mesh to the Cooper's ligament confers increased durability and reduces the possibility of recurrence in patients with suprapubic hernia.[8] Insufficient coverage of the incision scar is a risk factor for recurrence after LVHR. Therefore, the entire incision and not just the hernia must be covered with mesh.

CONCLUSIONS
LVHR is a safe and excellent procedure for the management of abdominal wall hernias. The technique offers the advantages of the laparoscopic approach (i.e., a short hospital stay and brief convalescence). The approach carries a higher risk of bowel injury during surgery, but it has a significantly lower risk of SSI. Laparoscopic repair offers a quality of life and patient satisfaction comparable to or better than that of open repair, and the recurrence rate is less. For the repair of large complex hernias, component separation technique is regarded as the gold standard. For all these reasons, LVHR is used with increasing frequency in everyday surgical practice.

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Bariatric Surgery

Pawanindra Lal

The Burden of Obesity

Obesity represents one of the primary causes of preventable deaths. In 2014, an estimated 1.9 billion adults were considered overweight and more than 600 million were obese, translating to 13% of the worldwide adult population.[i] Obesity is now a worldwide public health problem, an epidemic, with increasing incidence and prevalence, high costs, and associated comorbidities.[ii]

The term “metabolic syndrome” (MS) is generally used to indicate the cluster of central obesity, insulin resistance (IR), hypertension, and hyperlipidemia. Metabolic syndrome results in a greater risk of developing T2DM and cardiovascular disease, 2 of the principal causes of death worldwide.[iii]

Bariatric surgery causes significant and sustained weight loss and can considerably reduce IR, with dramatic clinical improvement or remission of insulin-resistant states (ie, dyslipidemia, hypertension, hyperuricemia, sleep apnea). Experimental evidence from animals shows that the effects of bariatric surgery on insulin sensitivity and glucose homeostasis are not just the consequence of mechanical reduction of food intake or energy absorption but derive from a variety of physiologic mechanisms, including changes in gut hormones, biliary acids metabolism, nutrient sensing, and microbiota.[iv]

This knowledge corroborates evidence of a critical role of the gut in glucose and energy homeostasis and supports consideration of the gastrointestinal (GI) tract as a rational biological target for interventions aimed at treating obesity, diabetes, and metabolic disorders.[v] Based on such mounting mechanistic and clinical evidence, conventional bariatric procedures are now increasingly being proposed not only as mere surgical management of obesity but also as a valuable approach to intentionally treat T2DM—a new concept and practice referred to as “metabolic surgery.[vi]

Who has classified obesity as:

- BMI < 18.5, it falls within the underweight range.
- BMI 18.5 to <25, it falls within the normal.
- BMI 25.0 to <30, it falls within the overweight range.
- BMI is 30.0 or higher, it falls within the obese range.

Obesity is frequently subdivided into categories:

- Class 1: BMI of 30 to < 35
- Class 2: BMI of 35 to < 40
- Class 3: BMI of 40 or higher. Class 3 obesity is sometimes categorized as “extreme” or “severe” obesity.
- Super Obese: BMI > 50

For the Asian population, Obesity has been modified by the Western Asia Pacific WHO as follows:[vii]

- Class 1: BMI of 25 to < 29.9
- Class 2: BMI of > 30

Gut microbiota

The human gut microbiota (GM) is a complex entity composed of more than 1000 species of comensal microorganisms. GM is present across the GI tract with greaterconcentrations in the ileum and colon.[viii]In physiologic conditions, the GM contributes to intestinal system maturation, host defense against pathogens, degradation of nondigestible polysaccharides and plays an important role in body fat distribution and control of energy homeostasis.[ix] The GM is influenced by diet, lifestyle, physical exercise, antibiotics, and genetic background.[x] GM modulates energy harvesting from dietary fibers, fat storage, lipopolysaccharides (LPS) content, and the production of short-chain fatty acids which in turn regulate host food intake, insulin signaling and Gut Adaptation to Bariatric/Metabolic Surgery (BMS)

Gut Adaptation to Bariatric/Metabolic Surgery

BMS is currently the most effective treatment for severe obesity and T2DM, providing sustained weight loss as well as reduction and prevention of obesity-related cardiometabolic comorbidities.[xi]Given its dramatic clinical effectiveness, BMS provides an opportunity to better understand the role of the gut in physiology and disease. In addition to weight loss, BMS can cause changes in various mechanisms of GI physiology, including changes in satiety-promoting gut hormones (ie, glucose-dependent insulinotropic peptide, glucagon-like peptide 1 [GLP-1], peptide YY, and Oxyntomodulin) and increased gastric emptying. Certain bariatric/metabolic procedures such as Roux-en-Y gastric bypass (RYGB) and sleeve gastrectomy (SG) cause a shift in bile acids (BAs) metabolism composition, bile flow, and increased BAs signaling through the BAs nuclear receptor Farnesoid X (FXR). GI modifications imposed by certain procedures, particularly those involving a re-re-routing of the small intestine (ie, RYGB, duodenal-jejunal bypass, DJB), can cause changes in microbiota composition and nutrient sensing; all of these effects appear to be involved in the metabolic benefits of BMS.[xii]

Gastrointestinal hormones

RYGB and SG are characterized by an excessive postprandial response of the enteroendocrine intestinal L cells responsible for a rapid increase in postprandial GI hormones.[xiii] The increase in GLP-1 causes a rapid postprandial "incretin effect," increasing insulin secretion. This mechanism is thought to be at least in part responsible for the improvement of glucose tolerance observed after these procedures.[xiv] Ghrelin, a hunger promoting hormone, is mostly produced in the stomach. Although no specific pattern was observed regarding Ghrelin serum level changes following gastric banding, RYGB, and biliopancreatic diversion, serum levels appeared consistently reduced after SG.[xi]

Bile acids

Beyond their role in the absorption of fat-soluble vitamins and dietary lipids, BAs are key regulators of glucose and lipid metabolism as well as energy expenditure thanks to the interaction with GM. [iv] The BAs are produced from cholesterol in the liver (primary BA). Primary BAs are transformed into secondary BAs by GM in the intestine; these are absorbed in the terminal ileum, returned to the liver, and are then secreted again into the bile (enterohepatic cycle). Increased BA serum levels are observed after RYGB and SG, but not following gastric banding, suggesting that elevated serum BAs levels in procedures that modify GI anatomy could improve insulin sensitivity, incretin secretion, and postprandial glycemia.[xv]

Obstructive Sleep Apnea Syndrome

Obstructive sleep apnea (OSA) is linked to obesity and affects 15% of men and 6%of women.[xvi] OSA is characterized by airway obstruction during sleep, responsible for chronic hypoxia; this leads to the activation of the hypothalamic-pituitary adrenal axis, causing oxidative stress, systemic and tissular inflammation (adipose tissue and liver), and increased secretion of proinflammatory adipocytokines (Resistin, TNF-a, IL-6, plasminogen activator-1). These disturbances result in decreased insulin sensitivity and pancreatic b-cell dysfunction. OSA is known as a critical independent risk factor of cardiovascular disease, hypertension, MS, and T2DM.[xvii]

TYPES OF BARIATRIC PROCEDURES:

The failure of medical therapy for severe obesity and the success of surgery has, over the last six decades, produced a remarkable series of new techniques and procedures for the treatment of obesity and its comorbidities. Bariatric operations have traditionally been divided into three groups based on their mechanism of weight loss production. Malabsorptive procedures induce weight loss totally by interference with digestion and absorption. Restrictive procedures produce weight loss solely by limiting intake. Mixed malabsorptive and restrictive procedures limit intake and produce malabsorption.[xviii]

Table 1: Classification of types of Bariatric Procedures

Restrictive Alone: • Gastric Banding • Sleeve Gastrectomy
Restrictive & Malabsorptive • RYGB • BPD-DS • MGB
Malabsorptive Alone • Jejuno-Ileal Bypass

Morbid obesity is associated with a myriad of serious comorbid conditions, including hypertension, type 2 diabetes mellitus, dyslipidemia, osteoarthritis, and gallbladder disease.[xix] There have been numerous studies demonstrating the effectiveness in obtaining weight loss and marked resolution of comorbidities with bariatric and metabolic surgery.[xx]

Based on scientific evidence, it is becoming increasingly clear and accepted that the only existing therapy for severe obesity that has been shown to result in clinically significant and durable weight loss is bariatric surgery. Furthermore, it has been shown that weight loss after bariatric surgery results in significant improvements in obesity comorbidity, quality of life, and reduced mortality. Short- and long-term complications of surgery, although not insignificant, appear to be reasonable and justifiable compared with the long-term risks of severe obesity. Economic analysis has demonstrated that bariatric surgery is cost-effective and perhaps cost-saving in certain subgroups such as those with type 2 diabetes. In addition, there is evidence that bariatric surgery may reduce indirect costs of obesity by improving workplace productivity and reducing absenteeism.[xxi]

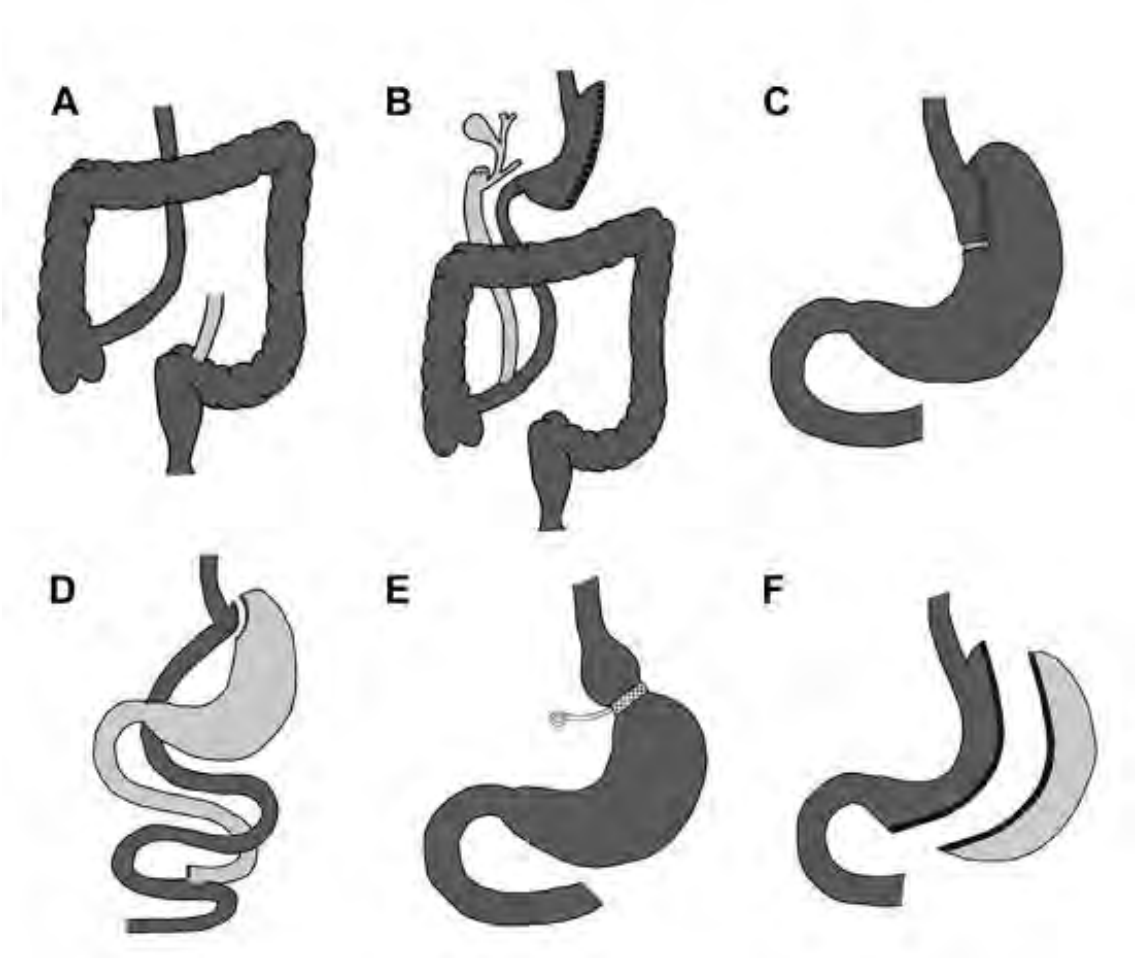

Fig. 1. Overview of bariatric surgical operations. (A) Jejunal-ileal bypass: end-to-end jejunoileostomy with ileosigmoidostomy. (B) Biliopancreatic diversion with a duodenal switch. (C) Vertical banded gastroplasty. (D) Roux-en-Y gastric bypass. (E) Adjustable gastric band. (F) Sleeve gastrectomy.[xxii]

ECONOMIC IMPACT OF BARIATRIC AND METABOLIC SURGERY

Details of Commonly performed bariatric procedures

Laparoscopic Adjustable Gastric Banding (LAGB):

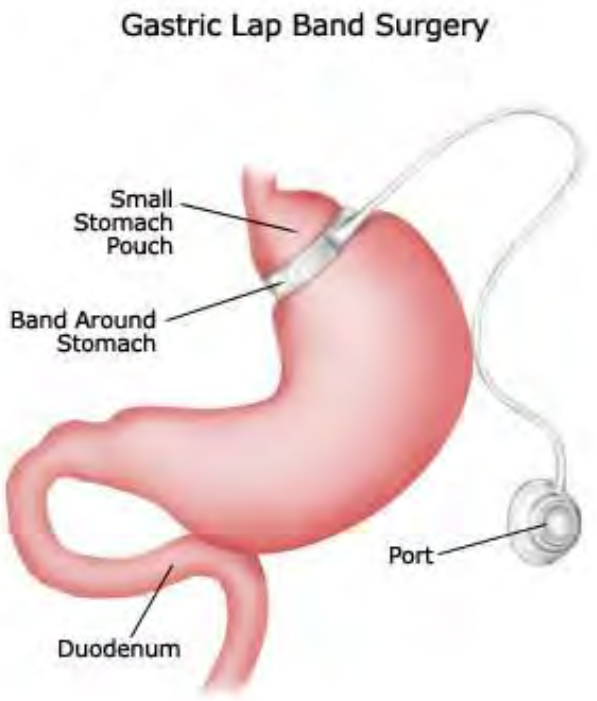

Fig 2: LAGB

Table 2. Potential complications of laparoscopic adjustable gastric banding[xxiii]

Band related
_ Slippage
_ Erosion
_ Pouch dilatation
_ Esophageal dilatation
_ System leak
_ Infection
_ Dysphagia
_ GERD
Port tubing related
_ Port displacement
_ Tube disconnection
_ System leak
_ Infection

Although several definitions are available, failure of weight loss is usually defined as less than 50% excess body weight loss.[xxiv] According to these parameters, 10.5% of the patients who underwent LAGB present with inadequate weight loss at 5 years and 14% at 10 years. Failure of weight loss remains the most prevalent reason for conversion surgery after LAGB in upto three fifths of the patients.[xxv]

LAGB is still regarded as a technically simple and relatively inexpensive bariatric
surgical option. Also, its safety is known in short-term and medium-term follow-ups. According to early studies, LAGB offered significantly lower morbidities and mortalities compared with the standard of care laparoscopic gastric bypass (mortality 0.05% vs 0.5%). Even the weight loss outcomes of the LAGB were more than satisfactory compared with the potentially more morbid LRYGB. If the initial weight loss was lower compared with the LRYGB, multiple studies reported up to 65% EWL after 2 or 3 years.[xxvi]

LAGB presents fewer short-term complications and shorter hospital stays than other bariatric operations. Although its efficacy in terms of comorbidity resolution seems adequate in many studies, the variability of results is such that without robust level 1data, final conclusions are difficult to draw. The main concern regarding LAGB remains with the long-term complications and durability of the procedure. Overall it is fair to conclude that the role

of the band seems limited at the moment. The availability of more effective procedures with acceptable short-term and long-term complication rates, such as LSG, has eclipsed the role of the formally popular LAGB.[iii]

At MAMC we performed 10 bands and have had to revise 2 for failure and 2 for erosion.

Laparoscopic Sleeve Gastrectomy (LSG)

LSG was initially created as the first step in a 2-part procedure (biliopancreatic diversion with duodenal switch) for super morbid obese patients in whom traditional bypass surgery was thought too high risk based on their associated comorbidities. Michel Gagner introduced this procedure in 1999 as a stand alone procedure for morbid obesity and there has been no looking back since. The sleeve gastrectomy has since been found to have comparable results to other weight loss procedures, including the Roux-en-Y gastric bypass, and has become an increasingly popular option among both surgeons and patients. Advantages of laparoscopic sleeve gastrectomy over the roux-en-Y gastric bypass includes acceptable use in patients with inflammatory bowel disease, patients who are transplant candidates (liver and kidney), and patients with complex prior abdominal surgery or complex abdominal wall hernias. It is also a pylorus-sparing procedure that eliminates the risk of dumping syndrome. Finally, there is no increased risk of marginal ulceration or internal hernias compared with traditional bypass surgery. It is not, however, considered an antireflux procedure. Therefore, Barrett esophagus may be a contraindication.[xxvii]

Many variations exist regarding surgical technique; however, the basic tenets of LSG should be stringently followed. These include pyloric preservation with gastrectomy beginning 2 cm to 6 cm proximal to the pylorus, mobilization of the entire greater curvature with exposure and identification of the left crus and base of the right crus, avoidance of stricture at the gastric incisura, and proper apposition of the anterior and posterior aspects of the stomach when stapling to prevent a corkscrewing effect of the sleeve and avoid a large retained fundic pouch. [xxvii] (Fig 3) Routine deep vein thrombosis prophylaxis consists of sequential compression device placement and subcutaneous heparin.

Long-term follow-up has demonstrated durable weight loss and metabolic benefits comparable with Roux-en-Y gastric bypass.[xxviii]. LSG evolved from a staged procedure as part of the biliopancreatic diversion and duodenal switch and has emerged as a sole procedure for sustained weight loss and improvement of metabolic derangements. The surgery continues to gain popularity due to its perceived technical simplicity coupled with promising short-term and long-term data, which suggest results comparable to more established bariatric procedures. The LSG has continued to gain popularity among both patients and surgeons due to its perceived technical simplicity compared with other bariatric surgical procedures. As data regarding patient outcomes after this procedure continue to accrue among institutions, promising results are being published more than 5 years out from surgery. Most publications report a mean percent excess weight loss of 55% or more over this time period.[xxix],[xxx]

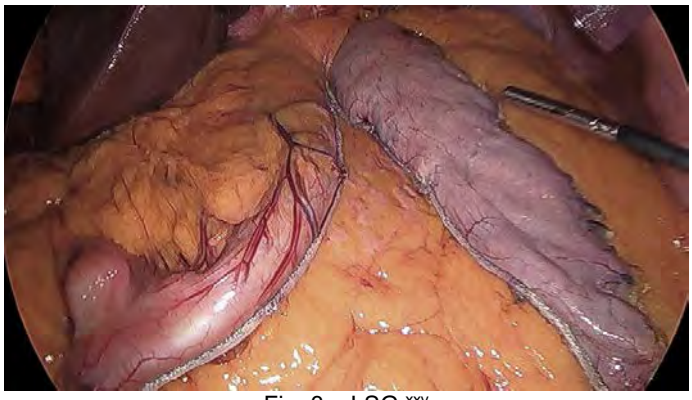

Fig 3 – LSG [xxv]

LSG compares favorably to long-term weight loss data for laparoscopic Roux-en-Y gastric bypass over the same time frame. Improvements of type 2 diabetes mellitus and metabolic syndrome abnormalities are also similar compared with gastric bypass. Data pertaining to the improvement of gastroesophageal reflux disease or new onset of gastroesophageal reflux disease after sleeve gastrectomy continue to evolve, and dedicated objective studies are needed to better delineate this potential outcome.[xxxi] Regarding the most feared complication, overall leak rates are reported between 0.7% and 3.7%, and a majority of these occur at the proximal third of the stomach staple line near the gastroesophageal junction.[xxxii]

At MAMC, out of 100 total bariatric procedures we have performed 68 sleeve operations with results comparable with the world literature. This procedure is successful so long as the patient is prepared to follow up regularly and adopt life style changing measures, with effective resolution of co-morbidities. Men tend to show a better long term success as compared to women in Indian setting.

Roux-en-Y-Gastrojejunostomy (RYGB)

The gastric bypass procedure was first introduced by Mason in 1967 as a variation of the Bilroth II reconstruction used after antrectomy in the treatment of peptic ulcer disease.[xxxiii] Over one-half of a century, numerous modifications led to the elegant minimally invasive procedures we perform today. The most noteworthy include the adoption of the Roux-en-Y configuration reported and advocated by Griffin in 1977[xxxiv] and the introduction of the laparoscopic Roux-en-Y gastric bypass (LRYGB) by Wittgrove and associates in 1993.[xxxv] Over the past 2 decades, the LRYGB has proven to be a highly effective operation against obesity and its associated comorbid conditions, and has a favorable metabolic side effect profile when compared with the more radical biliopancreatic diversion with duodenal switch. Numerous high-quality studies have demonstrated the efficacy and safety of the procedure. It has since become and remains the gold standard operation in the battle against the obesity epidemic.[xxxvi] (Fig 4)

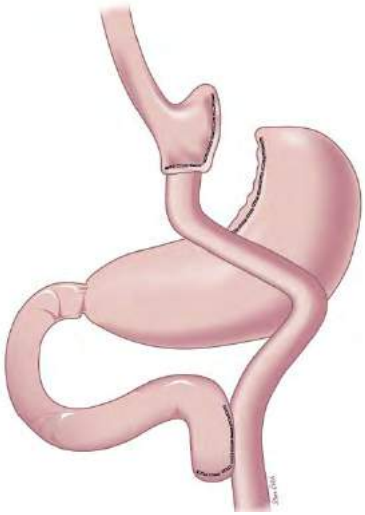

Fig 4 - Roux-en-Y gastric bypass.

COMPLICATIONS

There are multiple complications associated with the LRYGB, including but not limited to bleeding, infection, small bowel obstruction secondary to internal or port site herniation, marginal ulceration, anastomotic leak, anastomotic stenosis or stricture, hypopharyngeal or esophageal injury, omental torsion or necrosis, pulmonary embolus, death, development of symptomatic cholelithiasis, inadequate weight loss, nutritional deficiencies, and symptomatic dumping syndrome. The incidence of specific complications can vary with the technique used.[xxxvi] Anastomotic leak is a dreaded complication most commonly occurring at the gastrojejunal anastomosis site[xxxvii], and with experience has reduced to 0-3%.[xxxviii]. Stricture at the gastro-jejunal anastomosis is found to be reduced with the linear stapling technique as compared to the circular stapler technique from the comparison of metanalysis. [xxxix]

LRYGB vs Other procedures

LRYGB performed at specialty centers by fellowship-trained bariatric surgeons has excellent outcomes with short durations of hospital stay and low readmission rates. The 30-day mortality rate is 0.3% and major complication rate is 4.3%.[xl] The LRYG is highly effective with regards to excess weight loss when compared with other contemporary procedures.[xli] The average excess weight loss following LRYGB is 56% to 66% with average maintenance of 50% excess weight loss at 5 years.[xlii]

Recently, emphasis has been placed on adherence to Enhanced Recovery After Bariatric Surgery protocols. Enhanced Recovery After Bariatric Surgery interventions include shortened preoperative fasts, intraoperative humidification, early mobilization and feeding, avoidance of fluid overload, incentive spirometry, and use of prokinetics and laxatives. Short-term studies show Enhanced Recovery After Bariatric Surgery protocol adherence to be feasible and safe, and results in shortened duration of hospital stay and low 30-day readmission rates.[xliii]

The LRYGB is the gold standard metabolic/bariatric procedure used today to combat the growing morbid obesity epidemic. This procedure is highly effective at reducing excess body weight and has substantial efficacy against the multiple comorbid conditions associated with obesity. There are varying techniques for procedure performance, as described. The most common technique today is a circular stapled gastrojejunal anastomosis with antecolic Roux limb and stapled jejunojenostomy with hand sewn common enterotomy closure. Complications are associated to varying degrees with technique used. It is important to be aware of these complications and be prepared for expeditious management. Regardless of the technique used, the LRYGB performed at specialty centers by fellowship trained surgeons with adherence to evidence-based care protocols for perioperative care has excellent outcomes. [xxxvi]

centers by fellowship trained surgeons with adherence to evidence-based care protocols for perioperative care has excellent outcomes. [xxxvi]

At MAMC, we have performed this operation on two patients, both of whom are doing very well and we strongly feel that long term monitoring of macro and micro nutrients makes this procedure a challenging one to follow-up on long term basis in a country like India.

Bilio-Pancreatic Diversion with Duodenal Switch (BPD-DS)

The duodenal switch technique, without gastric resection, was originally described for the treatment of bile gastritis, by DeMeester and colleagues in 1987.[i] In addition, Dr Scopinaro and colleagues[ii] described in 1979 a technique of bilio-pancreatic diversion. This procedure combined a distal gastrectomy, a gastro-jejunostomy, and a jejuno-jejunostomy to create a 50-cm common channel and a 250-cm alimentary channel. This technique resulted in excellent outcomes, but the resection of the pyloric valve and the short, 50-cm, common channel resulted in post-gastrectomy syndrome, significant risks of marginal ulcer, and increased gastrointestinal side effects.[iii] The technique was thus modified in the late 1980s, to perform a longitudinal gastrectomy instead of a distal gastrectomy and to increase the common channel to 100 cm.[iv] By preserving the pyloric valve and first duodenum, the normal emptying of the stomach is preserved, the risk of marginal ulcer is decreased, and gastrointestinal side effects are reduced.[xivi] In short, bilio-pancreatic diversion with duodenal switch (BPD-DS) includes supplementations, decrease dissatisfaction with side effects, and set reasonable goal expectations.

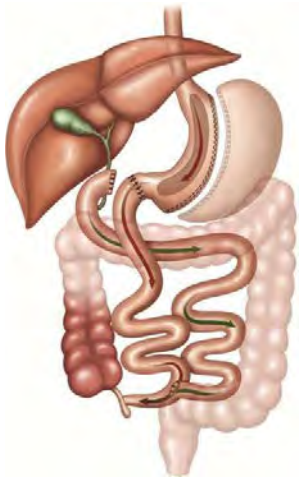

Fig. 5. BPD-DS. SG is performed and the first duodenum is anastomosed to the last 250 cm of small bowel. A 100-cm common channel is created.

A recent survey of the International Federation for the Surgery of Obesity and Metabolic Disorders member national societies reported that the proportions of BPD-DS were 4.9% in 2008, 2.1% in 2011, and 1.5% in 2013.[v] Even though the absolute number of BPD-DS procedures increased from 2008 to 2013, this suggests that other surgeries are performed preferentially (ie, SG, which has now become the predominant surgery in North America). This decrease in the percentage of duodenal switch can be related to the lack of exposure of many surgical teams to the BPD-DS technique, its greater complexity, and greater concerns about gastrointestinal side effects and vitamins and protein deficiencies. In addition, BPD-DS can only be offered to super–morbidly obese patients (BMI above 50 kg/m2) in some countries.[vi]

The complication rate after BPD-DS is usually higher compared with restrictive or mixed procedure, such as gastric bypass.[vii] This is partly due to the complexity of the technique but also to BPD-DS being specifically offered in superobese patients with a higher rate of metabolic complications. Intraoperative strategies can be used to minimize surgical complications, including the use of SG as a bridge to BPD-DS. Postoperative management involves active patient participation with follow-up and adherence to dietary recommendations, including lifelong vitamin supplements. The excellent long-term medical benefits and improvement in quality of life come at the expense of some gastrointestinal side effects and vitamin supplementation. [xiix]

Mini Gastric Bypass (MGB)

In 1997, Robert Rutledge reported a simple bersion of the gastric bypass based on the conventional Billroth II gastrojejunostomy which general surgeons were very familiar with. This was named as mini gastric bypass (MGB).[viii] Others reported this as one anastomosis bypass (OAB), or single anastomosis duodeno-ileal bypass with sleeve (SADI-S). [ix] This procedure was riddled with controversies in its initial years and surgeons refused to grant it acceptance as a bariatric procedure. However, the ease of the procedure and its effectiveness in achieving weight loss and resolution of co-morbidities could not remain undiscovered by surgeons across the globe and in the last 10 years has taken the world by storm. The procedure involves the creation of a sleeve like pouch from the level of the incisura of the stomach with anastomosis to a loop of jejunum 200 cm distal to the DJ flexure. (Fig 6)

One of the most significant reports came from Taiwan in a prospective randomized controlled trial comparing RYGB to MGB, which concluded that both LRYGBP and LMGBP are effective for morbid obesity with similar results for resolution of metabolic syndrome and improvement of quality of life. MGB is a simpler and safer procedure that has no disadvantage compared with LRYGBP at 2 years of follow-up.[x]

Controversies also arose due to the prolonged effect of bile in the stomach of such an operation and possible increase in alkaline reflux. This concern was also laid to rest by a landmark study, which compared LSG with MGB using high resolution impedance manometry concluded that In contrast to LSG, OGB did not compromise the gastroesophageal junction function and did not increase gastroesophageal reflux, which was explained by the lack of increased gastric pressures and maintained gastro esophageal pressure gradient.[xi]

Although the efficacy of this procedure for proven for resolution of diabetes for BMI > 35, another study also showed that MGB resulted in significant and sustained weight loss with successful treatment of T2DM up to 87.1%. Despite a slightly lower response rate of T2DM treatment, patients with BMI <35 still had an acceptable DM resolution, and this treatment option can be offered to this group of patients.[xii]

In our own experience at MAMC with 20 patients, we have found no difference in the occurrence of GERD or any increased alkaline reflux before and after MGB using manometry and 24 hour pH metry. These results also compared favourably with those of LSG.

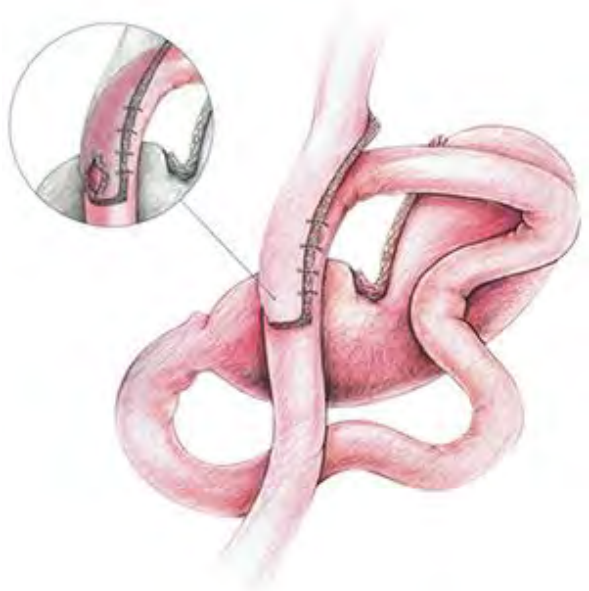

Fig 6. Mini Gastric Bypass showing a larger pouch like a sleeve anastomosed to a portion of jejunum 200 cm distal to the DJ flexure.

Complications of Bariatric Procedures (Table

Just like other surgical procedures, bariatric procedures have their share of complications which are common complications seen in other laparoscopic procedures as well. There are specific complications due to the surgical steps of the procedure which are specific to each type of operation. Diagnosis of complications in the early post-operative period can be challenging due to sheer size of the abdomen and difficulty in eliciting any abdominal signs. Reliance is therefore mainly on heart rate or pulse rate besides general condition. Pain has to be kept under control so that it does not produce tachycardia and to prevent shallow breathing and therefore causing pulmonary atelectasis. Incentive spirometry, and early ambulation is the key to preventing some of the life threatening complications like pneumonitis and DVT. Nutritional issues come up a bit later after the patient is on home diet and specific deficiencies are seen to occur depending on the type of procedure performed and degree of malabsorption induced. Regular follow-up with the metabolic clinic is essential to keep these nutrients under a tight control with addition of supplements.

Effects of Bariatric Surgery on Diseases

Although there is a lack of randomized controlled trials, there is an association between bariatric surgery and risk reduction for cancer. This association seems to affect women in a greater way. Obesity's link to cardiovascular disease, diabetes, and certain cancers is clear and well documented. Obesity is also associated with an increased risk of numerous other comorbidities. In general, the risk of a comorbidity increases as the degree of obesity increases. The risk of developing a comorbidity with increasing weight varies by sex, racial/ethnic group, and genetic factors. [xiii]The figures depict the body systems that are impacted with obesity (Fig. 6).

In addition to increased mortality, obesity is linked to increased incidence of obesity related comorbidities. Multiple studies have demonstrated improvement/resolution of weight-related comorbidities (ie, cardiovascular disease, diabetes, cancer, metabolic syndrome) after bariatric surgery. Some researchers have demonstrated a level of recalcitrance in remission of diabetes, particularly in patients with long-standing disease. More studies are needed to identify subgroups of patients that are at risk for non-responsiveness to bariatric surgery. However, overall results are supportive of surgical cure of obesity as a treatment of weight-related comorbidities and mortality risk reduction.[xiv]

Revisional Bariatric Surgery

Revisional bariatric procedures are becoming increasingly common. Inevitably 5–8% of primary bariatric procedures will fail requiring a revisional operation. The main reasons for revisional bariatric surgery are either primary inadequate weight loss, weight recidivism, or inherit specific complications related to the procedure itself. All bariatric surgical procedures, especially restrictive ones, are at risk for failure, from either poor weight loss outcomes or procedural-specific complications. The most successful conversion strategy relies on selecting the most appropriate revisional procedure, including one-stage versus two-staged and laparoscopic versus open, and involving a multidisciplinary team approach to the patient. The gold standard revisional option is usually to laparoscopically convert a restrictive operation like a Band or a sleeve to a Roux-en-Y gastric bypass (RYGB) in order to have the best balance of long term weight loss, resolution of complications related to the primary procedure and acceptable rate of perioperative complications.[xv] Detailed discussion about these is beyond the scope in the current con

Table 3: Complications & Follow-up after Bariatric Procedures[xvi]

A. Peri-operative complications

1. Intra-operative

- Entry onto peritoneal cavity
- Small Bowel / Hollow organ injury
- Solid Organ Injury
- Anastomosis revision for tension/ischemia
- Bleeding from Trocar site

2. Post-operative

- Bleeding – Intraluminal or extraluminal
- Obstruction
- Infections
- DVT
- Embolism

B. Nutritional complications – Multiple deficiencies

Follow-up testing requirement based on procedure

LAGB: 6 months, 12 months, and annual

CBC, Comprehensive Metabolic Panel, Folate, PTH, Iron and transferrin, Vitamin B12, Vitamin D, 25-OH

LSG: 6 months, 12 months, and annual

CBC, CMP, Folate, PTH, Iron and transferrin, Vitamin B12, Vitamin D, 25-OH

RYGB: 6 months

CBC, CMP, Folate, PTH, Iron and transferrin, Magnesium, Phosphorus, Zinc, Copper, Vitamin B12, Vitamin D, 25-OH

RYGB: 12 months and annual

Bone density: dual photon study, CBC, CMP, Folate, PTH, Iron and transferrin, Magnesium, Phosphorus, Zinc Copper, Vitamin B12, Vitamin D, 25-OH

BPD-DS: 6 months

CBC, CMP, Folate, PTH, Iron and transferrin, Magnesium, Phosphorus, Zinc, Copper, Vitamin A, Vitamin B1, Vitamin B12, Vitamin D, 25-OH, Vitamin E

BPD-DS: 12 months and annual

Bone density: dual photon study, CBC, CMP, Folate, PTH, Iron and transferrin, Magnesium, Phosphorus, Zinc, Copper, Vitamin A, Vitamin B1, Vitamin B12,Vitamin D, 25-OH,Vitamin E

Table 4: Common points to remember for Bariatric Surgery

Gold Standard bariatric procedure– RYGB
Commonest performed procedure globally - LSG
New Emerging Procedure – MGB
Dreaded complication after LSG – Staple line Leak near GJ
Serious complication after RYGB – Internal hernias
Long term complications – Multi-nutrient and protein deficiencies
Revision Bariatric surgery - Laparoscopic conversion of restrictive operation to an RYGB

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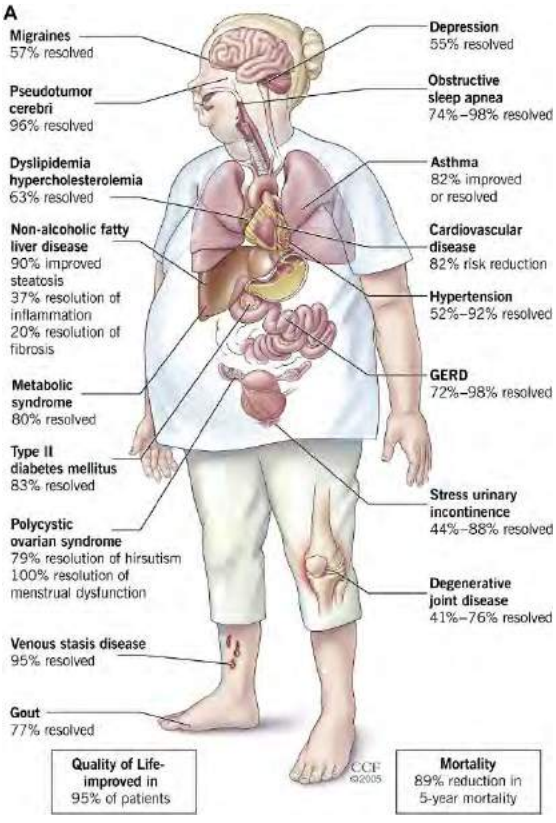

Fig. 7 (A) Body systems impacted by obesity in females. (Copyright The Cleveland Clinic Foundation 2014.)

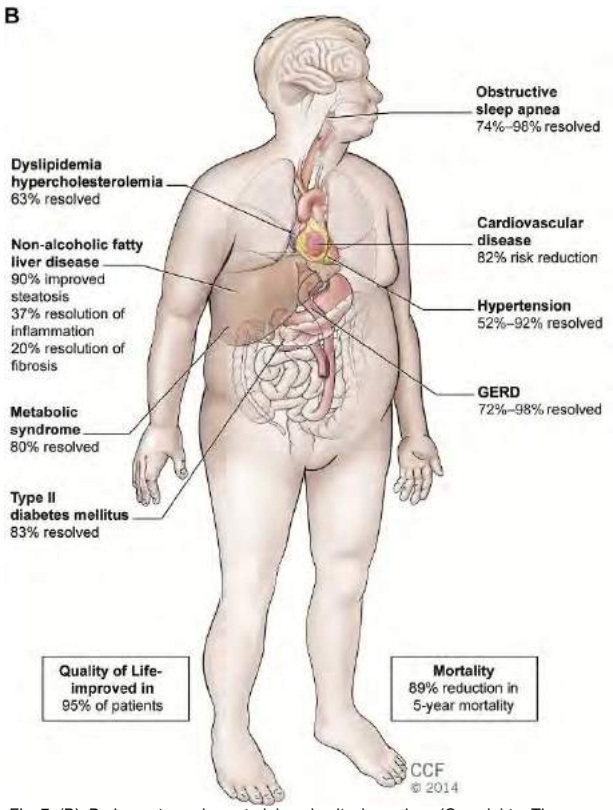

Fig 7 (B) Body systems impacted by obesity in males. (Copyright The Cleveland Clinic Foundation 2014.)

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Urologic Robotic Surgery

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Introduction

A robot is defined as “a mechanical device that sometimes resembles human beings and is capable of performing a variety of complex human tasks on command, or by being programmed in advance.” Robots resulted from the increased demand for automation in automobiles and are characterized by fast, strong and repetitive action. The word robot comes from the Czech word `robota`, meaning “forced work.” It was first used by Karel Capek, a Czechoslovakian playwright and author in the 1920s. His work was often centered around his views on the potential danger of these machines, incorporating the idea of human makes robot, robot kills human. The term `robotic` was introduced by Isaac Asimov in his novel `Runaround` in 1950 in which he defined the 3 novelistic laws governing the robots.

Classification

For a robot to be used medically, it must be precise, safe and accurate. From an operational point of view, a medical robot can be divided into 3 types: 1) remote controlled, 2) synergistic and 3) automated or semi-automated. In the remote controlled or synergistic type, the physician has direct real-time control of the robotic instruments either from a console or by handling the instrument itself. The best known remote system is the da Vinci® Surgical System (Intuitive Surgical, Inc. Sunnyvale, CA), and the synergetic type system is the MAKO orthopedics robot (MAKO Surgical Corp., Ft. Lauderdale, FL). In the automated type of robots, the physician does not have to continuously control the motion of the robot, but just defined its task and monitor its execution. Image-guided robots are commonly operated under this mode, for example, the AcuBot robot used for computed tomography (CT)-guided interventions.

Applications of robotics in medical science

Surgical robots were first used in the subspecialties of neurosurgery and orthopedics. In neurosurgery, stereotactic frames were developed using the fixed landmarks of the rigid cranium. These reference points were then used in conjunction with robots such as the Unimate Puma 560 (Programmable Universal Machine for Assembly, Danbury, CT) which enabled the surgeon to perform biopsies or the resection of mid-brain tumors. In orthopedics, robots such as the ROBODOC (Integrated Surgical Systems, Sacramento, CA) were introduced to ream bones with 10 times greater accuracy, allowing a reported 90% prosthesis contact. The first robots used in the field of urology were Probot, a robot developed for perform prostatectomies, and the URobot, designed to perform a transurethral and transperineal access to prostate for laser resection. The first robotic system to get Food and Drug Administration (FDA) approval to hold as endoscope was AESOP (Automated Endoscopic System for Optimal

Positioning). ASEOP is a robotic arm with motorized joints controlled by the surgeon and this idea was used to drive surgical tools and gave birth to the robotic surgical system. Such robotic systems were initially acquired by US military for telesurgery at borders and were later made available for general use giving birth to Zeus. The Zeus robotic system had a surgeon's console and three separate robotic arms that were attached to the operating room table, but it could not get FDA approval. Later the da Vinci® robotic system, Intuitive Surgical, was introduced, which has opened the field of robotic surgery. The da Vinci® robotic platform is a master–slave system with three or four arms allowing endowrist capabilities and a three-dimensional visualization of the surgical field. This system popularized the concept and instrumentation of robotic surgery in several medical fields such as urology, gynecology, cardiothoracic and otorhingology. Even though the system was not purposely designed for urology, prostatectomy appears to be its best suited application.

Shortcomings of conventional surgery: Need of robotics

In early 1980s, the field of surgery experienced a revolution with the introduction of minimally invasive surgery, the laparoscopy. The goal of laparoscopy was to reduce patients' pain and recovery time by minimizing the trauma of the larger incisions of the traditional open surgery. But at the same time, it also increased the technical complexity for the operating surgeon and the shortcomings were immediately recognized. Having to look at a screen that projects the image from the endoscope rather than at his or her own hands interrupts the surgeons` hand-eye coordination. Conventional endoscopes provide only a two-dimensional image, which means the surgeon loses the depth of perception. Stereoscopic endoscopes do exist, but their performance has been limited by the resolution and contrast they are able to produce. Also, the instruments are introduced into the body through ports which are placed in the abdominal wall. These port acts as a fulcrum and the movement of the tip of the instrument occurs in the opposite direction to that of the surgeons' hand, making the movement counterintuitive. This fulcrum effect also amplifies the hand tremors making even a slight movement at the holding end of the instrument to cause significant deflection at its tip. The body wall also limits the movement of the instrument to only two directions, giving it just four degrees of freedom instead of the usual six. Also, there is a significant reduction in tactile sensation and feedback. Also, there is a need of human assistance to maneuver the camera and orientation errors and unstable camera control may compromise the smoothness of the operation. All these issues make minimally invasive laparoscopic surgery a complex new skill mix for a novice surgeon to learn, with most procedures having longer learning curves than their open equivalents.

Application of robotics in urology

The limitations of conventional surgery encouraged the introduction of robotic systems that can carry out precise tasks quickly and repeatedly without tiring. The first clinical use of a robot in urology was the PROBOT in 1989, which was used to assist in transurethral resection of the prostate (TURP). Later, the SR8438 Sankyo Scara robot was developed to perform transrectal ultrasound guided prostate biopsy. But these devices never gained wide acceptance or FDA approval.

Robots developed for general minimally invasive surgery have also found a place in urologic laparoscopic surgery. AESOP, or Automated Endoscopic System for Optimal Positioning, can position an endoscope in response to the surgeon's commands, using either voice, foot, or hand control (figure 1). With precise and consistent movements, AESOP gives the surgeon direct control over a steadier operative field of view. Through simple commands such as "AESOP, move up," the surgeon can reposition the endoscope exactly where it is required. AESOP was the world's first U.S. Food and Drug Administration (FDA) approved surgical robot capable of assisting in minimally invasive procedures. Laparoscopic images with the AESOP were steadier with less camera changes and inadvertent instrument collisions compared with an inexperienced human assistant. It was regarded as a standard tool in performing laparoscopic radical prostatectomy and enabled independent operating. But after the introduction of da Vinci robotic system, AESOP has been gradually phased out. The VickY system is another very compact robot allowing to move a laparoscopic camera and is currently available, but seldom used.

Master-Slave Systems

The most advanced surgical robots currently are the "master-slave systems" where the robot just imitates the surgeons hand movements. Some have argued that these are not true robots because they lack automation and prefer the term *computer-assisted surgery* for operations performed with these machines. The master-slave systems comprise two major parts. One is the surgeon's console from which the surgeon handles the user interface and the electronic controller. The second is the patient side cart consisting of the robotic arms. Initially, 2 systems were developed by the names of Zeus and da Vinci (Intuitive Surgical), but in 2003 as a result of a corporate merger, the Zeus was acquired by Intuitive Surgical which has been phased out, making the da Vinci the current unchallenged master-slave system.

Image guided robots

Within the realms of endourology, significant advances in equipment and armamentarium have made endoscopic interventions the standard of care for a renal stones. But gaining a safe percutaneous access to the kidney for stone removal is still considered a technically demanding and difficult task. The state-of-the-art robot for percutaneous access, the PAKY-RCM, has been developed to accurately position and insert a standard 18-gauge needle percutaneously into the kidney (figure 2). PAKY-RCM stands for the Percutaneous Access of the KidneY robot - Remote Center of Motion. A comparison of robotic percutaneous access to the kidney to conventional methods on 23 patients proved robotic access to be a feasible and safe (1). A Smart Needle has also been

developed to be used in conjunction with the PAKY-RCM system. The needle detects the change in electrical impedenca upon successful entry into the urine containing renal collecting system and thus can indicate successful placement.

AcuBot, is a novel, completely automated, robotic system capable of needle placement based on imaging data such as CT scan (Figure 3). This robotic system is currently being tested for placing needle into renal parenchyma percutaneously for image guided thermal ablation of renal masses and has the potential to improve both accuracy and operative time, thus decreasing complications and improving clinical outcome.
MrBot is being developed at John Hopkins hospital and is a MRI-compatible robot for perineal prostatic access (figure 4). The robot is controlled from a unit remotely and various task specific needle drivers can be mounted to perform interventions like prostate biopsy or placing seeds of brachytherapy.

Da Vinci Surgical system
Da Vinci is the only FDA approved master-slave system that is widely used and has changed the face of minimally invasive surgery. It overcomes almost all the shortcomings of conventional laparoscopy, albeit maintaining the advantage of minimal invasion. A total of 5 different models have been released till now: standard, streamlined (S), S-high definition (HD), S integrated (i)-HD and da Vinci X integrated (Xi) with the latest being the da Vinci Xi (figure 5,6,7). Si and Xi are also available in dual console mode (figure 8). The standard system was released in 1999 and was originally offered with one camera arm and two instrument arms. In 2006 the da Vinci® S system was introduced which had numerous improvements including a motorized patient cart, color coded fiber-optic connections, easier instrument exchanges, quick click trocar attachments, increased range of motion and reach of instrument arms. In 2007 the S system became available with an HD camera. Later, the Si-HD system was released with enhanced HD vision at 1080i, upgraded surgeon console and dual console capability. The dual console feature connects two surgeon consoles to the same patient cart thus enhancing mentoring capabilities. Recently Xi system has been introduced. The da Vinci Xi has a smaller profile and the robotic arms have a greater range of motion. The camera is 8mm instead of usual 12mm and can be placed on any of the arms, rather than the dedicated camera arm. Also, the docking of robot is easier and laser guided. Overall, there have been significant advances in both the surgeons console and patient cart, allowing for better vision, greater accessibility to operative site and range and freedom of motion of robotic instruments.

Every da Vinci system consists of 3 parts, the surgeons console, the vision cart and the patient cart. The surgeons console is the drivers` seat and from where the surgeon views a three dimensional image of the surgical field through the stero-viewer and controls the instruments arms using the master controllers and foot pedals. The stereo-viewer displays the real-time high-resolution three dimensional image of the surgical field by capturing images with two 5 mm endoscopes fitted into the 12mm stereo-endoscope and displays them into right and left optical channels separately. The surgeons console also houses the master controllers which are the manual manipulators the surgeon uses to control the instrument arms and the endoscope. These controllers are grasped with index finger and thumb and the surgeons movements are translated into movement of the instruments by a computer that scales, filters and relays without delay. There is an additional filtering mechanism that eliminates hand tremors. A panel of foot switches on the surgeons console allows the surgeon to pan the camera, swap between robotic arms and activate monopolar or bipolar cautery. In the dual console system, 2 surgeon consoles are attached to single patient cart, allowing the trainee to operate and the mentor to monitor. At any surgical step the mentor can take over, allowing better training and providing patient safety. The vision cart contains the light source, video processing equipment, camera focus control and several empty spaces which can be used to place insufflators, DVD recorders and extra-monitors. The patient cart has the camera arm and 3 instruments arms which house predefined sockets to place the Endowrist instruments. The EndoWrist® instruments carry out motions originating from the master controllers under surgeons control. These instruments have seven degrees of freedom with 180° of articulation and 540° of rotation and simulate the wrist and hand movements of the surgeon. Each instrument has fixed 10 uses after which it becomes deactivated automatically. Currently, there are more than 40 types EndoWrist® instruments available in 8 mm or 5 mm shaft diameters. The 8 mm instruments operate on an “angled joint” compared to the 5 mm on a “snake joint”. The angled joint allows the tip to rotate using a shorter radius compared to the snake joint (figure 9).
Indications of using a robotic platform

There are no specific indications for using a robotic platform, any procedure that can be performed laparoscopically can be performed robotically. Commonly performed robotic surgeries in the field of urology are radical prostatectomy, radical cystectomy, partial nephrectomy and pyeloplasty. There are no specific contraindications for robotic surgery. A patient who is medically fit to undergo a laparoscopic surgery is deemed fit for a robotic procedure.

Advantages of using a robotic platform
Perceived advantages of robot-assisted surgery include precise movement of robotic arms, endowrist technology, and 3D stereoscopic vision. With the seven degrees of freedom and wrist like movements of robotic instruments, robotics makes intracorporeal suturing easier compared with pure laparoscopic surgery. There is “fulcrum effect” in conventional laparoscopic surgery, whereby the instrument tips move in the opposite direction to the surgeon’s hand around the port site, thus the movement is counterintuitive. Conversely, robotic movements are intuitive, that is the instrument tips move in the same direction as the surgeon’s hands. Most laparoscopic surgeons, although

seeing objects in two dimensions on a flat screen, think in three dimensions where as robotic stereo-scopic vision provides immersive 3D high definition operative images. And the need to look down into the binocular vision gives better hand eye co-ordination, making the surgeon believe that his hands are actually operating. Motion scaling is also possible, thus finer dissection is made easy and there is muting of the tremors. All this is done while the surgeon is comfortable seated, which is more ergonomic.

Disadvantages of using a robotic platform
The costs of installing a robotic system, its subsequent maintenance, and the price of disposable instruments are prohibitive. Also, the current robotic systems lack haptic feedback. Whereas most of the robots are designed to make the surgeon independent, the da Vinci cannot function without a table side assistant, who will change the instruments as well as provide intra-operative assistance, retraction and keeps the field clean by suction and irrigation.

Robotics in Urology

Almost all the abdominal urologic procedures can be performed robotically; adrenalectomy, simple, radical, partial nephrectomy, pyeloplasty, pyelolithotomy, ureterolithotomy, primary uretro-ureterostomy, retro-peritoneal lymphnode dissection, ureteric reimplantation, partial and radical cystectomy, simple and radical prostatectomy. Various surface procedures such as inguinal lymphnode dissection and vaso-vasostomy have also been preformed.

Outcomes of robotic surgery as compared to laparoscopy
To better assess the advantages of robotic surgery over conventional laparoscopy, several head to head comparison have been performed amongst the most commonly performed urologic surgeries.
Robotic vs laparoscopic radical prostatectomy

It is believed that the greatest benefit of robotic platform is seen for radical prostatectomy. Operating deep inside the pelvis with pure laparoscopic instruments is a tedious task, making the vesico-urethral anastomosis the most difficult part of laparoscopic radical prostatectomy (figure 10). Seven degrees of freedom provided by robotic instruments make this tedious task easy. However, this benefit was not reflected in direct comparative studies, which demonstrated similar oncologic outcomes, complication rates and hospital stay (2). A recently published meta-analysis with stringent inclusion criteria showed that although the oncologic outcomes are the same, there is a higher chance of recovery of erectile and continence function with robotic platform as compared to laparoscopic radical prostatectomy (3).

Robotic vs laparoscopic pyeloplasty:

A meta-analysis of robotic pyeloplasty showed that success rate of a primary procedure is 94-100%, whereas for a redo it is 85-100%. The conversion and re-intervention rates are low, 0-2% and it is likely to emerge as new standard of care wherever available. On comparing with laparoscopy, robotic pyeloplasty has shorter learning curve, offers better suturing and has shorter operative time by 27min (figure 11). Other outcomes such as complication rates, success rates and hospital stay were similar between the two (4).
Robotic vs laparoscopic partial nephrectomy

The most apparent benefit of robotic platform is faster and easier suturing, a crucial step in partial nephrectomy which determines warm ischemia time and thus functional recovery. This is reflected in comparative studies, which show similar operative times, blood loss, conversion rates, complication rates and hospital stay but the warm ischemia time was significantly shorter for robotic partial nephrectomy (5).
Robotic vs open radical cystectomy

A systematic review comparing robotic to open radical cystectomy found robotic cystectomy to be associated with longer operative time but significantly lower complication rates, less blood loss, more lymphnode yield and shorter hospital stay and similar positive surgical margin rates (6). Another important discussion against performing robotic radical cystectomy is the eventual need of exploratory laparotomy to make the urinary diversion. Although intracorporal ileal conduit and neobladder have been described, but these procedures are limited to specialized centers only.

The Future

Telerobotics

Telerobotic control is achieved by ISDN lines, internet connections or satellite links. The concept of having a surgeon in one country performing an operation in another via a computer-assisted link became reality in 2001, when a laparoscopic cholecystectomy was performed on a patient in Strasbourg by a surgeon in New York using the Zeus telerobotic system.

Haptic feedback

The NeuroAm robot underdevelopment in Canada is planned to be small enough to operate inside a MRI scanner gantry and have force feedback. Although currently being designed with neurosurgical intentions, this technology may eventually find its way to other fields.

Images
Figure 1: AESOP robotic arm

Figure 2: PACKY-RCM for percutaneous access to kidney

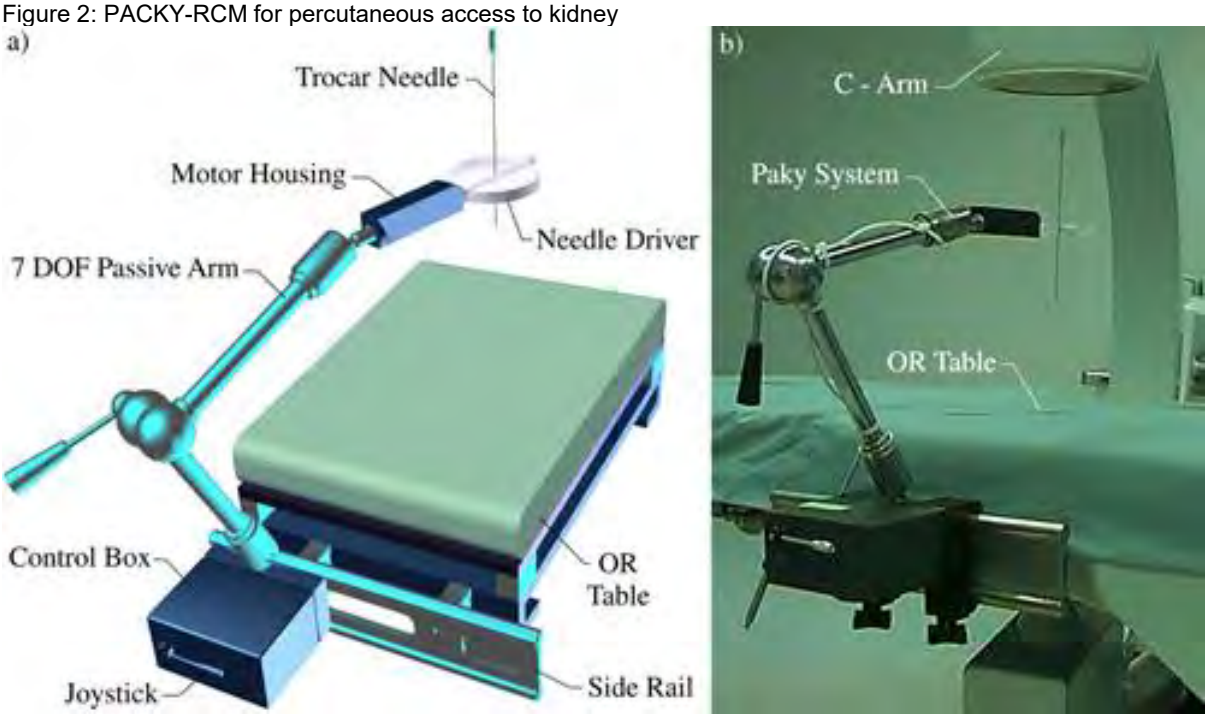


Figure 3: the AcuBot used to place needles for thermal ablation into renal parenchyma percutaneously

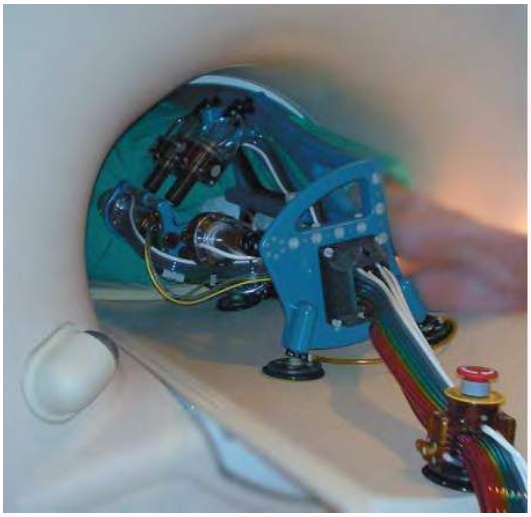


Figure 4: MrBot : to gain perineal prostatic access
Figure 5: da Vinci standard patient cart:

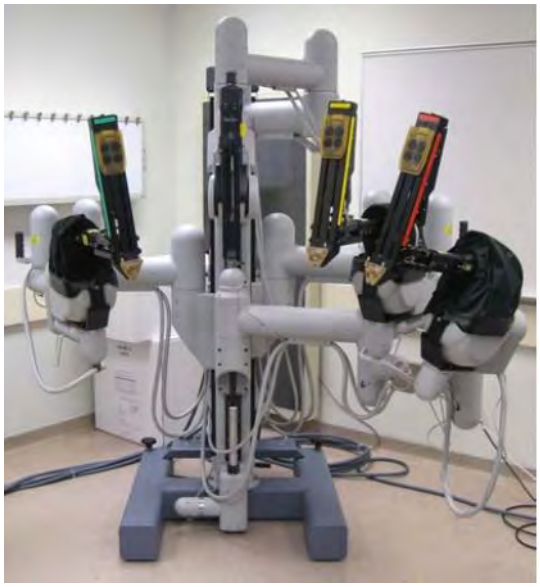


Figure 6: da Vinci S robotic system

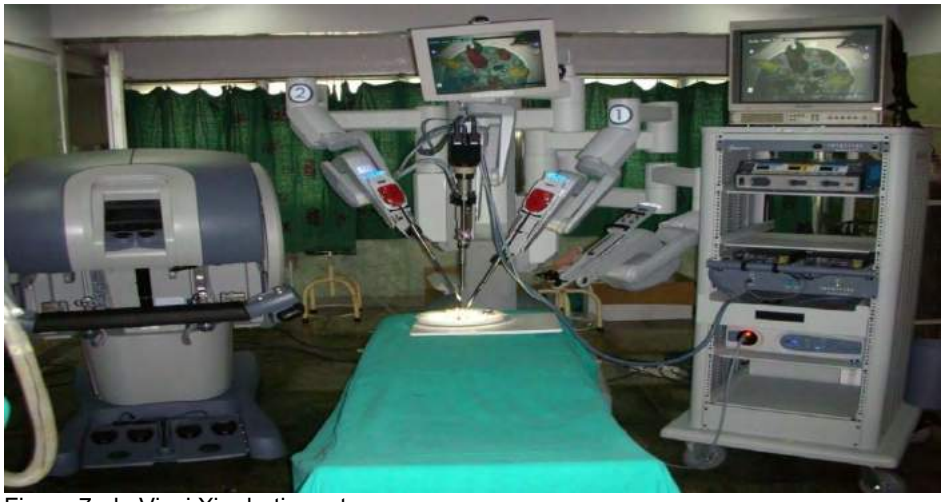


Figure 7: da Vinci Xi robotic system

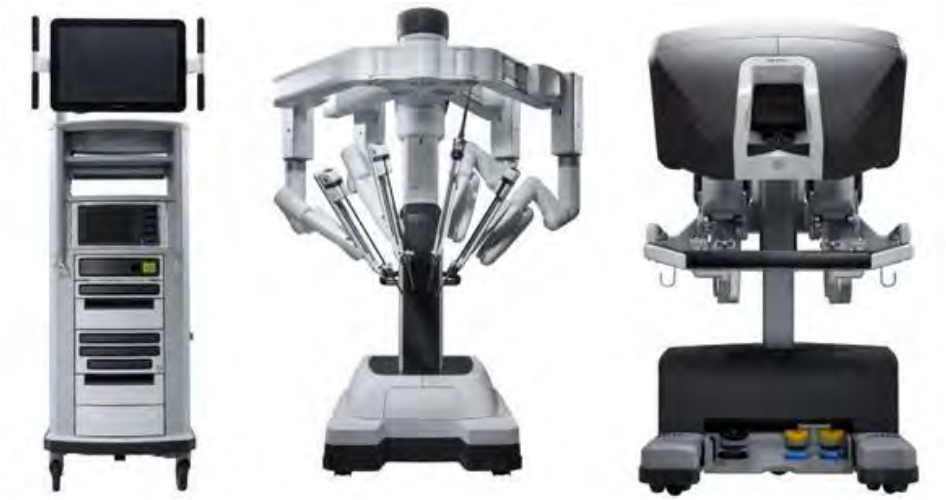


Figure 8: daVinci Xi – dual console

Figure 9: Angled and snake joint EndoWrist instruments

Figure 10: Intra-operative image of radical prostatectomy showing vesico-urethral anastomosis

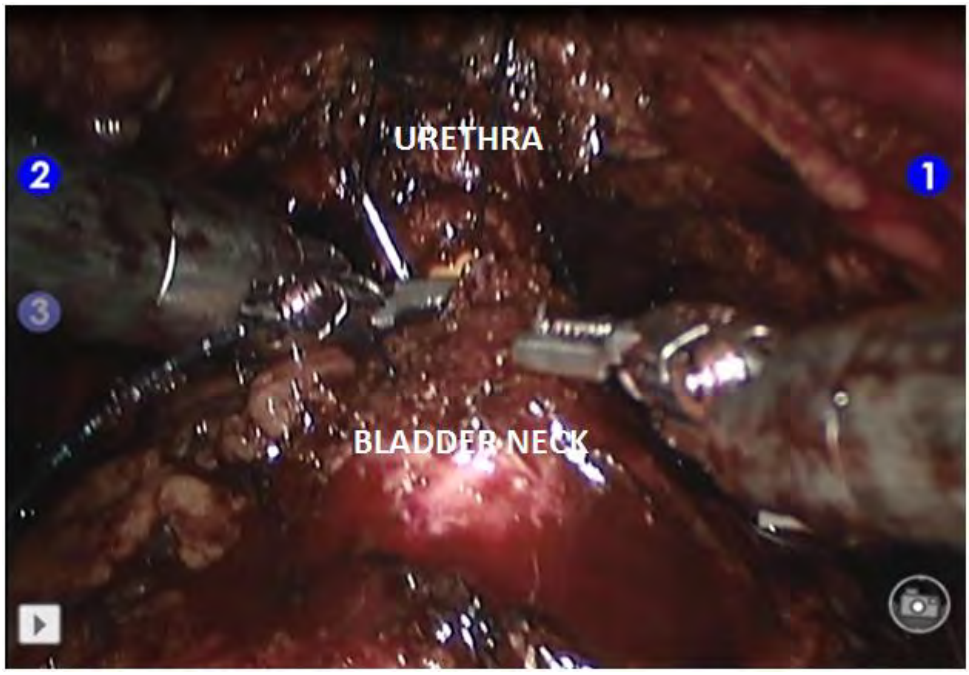
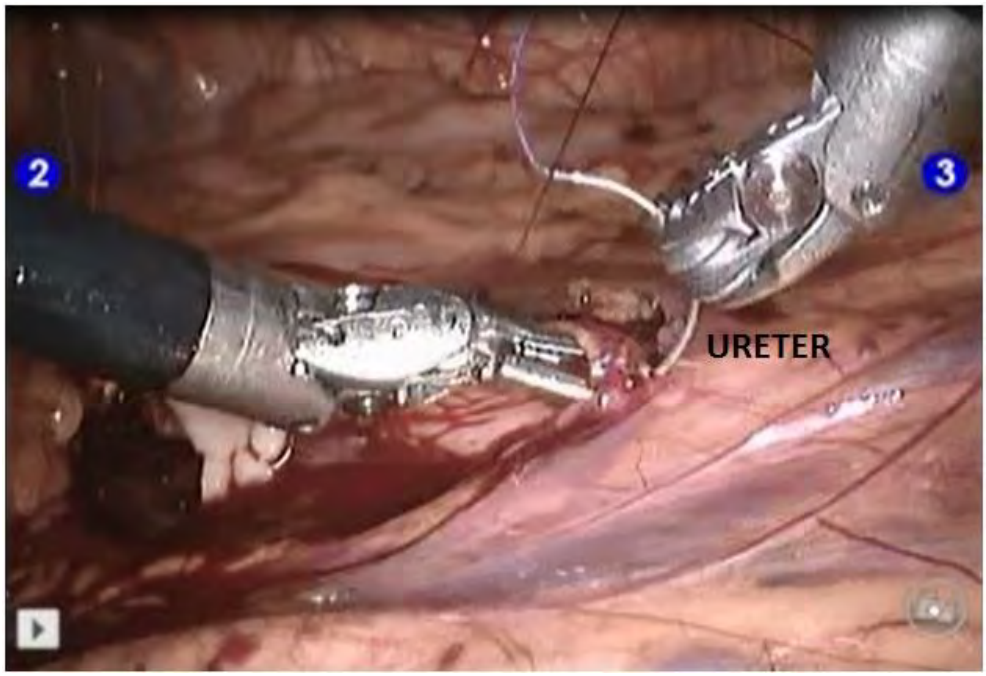


Figure 11: Intra-operative image of pyeloplasty showing taking apex stitch at spatulated ureter.



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Venous ulcers

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Venous ulcer or stasis ulcer accounts for 80% of the lower extremity ulceration [1]. Venous ulcers are difficult to treat owing to its chronicity and high recurrence rate , which ranges from54% to 78% [2].Studies have shown that an estimated 5% to 8% of the world population suffers from the venous disease and approximately 1% develops venous ulcers [3 4]. Venous ulcers most commonly occur in women & elderly persons [5 6 7 8]. Advancing age , obesity , previous leg injuries, deep venous thrombosis & phlebitis are the risk factors that have been described with venous ulceration [9]. Nonhealing ulcers can be complicated by cellulitis, osteomyelitis, & malignant transformation. Although the overall prevalence of venous ulcers are low but the refractory nature of these ulcers & complications associated with these ulcers increases the morbidity & mortality of the patients and adversely impact the quality of life [10 11] .

Pathophysiology

The pathophysiology of venous ulcer is not completely understood , however venous incompetence & associated venous hypertension are thought to be the primary predisposing factors for ulcer formation. Therefore it is imperative to know the venous anatomy of the lower limb to understand the overall effect of the venous incompetence and venous hypertension on the development of chronic venous insufficiency and venous ulceration. The venous system of the lower extremity comprises of three components: the superficial veins , perforator veins & deep veins . The deep veins lay within the muscle of the lower extremity , whereas the superficial vein lie above the fascia overlying the muscles. The perforators or communicating veins connects the superficial and the deep systems. The superficial veins are low pressure systems whereas the deep veins are high-pressure systems. All three venous system have one way valve , which only open towards the deep venous system and in normal circumstances, prevent reflux of blood .During ambulation, as the calf muscle contracts , the deep veins are compressed ,thus propelling blood proximally towards the heart. With brief rise in pressure , the valve of the all three system close preventing retrograde flow of blood [12 13 14 15 16] . As the calf muscle relaxes , the deep veins empty thus allowing a drop in pressure. The venous valve open during this phase, allowing the blood to flow from the superficial veins through the communicating veins to the deep venous system [17] . In patients with venous insufficiency, this series of events does not occur [17] .

Venous hypertension , a sustained elevation of ambulatory pressure, is the hallmark of venous disease and may be caused by an abnormal calf muscle pump. An abnormal calf muscle pump may occur due to incompetent veins or valves of the lower extremities , muscular dysfunction , limited mobility or combination of the three [18] .Vein incompetence may be acquired or congenital often due to absence or dysfunction of valves [19] . Contraction of the calf muscle ,specifically the gastronemicus and the soleus muscle empty the intramuscular deep veins and decrease the volume of venous blood present in the lower extremity [20] . Anatomically, the plantar venous plexus of the foot has a smaller vessel diameter than does the outflow tract of the posterior tibial deep veins, thus adding the cephalad flow of venous blood. Compression of the plantar plexus is assisted by ambulation thereby decreasing the strain on calf muscle pump. Venous ulcer may occur in some of these patient who lack the benefit of the calf muscle pump and the plantar plexus that facilitate the movement of blood back to the heart.

Erect ambulatory patients who lack proper compensation of the venous system develop venous pooling near the ankle. Increased venous pressure with concomitant reduced differential between the arteriolar and the venular side of the capillary bed may trap leukocytes in post capillary venules[21] . These leukocytes may activate and release proteolytic enzymes , which leads to the formation of free radicals which may lead to local tissue damage [21 22] . Activated leukocytes also can release various cytokines such as tumor necrosis factor(TNF) & Interleukin 1(IL 1).In addition to leukocyte activation, margination of white cells can act as diffusion barrier to oxygen and nutrients necessary for tissue survival [23] . Venous blood pooling in the lower limb increases the capillary intraluminal pressure leading to stretching of the interendothelial pores with subsequent increase in the capillary permeability and edema formation. Additionally macromolecules such as fibrinogen and alfa-macroglobulin may leak into the dermis through the dilated capillary pores [23] . Alpha-macroglobulin may bind growth factors such as TNF & transforming growth factor beta(TGFb),which are required for wound repair [24] . Entrapment of these growth factors may make them unavailable for the tissue repair. Fibrionogen leaking into the dermis leads to the formation and deposition of fibrin cuff around the dermal blood vessels, which also may act as an additional diffusion barrier to oxygen and nutrients

Recently, it also has been proposed that arterio-venous(AV) shunting may play a role in the pathogenesis of venous ulcers [20] .This theory is supported by presence of elevated oxygen content of the venous blood, premature venous filling, increased blood flow in the skin of legs on angiography,and decreased capillary density in leg skin in patients with venous insufficiency – possibly representing hypoperfusion of nutritive capillaries.

Clinical examination & Diagnosis

History

The patient's history provides important information necessary for the differentiation of the types of ulcers that develop in the lower extremity. The following symptoms are common to the most venous disorder & focused

question to elaborate these symptoms may provide the essential information for defining the etiology of ulcer formation.

- Aching
- Swelling
- Distended superficial veins
- Bleeding
- Skin discolouration
- Ulceration
- Restless leg syndrome
- History of past DVT
- History suggestive of Pelvic pathology
- Family history

Most of the patients usually describe an increase in symptoms with prolonged standing. They deny pain but acknowledge a more subtle dull ache or fatigue. Often these symptoms have been present for many years and have been attributed to age or other factors. The symptoms are typically less noticeable in the morning but get worse throughout the day are often exacerbated in women by menstrual cycle. Nighttime cramping and restless legs also may be due to venous disease and often are noticeable after a particular long or active day. Patients often experience itching in the lower leg which may be accompanied by stasis dermatitis or the other features of chronic venous insufficiency. Many of these symptoms are significantly or completely relieved with treatment of the superficial venous reflux.

Physical examination

A complete physical examination must always be performed . In addition attention should be directed towards the involved extremity's circumference, edema, Skin changes, color , temperature, pulse as well as the location, size and appearance of the ulcer.

Differential diagnosis of leg ulcer:

The differential diagnosis of leg ulcers are endless. Common causes of leg ulcers are as follows.

1) Vascular
   - Arterial
   - Venous
   - Lymphatic
2) Vasculitis
   - Periarteritisnodosa
   - Rheumatoid arthritis
   - Lupus erythematosus
   - Hypertension
   - Hematological – Sickle cell anemia, Thalassemia , Polycythemia vera
3) Metabolic disorders :
   - Diabetes mellitus
   - Pyoderma gangrenosum
4) Tumors
   - Squamous cell carcinoma
   - Mycosis fungoides
5) Miscellaneous
   - Drugs
   - Factitial

Arterial ulcers

Arterial occlusive disease is a frequent cause of lower extremity ulcerations. These are located on the distal end of the extremities. The ulcer appear as punched-out lesion. These ulcers are painful and the signs of chronic ischemia are present in the involved extremity.

Venous ulcers

On physical examination, venous ulcers are commonly irregular in shape and shallow. Granulation tissue and fibrin are often present in the ulcer base. These ulcers are commonly located above the medial malleolus Other findings include lower extremity varicosities; edema; venous dermatitis associated with hyperpigmentation , hemosiderosis or hemoglobin deposition in the skin; and lipodermatosclerosis associated with thickening and fibrosis of normal adipose tissue under skin. A clinical severity score based on the CEAP (clinical, etiology, anatomy, and pathophysiology) classification system can guide the assessment of chronic venous disorders. The highest CEAP severity score is applied to patients with ulcers that are active, chronic (greater than three months duration, and especially greater than 12 months duration), and large (larger than 6 cm in diameter) . Poor prognostic factors for venous ulcers include large size and prolonged duration .

Vasculitis ulcers

Ulcer formation secondary to vasculitis falls in broad category of diseases including polyarteritisnodusa, hypersensitivity angitis ,Wegeners granulomatosis & necrotizing vasculitis*. The important points in making the

diagnosis are the history, laboratory testing and a biopsy to document the presence of vasculitis.These ulcer appear primarily on the lower extremity from the midcalf to the dorsum of the foot.These lesion also have a punched-out appearance with gangrenous central tissue. They can be unilateral or bilateral and are frequently painful.

Hematologic ulcers

Sickle cell anemia : Ulceration occurs in approximately 75% of patients with sickle cell anemia. The pathophysiology of this process involves a lowered oxygen tension and pH in areas of stasis in the distal portion of lower extremities. The shape is usually round or oval and they are very refractory to healing.
Thalassemia : The presence of ulceration with thalassemia is not common. The mechanism for tissue damage is probably inadequate tissue oxygenation.These ulcer appear similar to those of patients with sickle cell anemia.
Polycythemia Vera : Ulcer formation in this group of patients most likely has a dual origin. Either the increased viscosity of the blood results in venous thrombosis ,valvular incompetence and venous ulceration,or local hypoxia occurs at the capillary level and causes tissue damage.

Metabolic Leg ulcers

Diabetes Mellitus
The etiology of ulcer formation in patient with diabetes is multifactorial .Microangiopathy , sensory neuropathy & infections predisposes these patients to ulcer formation. There are a number of rare cuases of ulcers in the lower extremities of diabetes , including necrobiosis lipoidicadiabeticorum, diabetic dermopathy ,and bullae diabeticorum.

Pyoderma Gangrenosum
It presents as an acute necrotizing ulcer predominantly on the lower extremities. Pyoderma gangrenosum frequently produces an irregular ulcer with a necrotic base. This skin lesion begin as a deep-seated painful nodule or as a superficial hemorrhagic pustule either de novo or after minimal trauma. This lesion was once pathognomonic for ulcerative colitis but has been observed in many other conditions.

Tumors causing ulcers
Squamous cell carcinoma : These lesions occurs most commonly on sunexposed areas of the face neck and extremities. The ulcers are shallow with a raised and everted border and never heals. When a chronic leg ulcers of any etiology has been present for a long period and not healing,squamous cell carcinoma should be considered.

Mycosis Fungoides : This is the most common type of lymphoma affecting the skin.There are three stages of presentation: patch,plaque and tumor. Ulceration occurs secondary to necrosis of the tumor.

Miscellaneous causes of leg ulcer
Medications : Bromide and iodide compound can produce skin lesion.These ulcers usually occur on the anterior surface of the tibia and are extremely painful.

Radiation : Ionizing radiation to the lower extremities in doses above 10 Gy may cause acute dermatitis which can ulcerate 6 to 8 weeks following the acute reaction.

Decubitus ulcers: They are seen frequently in bedridden patients secondary to neurologic causes or general debilitation.The lesion occur from prolonged pressure to a small surface area, on the lower extremity primarily the malleoli and heels.

Diagnostic studies
The clinical diagnosis may be supported by further diagnostic testing as indicted, specially if other diagnoses are being considered in differential.

Vascular studies
The initial evaluation of a venous ulcer should rule out concurrent arterial disease. Using a standard a sphygmomanometer , the clinician can determine an ankle to brachial pressure index (ABPI).If the patient has an ABPI between 0.5 to 0.8 ,it indicates that there may be concurrent arterial disease and venous disease. If the ABPI is less than 0.5,the ulcer is more likely to be arterial in origin [26].

Duplex Ultrasound
It is often the initial choice for patient evaluation because it is widely available and easy to use. With this technique one can delineate vascular architecture , site of venous reflux and status of deep venous system. For venous evaluation patient is examined in the standing position , compression of the calf by manual pressure produces a systolic flow of blood in the anterograde direction. After the release of the calf muscle, a patient with valvular incompetence will demonstrate retrograde flow in the vein being evaluated.*Despite the widespread use of this technique , considerable skill is necessary for a thorough evaluation of the deep veins.Functional testing such as Plethysmography can be a complementary method alongside ultrasound to evaluate the calf muscle dysfunction [27 28].

Invasive Techniques

The gold standard for defining the patient's venous anatomy and demonstrating reflux is venography. In ascending venography , the patient is upright while a tourniquet is applied above or below the knee. Contrast dye is introduced,and if the dye is seen distal to the tourniquet , the patient is assumed to have venous reflux. In descending venography ,the patient is placed in supine position and the contrast is injected into the common femoral vein. The patient is then tilted downward , and the level to which the contrast dye leaks is observed.A leak below the level of knee considered significant for reflux.

A comparison between various invasive and noninvasive techniques were performed by Mantoni's group. They found continuous wave Doppler and ambulatory strain guage plethysmography are of little value in the work up of patients with deep venous insufficiency.They suggested colour duplex ultrasound should be used as a first line diagnostic tool , with ascending phlebography used only when the triple ultrasound is inconclusive [29].

Radiological studies

Magnetic resonance imaging is becoming more popular as a diagnostic tool in the evaluation of these patients. Magnetic resonance venography can show occluded vessels and alteration of blood flow, in addition they may display subcutaneous fibrosis and infiltration of extrafascial spaces [30].

Biopsy & Tissue culture

These investigations are rarely warranted in the cases of classical venous ulcer. However in certain cases biopsy can be performed to rule out malignant transformation. Although tissue culture has been considered as gold standard in the assessment of wound infection, recent studies have shown a culture swab to be equivalent in the initial evaluation of bacterial wound infection[31].

Therapy

General principles

The core principles for management of venous ulcerations are

1) Clean wound base
2) Compression
3) Surgical interventions/procedures
4) Medications

The clean ulcer

The aim of wound care is to provide an optimum environment for healing. A clean ulcer with healthy appearing granulation tissue at its base is considered as the best environment for healing. It may be achieved by applying the following methods

- Debridement :
- Treating infection:
- Wound care : Dressings,Topical agents

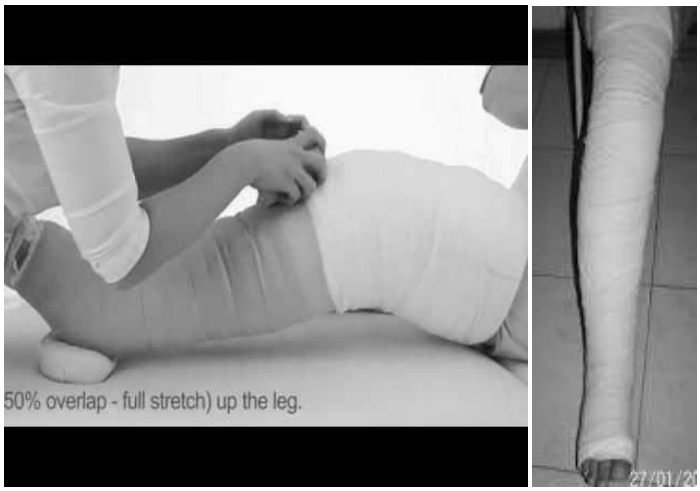
Compression

Compression is undoubtedly one of the most important factors in the healing of venous ulcer [32].Compression not only supplements the pumping action of the calf muscle but also increases tissue pressure to reverse the gradient between the capillaries and intravascular space , thus leading to reduction in tissue edema [33].It is important to rule out concomitant arterial disease before initiating compression therapy.

Compression therapy should be performed in two consecutive phases. The first treatment phase is decompression phase, which should take place at the time of active leg ulcer. The goal of this phase to reduce edema and promote wound healing. For decompression phase three types of compression may be utilized : 1) inelastic compression bandage ,2) multi-layered elastic bandage, 3) mechanical compression using intermittent pneumatic compression boots [34].

Inelastic compression bandages provide limited pressure at rest, but high pressure with activity. The prototype of inelastic bandage is the Unna boot, a moist, zinc oxide impregnated paste bandage that hardens to an inelastic form. Unna boots require frequent reapplication because they do not accommodate for changes in leg volume as edema subsides and they have limited absorptive capacity for highly exudative wounds. The multi-layered elastic bandage system is comprised of a cotton or wool layer for absorption of exudates , one or two elastic wraps, and self-adherent wrap that maintains the bandage in place. Multi-layered elastic bandage exert continuous pressure (40-45 mmHg at the ankle) at rest and with activity. They require less frequent reapplication than inelastic bandages because they have the ability to conform to the lower extremity better and have superior absorptive capacity for highly exudative wounds. The disadvantage to multi-layered inelastic compression bandage is that they require a certain degree of expertise for adequate application. Mechanical compression is reserved for patient who are unable to ambulate and for those who fail to respond to standard compression therapy.

Pictures of Unna boot



Triple layer compression bandage

For the second phase or maintenance phase, which occurs after wound healing, elastic graduated compression stockings are used to control venous HTN and prevent ulcer recurrence.
Surgical intervention/procedure

The main objective of surgical treatment in these patients are to achieve ablation of the hydrostatic forces of axial reflux (i.e disconnection of SFJ , SPJ & stripping) and removal of hydrodynamic forces of perforator venous reflux. Various studies have shown that no more than 15% of patient have isolated deep venous reflux , whereas 53% of patients have isolated superficial reflux[35].Patients with reflux in the superficial and perforating veins are more amenable to surgical treatment and may actually have clinical cure after surgery. The surgical intervention may help to reduce venous reflux, hasten healing, and prevent ulcer recurrence. Venous insufficiency may be taken care of surgically by saphenous vein ablation, subfascial endoscopic surgery for the interruption of the perforating veins; stenting for treatment of iliac vein obstruction and removal of incompetent superficial veins with phlebectomy, stripping, sclerotherapy, or laser therapy[36 37 38]. Surgical management has been shown to achieve an ulcer healing rate of 88 percent, with only a 13 percent recurrence rate over 10 months [39]. There should be an early evaluation for possible surgical intervention however the superiority of surgery over medical management has never been proved [40].By repairing or eliminating or repairing venous incompetence one can reduce the risk of recurrent venous ulceration [41]. Subfascial endoscopic perforator vein surgery has been described for treatment of venous ulceration with proven incompetent perforators [42].

Available surgical options are:
A. Saphenofemoral Junction Ligation

Saphenofemoral junction ligation alone, sometimes referred to as a —Trendelenburg‘s procedure, is associated with a high rate of recurrence of varices. Recent research has shown that it is necessary to remove the saphenous vein to ensure that as much venous reflux as possible is eliminated.

A few sound principles:

1. In a patient of normal build the SFJ lies directly beneath the groin crease; in the obese it lies above. An incision made below the crease is likely to be too low.

2. Do not divide any vein until the SFJ has been unequivocally identified.

3. Beware of the superficial external pudendal artery that usually passes between GSV and CFV but passes superficial to the GSV in 5% of cases.

4. Follow and divide all tributaries (Superficial circumflex iliac, superficial inferior epigastric, superficial external pudendal) beyond secondary branch points. Failure to do so leaves a network of superficial veins connecting the

veins of the thigh with those of the perineum, the lower abdominal wall and the iliac region. These cross-groin connections are a frequent cause of recurrence.

5. Ligate the GSV deep to all tributaries flush with the CFV.

6. Divide the deep external pudendal vein as it comes off the CFV

7. Retract the lower margin of the wound to identify and ligate the posteromedial thigh branch that often joints the GSV high in the thigh. Failure to do so increases the risk of haematoma formation after stripping above the bandage, as well as medial thigh recurrence. A high anterolateral branch should be dealt with similarly.

B. Stripping

Several randomized trials have clearly shown that routinely stripping the GSV reduces the risk of recurrence developing through the Hunterian perforating veins and to remove a vein in the thigh which is difficult to treat later by sclerotherapy. Stripping markedly reduces the risk of recurrence by:

1. Disconnecting the thigh perforators and saphenous tributaries
2. Preventing any neovascularisation arising from the saphenous stump reconnecting with the GSV.

Perhaps the most common problem with conventional stripping of the GSV has been that of saphenous nerve damage. Stripping the vein either to or from the ankle has long been recognized as carrying a significant risk of this unpleasant complication. It is interesting to speculate on the mechanism of saphenous nerve damage when the vein has been stripped only as far as the knee. Trauma within the femoral triangle is one possibility. Inadvertent passage of the stripper out of the LSV and through the fascia lata is another. For this reason, and because the main GSV below this level is rarely varicose, many now recommend stripping to the knee. The GSV should be stripped to approximately one hand‘s breadth below the knee. At this level the below knee perforator (Boyd) would have been crossed but the saphenous nerve would not yet have joined the vein. Also, important perforating veins below the knee are a part of the posterior arch circulation and not the great saphenous vein.

Alternatives to stripping
New venous surgical techniques have been developed in an effort to reduce the number and size of lower-extremity incisions and hematomas, to eliminate postoperative discoloration, and to reduce the recuperation time.

Radio frequency (RF) ablation*:* The intervention employs radiofrequency (RF) energy mediated heating of the vein wall to destroy the intima and denature collagen in the media with resulting fibrous occlusion of the vein.24 the Closure® system (VNUS Medical Technologies Inc., San Jose, CA) consists of a bipolar heat generator and collapsible catheter electrodes suitable for use in veins ranging from 2 to 12 mm in diameter. The procedure is usually performed under conscious sedation and local anesthesia in an outpatient setting. The catheter is preferably introduced into the saphenous vein at the knee percutneously under ultrasound (US) guidance or through a small incision and direct exposure of the vein. The position of the catheter at the saphenofemoral junction is confirmed by US. Local tumescent anesthetic is instilled in the subcutaneous tissues superficial to the vein under US guidance. The vein wall temperature is allowed to equilibrate at 85°Cafter turning on the circuit and graduated withdrawal of the catheter is performed at a rate of 3 cm/min. The heating is controlled by monitoring temperature and impedance of the vein wall via a feedback system. Veins up to 12 mm in diameter are treated. The mechanics of the surgical procedure are relatively straight forward with a few caveats. The treated vein should be relatively straight, free of severe tortuosity or thrombus and without aneurysm. Contraindications include a post phlebitic vein that cannot be accessed, a mega saphenous vein (>12 mm), and significant dilation of the proximal saphenous vein with an aneurysmal SFJ.

Endovenous laser therapy: Endovenous laser therapy (EVLT) is similar to RF ablation, but laser energy is used for ablation of the saphenous vein.25 The procedure is faster and easier to perform than RF ablation and there is no size limitation of the saphenous vein that can be treated. Both the 810-nm and the 940-nm diode lasers are effective in inducing thrombotic vessel occlusion. Laser-induced indirect local heat injury of the inner vein wall by steam bubbles originating from boiling blood is proposed as the pathophysiological mechanism of action of EVLT. This causes collagen contraction and endothelial damage. The result is thickening of the vein wall and contraction or thrombosis of the lumen.

The use of diode laser energy to ablate the saphenous vein is a method that obviates the need for general anaesthesia and is associated with less pain than traditional surgical stripping of the great saphenous vein. This procedure can be performed in an office based setting using local anaesthesia following preoperative assessment with duplex ultrasound.

Foam Sclerotherapy: An increasing number of authors have recently reported successful injection of incompetent GSV with 3% polidocanol in the form of foam.26 The foam is generated by mixing liquid and air in a standardized procedure of forward and backward movements within a close double-syringe system. The GSV is punctured directly under US guidance, and the foam injected. Results are verified by serial post treatment duplex examinations

C. Saphenopopliteal Ligation

Some surgeons advocate routine stripping of the short saphenous vein should be disconnected and never stripped. The short saphenous vein operation should be carried out first, if a long saphenous vein operation is to be performed under the same anaesthetic.

Failure to mark the SPJ preoperatively will lead to a misplaced incision in a significant number of cases that will necessitate further blind incisions or abandonment of the procedure. Clinical examination and hand held Doppler are not reliable. Insist on a duplex ultrasound.

D. Ligation of the Lower Leg Perforating Veins

Surgery for these veins is usually required in patients with lipodermatosclerosis or ulceration. The presence of incompetent perforators in patients with advanced CVI (clinical classes 4 to 6) is an indication for surgical treatment in a fit patient. Whereas open perforator ligation is done only in those with healed ulceration, a clean, granulating open ulcer is not a contraindication for subfascial endoscopic perforator vein surgery (SEPS).

Subfascial ligation of the medial communicating veins (Linton's operation): In view of considerable wound complications associated with Linton's radical operation of subfascial ligation, which included long medial, anterolateral, and posterolateral calf incisions, it was soon abandoned and he advocated only a long medial incision from the ankle to the knee to interrupt all medial and posterior perforating veins53 A long vertical incision is made through the skin and subcutaneous fat down to the deep fascia, approximately 1 cm behind the subcutaneous posterior border of the tibia. Any subcutaneous veins that are divided are ligated. The deep fascia is incised in the same line as the skin incision and is held open gently with a self-retaining retractor. As the subfascial space is opened, leashes of communicating vessels can be seen passing from the posterior tibial vessels between the muscles to the undersurface of the deep fascia. These vessels are isolated, divided and ligated. When all the communicating veins have been ligated, the deep fascia and skin are carefully approximately. The disadvantage of Linton procedure is that the lateral perforating veins can not be taken care by this procedure.

Extrafascial ligation of perforators (Cockett's procedure): This operation is not commonly employed today. The aim of surgery is to clear all the extrafascial enlarged veins and to divide perforating veins. However, the perforating veins may be difficult to accurately locate in this plane and the dissection tends to be traumatic because of adherence of subcutaneous fat and connective tissue to the fascia due venous ulcer and lipodermatosclerosis and associated with a higher incidence of skin necrosis.

Posterior approach (Robs procedure): This is done if the perforators on the lateral side are also to be ligated. The incision is a posterior subfascial one and the perforators on both the sides are ligated and divided. This procedure offers advantage in the fact that the incision is away from the areas of ulceration and thus results in good healing.

Subfascial endoscopic perforator surgery (SEPS): The major drawback of open procedure was a high incidence of wound complications. Edwards in 1976 designed a device called the phlebotome to ablate the incompetent perforators from sites remote from the diseased skin. The phlebotome is inserted through a medial incision just distal to the knee, deep to the fascia, and advanced to the level of the medial malleolus. Resistance is felt as perforators are engaged and subsequently disrupted with the leading edge. Hauer28 introduced the endoscopic technique for division of perforating veins in 1985. His work was soon followed by other investigators in Europe, who used different types of endoscopes or mediastinoscopes to perform the surgery with direct vision through a single incision made in the proximal calf.

The use of laparoscopic instruments was described by O'Donnell, who infused saline beneath the fascia to facilitate the visualization and dissection of the subfascial plane. In Australia, Conrad29 began using carbon dioxide insufflation in 1993 and published a report on his first seven patients in 1994. This technique, the 'two port' technique, employs one port for the camera and a separate port for instrumentation, thereby making it easier to work in the limited subfascial space. All perforators encountered are divided either with the harmonic scalpel or electrocautery or sharply between clips. The surgeons apply metal clips to the perforating vein before the transection or simply use electrocautery to cauterize the veins. However, the use of metal clip in a potentially infected wound with chronic unhealthy skin and ulcer may not be desirable. The repeated movement in and out of the operative field to reload metal clips can be time consuming when multiple perforators are found. On the other hand, the application of electrocautery in the limited subfascial space may cause inadvertent damage to the surrounding soft tissue by the electrical currents. The production of smoke during dissection by electrocautery may obscure the operative field, and intermittent evacuation of smoke is needed. The ultrasonic scalpel uses precise ultrasonic vibration to coagulate and transect the vessels in a smoke-free environment.30,31 It has been widely used in different areas, both in laparoscopic and open surgery. The scalpel vibrates at a rate of 55000times/sec. This mechanical action results in protein denaturation and the formation of coagulum, which seals off blood vessels. The same action causes vaporization of cells resulting tissue fragmentation. This dual action makes dissection quicker resulting in decreased operating time.

Complications

1. Major venous damage: Deep veins can be damaged during varicose veins surgery through attempts to control bleeding and misidentification of anatomy. Complete division of the common femoral vein is estimated to occur once in every 10,000 varicose veins operations.

2. Arterial damage.

3. Nerve damage. Popliteal dissection, stripping and distal avulsions may result in damage to the divisions of the sciatic nerve (usually the common peroneal nerve), saphenous and sural nerve.

4. Haematoma. This is the commonest cause of discomfort after varicose veins and can be minimized by operating the patient in the head-down position, careful hemostasis, and evacuation of all clots from the stripper tunnel and use of a tourniquet.

5. Venous thromboembolism.

6. Necrosis of the wound edges: this is the most common and troublesome complication of both the subfascial and extrafascial operations. It appears to occur more frequently after the extrafascial operation

E. Elimination *of Residual Varicosities*

Sclerotherapy: The aim of injection sclerotherapy is to place a small volume of sclerosant in the lumen of a vein empty of blood, and then appose the walls of that vein with appropriate compression. The vein fibroses and gets closed without the formation of clot. The sclerosant must remain localized within the segment of vein to be treated. The vein must be kept empty of blood both during and after the injection. Patients should be mobilized immediately afterwards and be encouraged to walk on a daily basis. This measure allows symptoms and signs of allergic reactions to appear and be treated. The comfort of elastic compression can be evaluated, and the deep venous circulation is stimulated and any sclerosant that has entered from the superficial injection is flushed. Immobility is a relative contraindication to sclerotherapy.

Indications of sclerotherapy:

1. Telangiectasia
2. Reticular varicosities and reticular veins
3. Isolated varicosities
4. Below knee varicosities
5. Recurrent varicosities

Contraindications:

1. Presence of arterial occlusive disease
2. Patient immobility
3. Hypersensitivity to the drug
4. Acute thrombophlebitis
5. Huge varicosities with large communications to deep veins

Technique:

1. The patient is examined standing and varices are marked with an indelible pen.
2. A number of 2ml syringes fitted with 26 gauge needles are filled with 0.5 ml of sclerosant. Maximum volume that can be given during one treatment is around 10 ml of sclerosant.
3. The skin is cleaned and venepunctures are made at 5 cm intervals along the course of each vein.
4. The patient lies down, veins are transfixed and the needle is slowly withdrawn. As soon as the blood appears in the vein, the vein is emptied and the sclerosant is injected into the ‗empty' vein.
5. Cotton wool balls are placed and fixed with micropore tape.
6. When all injections have been completed, crepe bandages are applied and the patient is encouraged to walk.
7. Compression bandages are worn for 3 weeks. After this period the legs are carefully inspected and untreated varices or failed injection sites are re-injected.

Complications

The complications of injection sclerotherapy include:

1. Anaphylaxis.
2. Allergic reactions. Typically symptoms include urticaria, peri-orbital and oral swelling, bronchospasm and migraine.
3. Ulceration. Ulceration follows extravascular injection. Commonly it is due to arterial occlusion caused by sclerosant reaching a terminal arteriole. Another cause is reactive vasospasm because of a large volume of injection. Treatment is symptomatic. Unless the ulcer is obviously ‗infected' (rare) antibiotics have no role.
4. Arterial injection. This is a serious complication that is accompanied by severe pain distal to the injection site. The most vulnerable artery appears to be the posterior tibial artery at the ankle. Treatment includes analgesia, cooling of the foot, and infusion of heparin and dextran.
5. Pigmentation. Pigmentation is due to the deposition of haemosiderin, often following superficial thrombophlebitis. Most commonly seen in those treated with sodium tetradecylsulphate and hypertonic saline and least common with polidocanol.

6. Superficial thrombophlebitis. This occurs when clot remains in the lumen of the sclerosed vein and is largely due to inadequate compression. Localisedhaematoma is particularly painful and may be eased by aspiration with a needle or scalpel under local anaesthesia.
7. Deep venous thrombosis. The risk is reduced by careful patient selection and by advising patients to walk immediately after injection treatment and thereafter on a regular basis each day.
8. Nerve damage. Can occur due to approximate injection and/or pressure from bandaging.
9. Telangiectatic matting: or neoangiogenesis is the new appearance of red telangiectasias in a site of prior sclerotherapy. It is believed to be a complex process in which new vessels grow in response to endothelial growth factors or platelet-derived growth factors. Prevention is best achieved through use of dilute solutions and in small volume

Skin Grafts and Flaps

Skin grafts and flaps have been used for the management of chronic ulcerations. They should only be applied to a clean, uninfected ulceration with an adequate vascular supply. It has been suggested that the benefit of skin grafts are the transplanted cells, which can secrete growth factors and other products that might enhance healing. Full-thickness or split-thickness grafts can be used. Allogeneic (cultured) keratinocytes also may be used but can be expensive. There is increasing interest in tissue-engineered skin. Graft skin (Apligraf) is a bilayered skin equivalent that includes dermal and epidermal components and is manufactured by harvesting neonatal foreskins and extracting both keratinocytes and fibroblasts that are then cultured separately to create the epidermal and dermal components. Graftskin has been approved by the Food and Drug Administration (FDA) for use in diabetic neuropathic ulcerations and venous ulcerations. Dermagraft is comprised of human fibroblasts on a bioabsorbable scaffold; studies indicate that this product also may be useful for venous ulcerations.

Prevention of recurrence

The cornerstone of prevention of recurrence of venous ulceration is compression [38].A Cochrane review cited circumstantial evidence for the benefit of compression as a whole ,and referred to evidence that high compression is superior to moderate compression for the prevention of recurrence. Patient education is important in the prevention of recurrences as well.

Oral agents for the treatment of venous ulcers

Pentoxifylline is xanthine derivative that is thought to treat occlusive disease by decreasing blood viscosity with approval by the FDA for the treatment of claudication [39].In a systemic review of clinical trials , it has been found to be helpful in treating venous ulcers and has been recommended as an adjunctive treatment [40].

Zinc was popularized as a topical treatment for leg ulcers during the past century , and one study found it helpful for arterial and venous ulcers [41].Although it might have a mild antimicrobial effect , there is no evidence that zinc can improve wound healing [41].It is argued that although Unna boots(made with zinc paste) are used in the treatment of venous ulcers , they may be effective because of compressive effect and not because of the composition of the plaster [42].A metaanalysis did not find sufficient evidence that oral zinc sulfate could improve the wound healing of venous ulcers [43].

Diuretic treatment of peripheral edema caused by CVI is a temporizing measure that does not address the true physiological problem [44].In the treatment of venous ulcers, however they may occasionally found to be useful to acutely decrease the volume of leg edema.

Oral micronized purified flavonoid fraction modulates leukocytes adhesion and prevent endothelial damage and it may also promote healing of venous ulcer [45].
Aspirin & Iloprost are also used as an adjunct to compression therapy, however there are insufficient data to recommend their routine use.

Adjunctive management/ Advanced / Investigational Techniques

Several supplemental techniques have tried or are under investigation. The topical application of Simulium vittatum erythema protein extracted from black flies may locally increase blood flow to aid in wound healing[46].Topical autologous platelets have no significant adjuvant effect on healing of chronic venous ulcers [47] [48]. Platelet derived growth factors , however have become popular in wound care centre,and have been shown to be helpful in diabetic [49],neuropathic[50],decubitus[51]ulcers. However the role of PGDF in chronic venous ulcer is inconclusive [52].Recombinant PDGF.BB (Becaplermin) has been approved by the FDA for use in diabetic foot ulcers.* and a recombinant GCSF product (Filgastrim) is proven to be effective as a subcutaneous injection for the treatment of infected diabetic foot ulcers.*At this time,none of these treatments have been comprehensively studied for the treatment of venous ulcers.
Further clinical studies are needed to elucidate the role growth factors may play in venous ulcers.*

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Clinical approach and rationale for investogations in a patient with thyroid swelling

Deepak Ghuliani, Ankit Jain

Any enlargement of thyroid gland is called goitre. Thyroid enlargement may be due to a solitary nodule or enlargement of the entire gland, which may be diffuse or multinodular. A normal thyroid gland is not palpable. Therefore any abnormality in form of a diffuse swelling or nodular makes thyroid gland palpable. Goitres can be classified as:

A) Simple/Non toxic goitre:
   1. Diffuse
   2. Multinodular
   3. Solitary thyroid Nodule

B) Toxic goitre:
   1. Diffuse Toxic Goitre
   2. Toxic Multinodular Goitre
   3. Toxic nodule

C) Neoplastic:
   1. Benign
   2. Malignant

D) Inflammatory:
   1. Autoimmune like hashimoto's thyroiditis
   2. Granulmatous like De Quervain's thyroiditis
   3. Fibrosing like riedel's thyroiditis
   4. Infective

A generalised enlarged thyroid swelling is labelled as a diffuse goitre while the term Multinodular goitre(MNG) refers to a diffuse enlargement of thyroid gland with multiple nodules. Solitary thyroid nodules(STN) is presence of a single discrete nodule is in thyroid gland. It may be actually a single isolated nodule in the thyroid gland or may be a dominant nodule of a multinodular goitre where other nodules are detected on Ultrasonography.
A patient with thyroid swelling could present with symptoms and signs of hyperthyroidism when it is called toxic goitre or patient could be euthyroid when it is labelled as simple goitre. Some patients may also present with goitrous hypothyroidism.

DIFFUSE GOITRE
Diffuse goitre means generalised enlarged thyroid gland with no nodules. It could be toxic, euthyroid or hypothyroid. Various causes are:

1. **Physiological Goitre**: Diffuse enlargement of the thyroid gland at puberty or in women during pregnancy in response to increased metabolic demands is labelled as physiological goitre. These goitres are simple as they are not associated with hypo or hyperfunctioning of the thyroid gland.
2. **Grave's disease:** It is an autoimmune disease with peak incidence between 40-60yrs and female to male preponderance by 5:1(Schwartz). It is characterized by thyrotoxicosis, diffuse goitre and exytrathyroidal conditions like ophthalmopathy, dermopathy, thyroid acropachy and gynaecomastia . In this autoimmune disease, antibodies are formed against TSH-R which causes chronic thyroid stimulation and thyrotoxicosis. Overexpression of TSH-R also occurs in retrobulbar tissue and muscles of eye causing cell infiltration with deposition of glycosaminoglycans leading to opthalmopathy.
3. **Thyroiditis:** It could be acute, subacute or chronic.

1. Chronic lymphocytic type is also called Hashimoto's thyroiditis which is the most common type of thyroiditis and the most common cause of Goitrous hypothyroidism. It is commonly seen in middle aged female(M:F::1:10-20). In this auto immune disease antibodies are formed against TPO(95%), Tg(60%) and TSH-R(60%). This leads to destruction of thyrocytes. Destruction of thyrocytes leads to release of stored thyroid hormones initially leading to transient thyrotoxicosis which eventually is followed by hypothyroidism.
2. Acute thyroiditis is bacterial infection of thyroid which is more common in children. Preceeding history of URI/otitis media is present.
3. Subacute thyroiditis is a self limiting viral or post viral contition which produces destruction of thyrocytes followed by slow recovery. Therefore patient passes through four stages: thyrotoxicosis - euthyroid - hypothyroid and then finally a slow recovery to euthyroid status.

C. Iodine deficiency
D. Goitrogens
E. Dyshormonogenesis

In these conditions goitre is regarded as the adaptive response of the thyroid follicle cells to factors that impair the thyroid hormone synthesis

Colloid goitre is a late stage of diffuse hyperplasia when all acini are distended with colloid which has not been released because the stimulation of TSH is dropped off.

Multi Nodular Goitre
Multinodular goitre(MNG) is a diffuse enlargement of thyroid gland with multiple nodules. It is formed by continuous stimulation of thyroid follicles and passes through different stages. The natural history of MNG is characterised by thyroid enlargement followed by nodule formation which in many cases progresses to nodular autonomy.

1. Persistent growth stimulation causes diffuse goitre with active follicles and uniform iodine intake. This diffuse hyperplasia is reversible with treatment.
2. With fluctuating stimulation, some follicles become inactive and some remain active.
3. Active lobules become more vascular which ultimately leads to haemorrhage and central necrosis.
4. Necrotic lobules coalesce to form nodules.

A. Simple MNG: In this patient is euthyroid or hypothyroid. Such patients have 5-10% risk of malignancy.
B. Toxic MNG: Approximately 22% of patients with MNG may develop subclinical hyperthyroidism and in more advanced stages overt hyperthyroidism develops . A simple MNG may turn toxic by either hyper functioning of inter nodular tissue or due to autonomous TSH non-dependent Nodules. This autonomy is more frequently seen in Iodine deficient areas and occurs due to presence of activating TSH receptor mutations seen after years of thyroid hyperplasia. Risk of malignancy in these patients is low. Such patients have history of long standing neck swelling followed by hyperthyroidism and therefore commonly seen in middle aged to elderly. Hyperthyroidism is sometimes precipitated by iodine containing drugs like contrast agents and Amiodarone (Jod basedow phenomenon). This is also called secondary thyrotoxicosis.

1º Thyrotoxicosis(Grave's)	**2º Thyrotoxicosis**
Young to middle age	Middle age to elderly
Hyperthyroidism severe	Hyperthyroidism mild
Heart Failure rare	Heart failure may be presentation symptom
Eye signs common (both due to sympathetic overactivity and deposition)	Only Lid Lag and Spasm presnt (only because of sympathetic activity)

SOLITARY THYROID NODULE

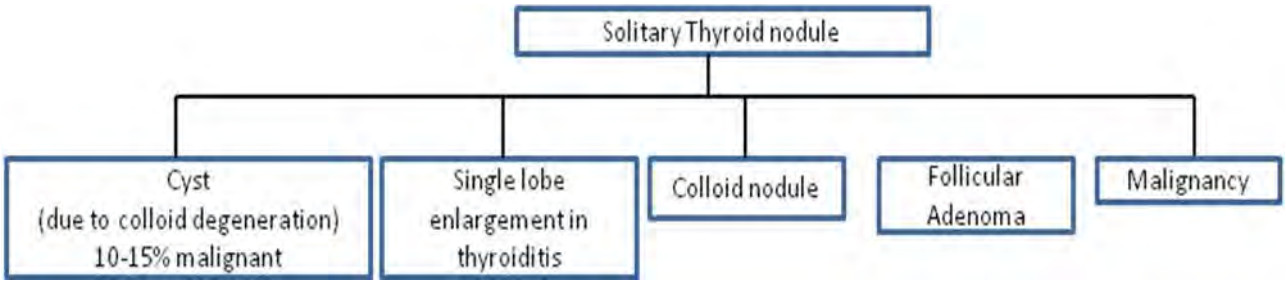
Solitary thyroid nodule is presence of a single nodule in thyroid gland with no clinical palpable abnormality in rest of the gland.

A. STN: Such patients could be or euthyroid or hypothyroid. Hypothyroid patients with STN are more commonly caseS of hashimoto's thyroiditis(sabi). Clinically palpable solitary nodules are present in 4-8 % of adult population. The risk of malignancy in a STN is about 5%-15% and therefore workup of STN is done keeping a diagnosis of malignancy in mind. Risk of malignancy is higher in :

B.

1. Male sex
2. Extreme of ages(<14 years or >50 years)
3. Familial history or history of radiation exposure
4. Presence of enlarged lymph nodes or recurrent laryngeal nerve palsy
5. STN >4cm in size
6. Fixed nodule
7.
8. Suspicious features on USG.

A STN of thyroid could be any of the following:



Toxic adenoma: This is due to autonomous hyper functioning nodule in otherwise normal thyroid gland and is commonly seen in young patients.

History of a patient with thyroid swelling

Thyroid gland can present majorly with groups of symptoms and signs:

- **Those connected with the swelling in neck**
- **Those related to endocrine activity of the gland**

A. History associated with swelling in neck: Presence of midline neck swelling is generally presenting complaint of these patients as position of thyroid in anterior aspect of neck makes it an early cosmetic deformity.

Detailed history should be taken for:

a) **Duration, onset, progression/appearance of swelling**. Majority of thyroid swellings grow slowly and painlessly. Patients may notice it co incidentally while washing or may have been pointed out by family or a friend. In some patients the swelling may be present for years before the patient seeks an advice and that is usually when the lump becomes painful or has a sudden increase in size. If nodular swelling, any sudden change in size of a nodule could be due to haemorrhage into a nodule or a fast growing carcinoma. Sudden increase in size due to haemorrhage is painful but rapidly growing malignancies are painless until they invade the neighbouring structures A thyroglossal cyst may be present at birth or present early in childhood.

b) **Discomfort**: Large swellings may produce a tugging sensation in neck especially when these patients swallow which is not a true dysphagia.

c) Any preceeding history of sore throat/URI/otitis media to rule out thyroiditis.

d) **Pain** : Not a common feature. Acute and subacute thyroiditis may present as a painful thyroid swelling. Hashimoto's thyroiditis presents as a uncomfortable ache in the neck.

e) **Any other neck swelling**: Lymph node enlargement could be present in a case of malignancy or could be only palpable swelling in which case it is called **Lateral aberrant thyroid.**

B. Pressure symptoms:

1. Patient may experience dyspnoea due to compression or deviation of trachea by a thyroid mass especially in case of a thyroid swelling with a retrosternal extension. Symptoms are worse at night on lying down or when the patient flexes the neck laterally and forwards. Long standing multi nodular goitres due to persistent tracheal compression cause tracheomalacia.(Scabbard trachea)
2. Thyroid swellings rarely obstruct the esophagus as esophagus is a muscular tube which is easily stretched and pushed aside. Dysphagia could be present without retrosternal extension if very large thyroid swelling is present. This is not a true dysphagia and happens because of extra work requires to move laryngeal box during first stage of deglutition.

3. Hoarseness of voice: When present it is be due to infiltration of recurrent laryngeal nerve, and is a significant feature pointing towards malignancy.

C. Thyroid functional status: History should be elicited to look for any endocrine dysfunction and establish a clinical functional thyroid status i.e whether the patient is euthyroid or hypothyroid or hyperthyroid.

	Hypothyroid	**Hyperthyroid**
CNS	Slow speech, slow thought, tiredness, menta lethargy, excessive sleepiness	Insomnia, nervousness, irritability, nervous instability,tremors, occasionally full blown thyrotoxic pshycosis
GIT	Decrease appetite, constipation	Increase appetite, diarrhoea
Gynaecology	Oligomenorrhoea, menorrhagia	Amenorrhoea, increased abortion
General	Facial puffiness, weight gain, hair loss especially loss of 2/3rd of eyebrows, dry skin "peaches and cream" complexion muscle fatigue, cold intolerance	Weight loss, heat intolerance, excessive sweating, palpitations breathlessness on exertion, chest pain, proximal muscle myopathy with wasting and weakness.

D. Symptoms of Metastasis: Malignant thyroid swellings may be associated with symptoms suggestive of distant metastases**.** Bone pains or scalp swelling could be present in a case of follicular carcinoma.
Besides, patient with a thyroid swelling should also be questioned for :

1. **Residence**: Presence of thyroidal swelling in neighbouring people could point to a endemic cause. Endemic goitres occur where the drinking water has low iodine content like the habitable valleys of Himalayas in India. According to the definition goitre occurs endemically when the goitre prevalence in children from 6- 12 years old is more than 5% or sporadically when it is less than 5%.
2. **Dietary and drug history**: History of intake of dietary goitrogens like vegetables of the brassica family or drugs which can act as goitrogens
3. **Family history**: If enzyme deficiency or dietary goitrogens is cause, then other members of family could also be affected. Thyroid cancers are part of familial syndromes like MEN and polyposis syndromes.
4. Endemic hyperplastic goitres are seen in childhood. Sporadic physiological hyperplastic goitres appear at puberty, pregnancy or during severe illness and emotional disturbance so they are also common in puberty or young adult life.
5. History of radiation exposure as it increases risk of malignancy.

Examination

Examination of a thyroid swelling should also include a combined approach including the nature of gland enlargement or abnormal configuration and change in the activity of gland**.**

A. General Physical Examination(Examination of the patient in whole): Various important findings can be found in general examination in patient of thyroid disease mainly due to hypo or hyperthyroid status.

B.

	Hypothyroid	Hyperthyroid
General appearance	Overweight with facial puffiness, large tongue, slow to response	Thin built with anxious and irritable look, Sweating may be present.
Skin (assessed by shaking hand)	coarse and dry palms, capillary fragility resulting in bleeding tendencies	Hot and moist palms, pretibial myxoedema palmar erythema
	Slight yellowish tinge of skin(due to decreased conversion of carotene to Vitamin A)	Facial flushing
Hairs	loss of lateral 2/3rd of eyebrows(madarosis Queen annie sign	Fine friable hair
Nails	Brittle	Plummer' s nails(Onycholysis), Separation o distal margin of nail from bed
Pulse	Bradycardia, irregular pulse if heart block present	Tachycardia with resting pulse> 90/ min wide pulse pressure(water hammer/collapsing Pulse) Atrial fibrillation may be present
		Gynaecomastia, eye signs and tremors

Tachycardia in a patient of hyperthyroid persists even on sleeping.

Eye Signs in Hyperthyroidism: There are two pathological basis of eye signs in Hyperthyroid patients.

1. **Increase Sympathetic activity** with overactivity of involuntary(smooth muscle) part of levator palpebrae superioris(Mullers muscle)

a) **Lid retraction:** When upper eyelid is higher than normal and the lower eyelid is in correct position.
b) **Dalrymple's sign:** Normally upper edge of cornea and upper sclera ares not visible but due to spasm of upper lid upper edge of cornea and upper sclera becomes visible
c) **Von Graefe's sign(Lid Lag):** Normally upper eyelid closely follows eyeball on downward gaze. But due to spasmupper eyelid does not keep pace with eyeball as it follows the finger from moving above downwards.
d) **Stellwag's Sign:** Infrequent blinking eyelids leads to staring look.
e) **Gifford's sign:** inability to evert eyelid which is otherwise possible in other cases of proptosis.

2. Due to infiltrative opyhalmopathy : Overexpression of TSH-R in retrobulbar tissues and muscles of eye. Therefore cell infiltration with deposition of glycosaminoglycans occurs mediated by auto antibodies produced in Grave' disease.

a) **Exopthalmos:** Eyeballs are pushed forwards by increased retroorbital edema, fat and cellular infiltration. The normal relationship of eyelids to iris is changed and the slera is visible below the lower edge of iris.
b) **Moebius sign:** Inability to converge due to involvement of medial rectus muscle.
c) **Joffroy's Sign:** Abscence of wrinkling on forehead on upward gaze. Since the eyeballs are pushed in front patient can look up without using the frontalis muscle
d) **Naffziger's:** visualization of eyeball beyond the line from supraorbital arch to cheek when examiner stand behind patient
e) **Ophthalmoplegia**: Exopthalmos stretches the eye muscles but does not affect their function. Weakness of ocular muscles occur because of oedema and cellular infiltration of the muscles themselves as well as occulomotor nerve. Muscles most commonly involved are superior rectus, lateral rectus and inferior oblique. This prevents the patient from looking upwards and outwards. Due to muscle involvement patients may also present with diplopia.
f) Patients with severe exophthalmos are unable to close their eyelids which might lead to corneal ulceration.
g) **Periorbital edema and conjunctival chemosis**: It is caused by obstruction of normal venous and lymphatic drainage of the cunjunctiva due to increased retro orbital pressure. Normally smooth conjunctiva on examination is thickened, wrinkled, oedematous and slightly opaque.

"NOSPECS " Classification of Opthalmopathy in thyrotoxicosis(American thyroid association)

Class	Mnemonic	Severity scoring		
		1	2	3
• 0	No signs or symptoms			
• 1	Only signs	Limited to lid retraction/lid lag and proptosis<21mm		
• 2	Soft tissue	Minimal	Moderate	Severe
• 3	Proptosis (mm)	21 – 23	>23 – 27	>27
• 4	Extra-ocular muscles	Infrequent diplopia	Frequent diplopia	Constant diplopia
• 5	Cornea	Slight stippling	Marked stippling	Ulceration
. 6	Sight loss	20/25-20/40	20/45-20/100	<20/100

Tremors could be seen in fingers when patient is asked to keep hand outstretched with fingers separated. Tremors are fine and therefore can be easily appreciated by keeping a paper on hand of patient. Tremors can also be seen in tongue of patient.

B. Local Examination of the neck

1. **Inspection:** It is done form front of patient. The gland could be made more prominent by doing **Pizzilo's method** in which patient is asked to place hands behind head and to push head against his own hands. Following points should be noted:
   a) Approximate size, anatomical position of swelling and lateral extent in relation to sternocleidomastoid muscle
   b) Shape: is it a single nodule or diffuse enlargement of gland
   c) Surface of the swelling is smooth or visibly nodular
   d) Any other swelling: lymph nodes could be seen.
   e) Presence of any distended neck veins. May be seen in masses obstructing the thoracic inlet.

f) Is swelling moving with deglutition and protrusion of tongue.
g) Is lower border visible.
h) **Trail's sign:** In large thyroid swelling, trachea may be pushed to one side making sternocleidomastoid of that side prominent.

2. **Palpation**: It is done from front and back but the most important part of palpation is done from behind. Palpation of individual lobe can be done by **Lahey's method** in which to palpate left lobe the right lobe is pushed to left by examiner right hand and then left lobe can be palpated or vice versa. Very small nodule can be palpated by **crile's method** in which thumb is kept on thyroid region and patient is asked to swallow.
   a) Anatomical size, position of swelling and lateral extent in relation to sternocleidomastoid muscle is confirmed
   b) Diffusely uniform/mutinodular/STN swelling should be clear after palpation
   c) Borders of thyroid should be clearly palpated especially lower border. The lower border should also be palpated while asking patient to swallow. The patient may be asked to sip some water. Thyroid swellings ascend during swallowing.
   d) In case of STN/ multiple nodules, consistency should be noticed although hard nodule may not be malignant and a cyst may turn out malignant later. A tense cyst could be hard on palpation or due to haemorrhage inside.
   e) All regions of neck should be palpated for lymph nodes
   f) Position of trachea below thyroid should be confirmed. It should be central in position at the suprasternal notch In case of retrosternal extension, tracheal cartilage position should be noted which is usually deviated if trachea is deviated.

g) **Berry's sign:** The deep fascia of neck after enclosing thyroid gland fuse in front of carotid sheath on both sides. A benign thyroid swelling, respecting tissue planes, only expand the deep fascia and pushes carotid sheath Laterally. Thus carotid pulsations are pushed laterally. Whereas a malignant swelling will invade tissue planes and carotid pulsations are not felt at level of thyroid swelling but are palpable at upper level.

h) In case lower border of thyroid is not palpable, patient may have retrosternal extension. This is further confirmed by **Pemberton sign.** Patient is asked to raise both arms above head with arms touching ears. Facial flushing and dilation of neck veins due to further narrowing of the thoracic inlet suggests a retrosternal extension.

Using the WHO grading system the enlargement of the thyroid gland can be graded depending on its present size

Grade 0: No goitre can be felt .(It is impalpable and invisible)

Grade 1: The thyroid is palpable but not visible when the neck is in normal position. A thickened mass moves upwards during swallowing.

Grade 2: The neck swelling which is visible when the neck is in normal position corresponds to enlarged thyroid that is found on palpation.

3. **Percussion**: This is done to confirm retrosternal exyension. Manubrium sternum is percussed. Normally it is resonant but becomes dull in cases of retrosternal extension of the goitre .Percussion over the neck lump is not helpful.

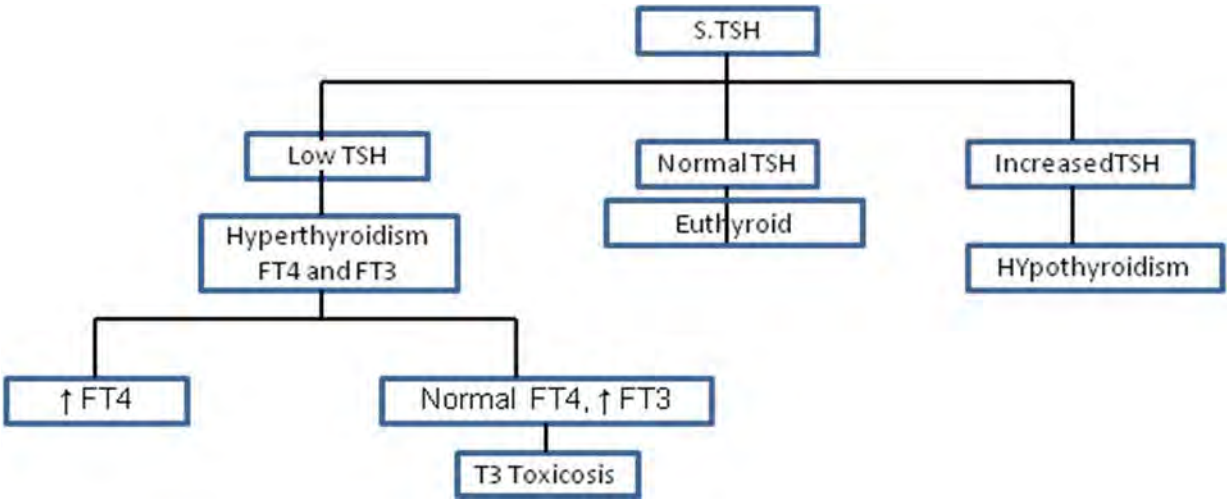
4. **Auscultation**: Bruit can be heard in cases of grave's disease due to increased vascular supply. It is heard at apex of thyroid glands in region of superior thyroid artery.

C. Systemic examination:

	Hypothyroid	**Hyperthyroid**
CVS	Heart sound may be muffled due to pericardial effusion	CHF with Raised JVP may be seen, Murmurs could be heard due to hyper dynamic circulation
Respiratory	Breath sounds may be decreased due to pleural effusion	Tachypnoea with decrease vital capacity
Musculoskeletal	Delayed tendon reflexes	Brisk reflexes

Investigations

A. S. TSH and Thyroid profile: Serum TSH measured in a higher sensitivity immunometric assay should be used as the first line screening test in patients presenting with thyroid swelling. The increased sensitivity and specificity of TSH assays has significantly improved the laboratory evaluation of thyroid function. Since Any alteration in T3 & T4 brings a dynamic change in TSH ,a logical method is to see whether the TSH is normal, elevated or suppressed. A normal TSH usually (with rare exceptions) excludes a primary thyroid functional abnormality. The immunochemiluminometric assays(ICMAs) for TSH are extremely sensitive and can differentiate between the lower limit of reference range and suppressed values of TSH. Highly sensitive(fourth generation) assays can detect the TSH levels a slow as <=0.004mIU/L.

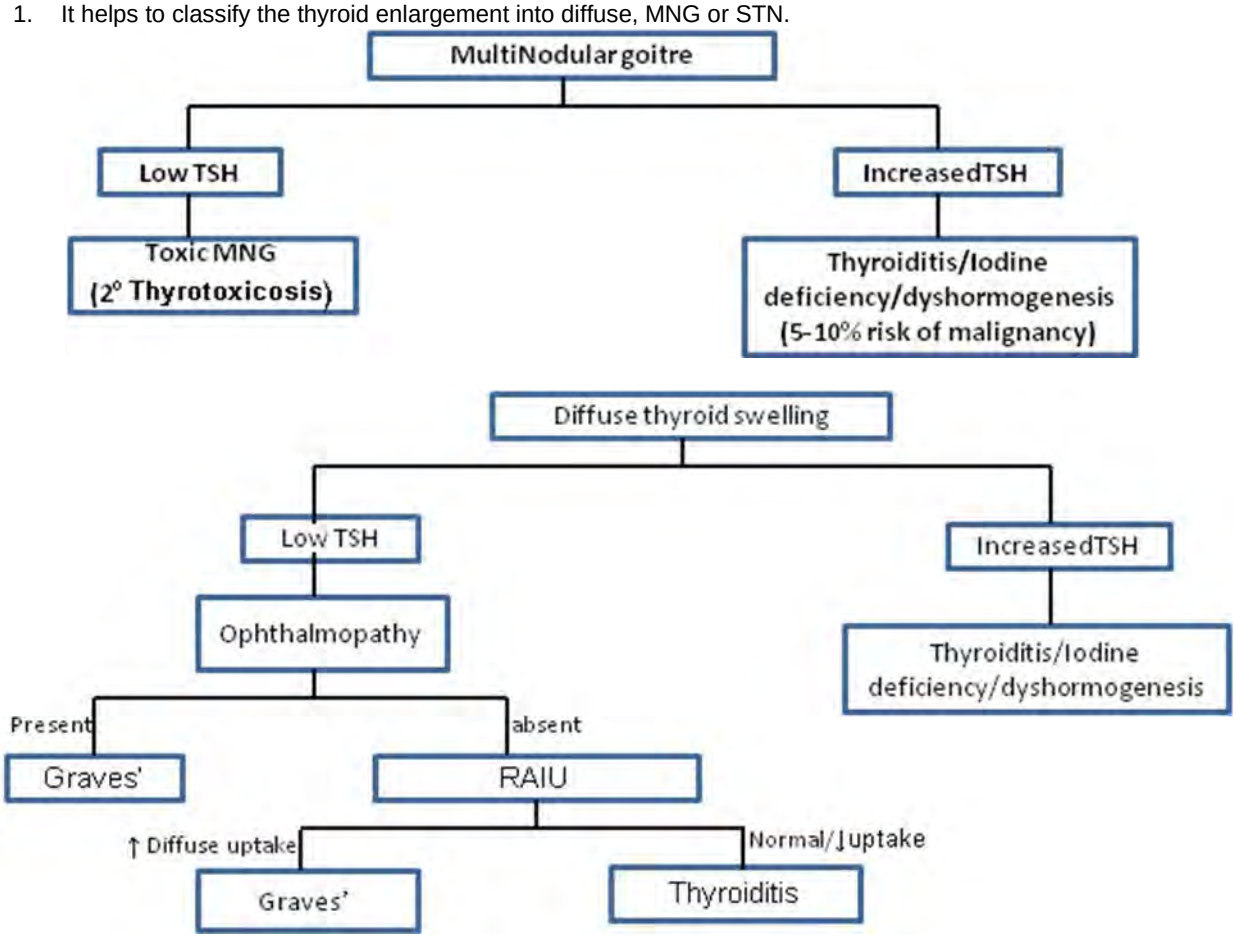


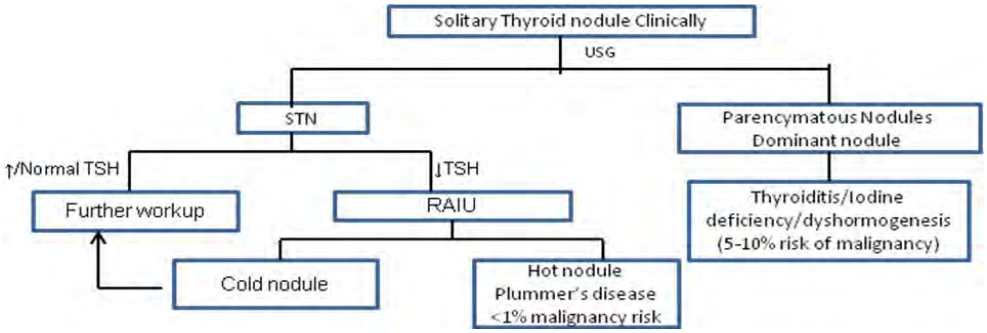
Measurement of Free unbound T3 and T4 which corresponds to the biologically active hormone pool is preferred over total T3 and T4 as it depends on the protein binding. Several factors like illnesses, medications and genetic factors can affect the protein binding. Two direct methods are used to measure the levels of unbound thyroid hormone.

1. Unbound thyroid hormone completion with radio labelled T4(or an analogue) for binding to a solid phase antibody.
2. Physical separation of the unbound hormone fraction by ultracentrifugation or equilibilirium dialysis

B. Ultrasound: it is an important radiologic investigation required in workup of a patient with thyroid swelling. USG examination of the neck requires high frequency transducers(7-15MHz). The patient lies supine and the neck hyperextended. USG can detect thyroid lesions as small as 1-2 mm. ATA recommends that Sonography should be performed in all patients with known or suspected thyroid nodules.

1. It helps to classify the thyroid enlargement into diffuse, MNG or STN.





2. Differentiate solid lesions from cysts

3. Also it helps in localizing high risk **features suggestive of malignancy**:

a) Hpoechoic lesion
b) Complex cyst with solid and cystic areas
c) Perilesional Halo due to increased vascularity
d) Microcalcification
e) Taller than wider on transverse view
f) Lymphadenopathy

These features are important to select nodule for FNAC in case of MNG or 2-3nodules in thyroid gland as presence of these features represents area of malignancy.

4. Also helps in targeting FNAC. This is more useful in case of dominant nodules with features of malignancy or cystic nodules to target their solid component. Using USG for FNAC results in lower non diagnostic rates and sampling errors.

Advantages of USG are that it is portable, cheap, easily available and easy to use. Major limitations include its inability to locate retrotracheal, retro clavicular and intrathoracic extension of thyroid.

C. Thyroid radionuclide uptake and imaging studies:

1. **Radiopharmaceuticals:** Three isotopes I123, I131 and Tc 99 are used for thyroid radionuclde studies. They have similar biological behaviour and are administered orally.

a. **I131**: It has a half life of 8 days with a substantial b eta particle emission and thus I131 has a higher role in therapy of hyperthyroidism and thyroid Ca.
b. **I123** : It is used preferentially for imaging of thyroid as well as metastatic cancer It ha S a half life of 13 hours and mainly emits a 159 Ke V gamma photon which is well suited for gamma camera imaging. The t1/2 is long enough for both membrane transport and organification of radiotracer resulting in high target/background ratio.
c. **Technitium Pertechnate(TcO4**)- This is transported by sodium Iodine symporter and quickly accumlates in follicular cells of thyroid following I.v injection. Imaging can be obtained easily at 20 minutes after injection. Since Tc pertechnate is not organified it quickly washes out from the thyroid and thus does not develop high target background uptake ratios. The absolute uptake of radiotracer is 1-2%, much lower than what is seen with radioiodine.

Thyroid radionuclide uptake studies : An important non imaging study is the determination of the fraction of ingested iodine reaching the thyroid gland 4-24 hours following its oral administration .This is useful in determining the cause of thyrotoxicosis. Patient's of Grave's disease or autonomous nodules have an increased radiotracer uptake values while patients with painless or subacute thyroididtis have a low radiotracer uptake. The fractional uptake is also used to determine the dose of I 131for treating hyperthyroidism. Both I 131 or I 123 can be used but I 123 is preferred because of its favourable dosimetry for imaging. The study can assess organification related accumlation.

Thyroid scan(Radioactive Iodine uptake scan) : It is done using Iodine radioisotopes such as $\mathbf{I^{123}}$ Tc99 Pertechnate **.** Thyroid imaging using I131 is not preferred because of its high radiation dose to thyroid and poor imaging quality. More the follicles are functioning, more of Iodine is taken up and nodules appear hot as compared to rest of tissue. For I 123 scan dose is in the range of 200 to 400 micro curies with the gamma camera images obtained 24 hours after ingestion. Tc 99 Pertechnate is routinely used in some centres for thyroid scan. It has a lesser cost, delivers less radiation to the thyroid and provides imaging fast between 20 -30 minutes of injection. Since the target to background ratio with 99Tc is not as high as I123 its usefulness in substernal goitres is limited. There can be nodules which are hot or warm with 99Tc but are non-functioning or cold with I123 scan. Thus some hot or warm nodules on 99Tc scan will require a follow up with I 123 scan to exclude the possibility of carcinoma which transports but does not progressively concentrate Tc99.

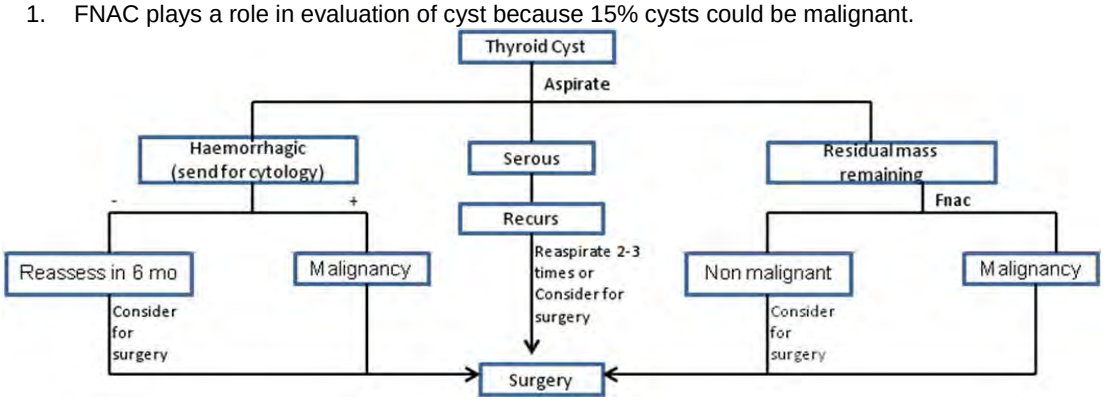
Indications: Assessment of thyroid nodules has been the major indication of thyroid scintigraphy. Recommendations of AACE/AME for thyroid scintigraphy include:

a. Solitary nodules with a suppressed TSH; FNAC not required if the nodule is hot.
b. MNG's even without suppressed TSH to determine the cold and in determinant areas for FNA biopsy and see the hot areas which do not require a cytological evaluation.
c. Large MNG's extending sub sternally
d. For diagnosis of ectopic thyroid tissue
e. In cases of subclinical hyperthyroidism to diagnose the focus of occult hyperfunctioning tissue.
f. In follicular lesions to identify the functioning cellular adenoma
g. To determine a high or low uptake thyrotoxicosis and plan the treatment accordingly.
h. In Iodine deficient areas scintigraphy should be considered to evaluate autonomy of a thyroid nodule or MNG even if the TSH is normal.

D. Xray Soft issue neck: This can be used to see deviation of trachea or in case of retrosternal extension, thyroid shadow can be seen to extend behind sternum.

E. Fine Needle Aspiration Cytology(FNAC): It is an important tool in diagnosis of a thyroid swelling. It is done using 23 to 27 gauge needle. It is a cheap and easily available investigation with only 1-4% false negative and positive result. Various indications of FNAC include:

1. FNAC plays a role in evaluation of cyst because 15% cysts could be malignant.



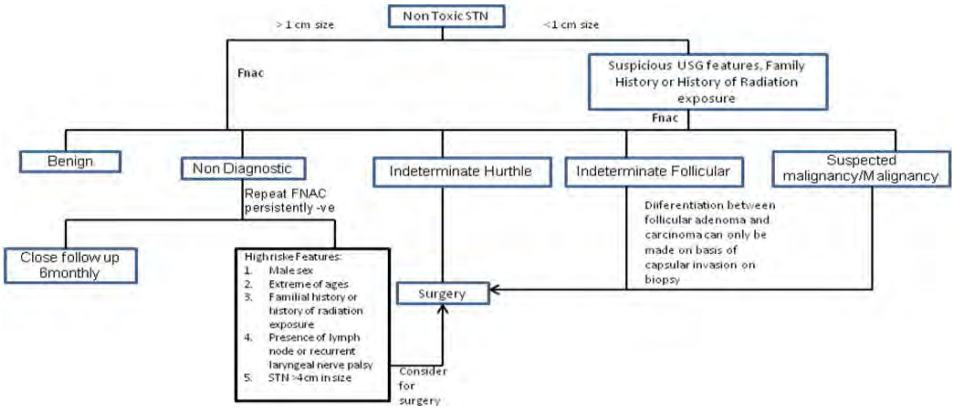
2. Patient with non toxic dominant neck swelling, FNAC should be done. FNAC is to be targeted from both dominant nodule as well as any other nodules which are:

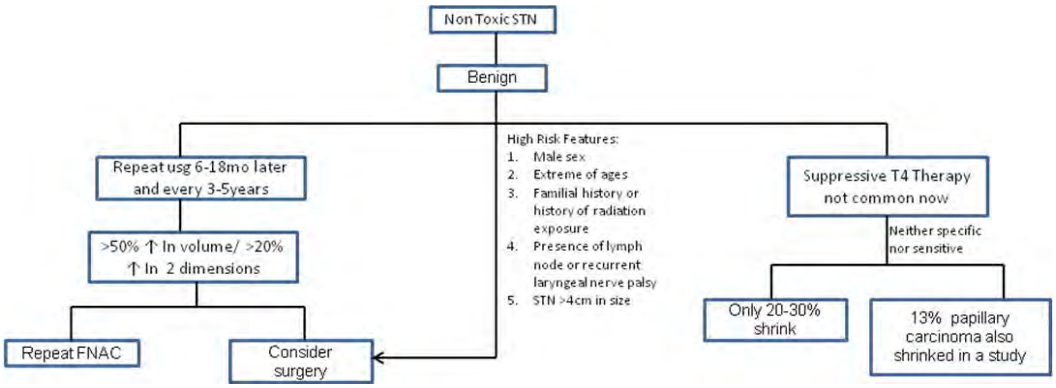
a) Painful or rapidly enlarging.
b) Suspicious features on USG

3. Patient with non toxic MNG, FNAC is to be done in case:

a) Painful or rapidly enlarging nodule.
b) Suspicious features on USG of a nodule

4. Solitary thyroid nodule other than cyst:





Patients with familial history or history of radiation exposure have multifocal tumours. There is a 60% chance of having malignancy in the dominant nodule and 40% chance of malignancy being present in some other nodule. Therefore if FNAC comes out to be negative they should be still strongly considered for surgery.

ATA recommends that FNAC should be considered for all isofunctioning(warm) or hypofunctioning nodules which have sonographic suspicion of carcinoma.

F. CT/MRI: There is limited role of CT or MRI in evaluation of Thyroid nodules. They are mainly used in two situations:

1. In case of retrosternal extension to look for extent and vascular supply of thyroid
2. In case of bulky thyroid enlargement with clinical suspicion of Local invasion.

CT scan is widely used in evaluating opathlmopathy. Large difference in contrast between bone, muscle and fat allows recognition of proptosis and the risk of optic neuropathy.

G. PET Scan: Role of PET scan in thyroid workup is debatable although some centres use it for detecting thyroid metastasis especially in non functioning thyroid tumours like medullary carcinoma.

H. Thyroid antibodies: Assays for anti TPO, anti Tg and anti TSH-R antibodies are available but they are very non specific with limited diagnostic role whatsoever.

I. S.Thyroglobulin levels: It has no diagnostic role as its level may be increased in malignancy, thyroid follicle destruction like thyroiditis and overactive state like graves' disease. It is mainly used for follow up of well differentiated thyroid malignancies

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J. S.Calcitonin: It has not much diagnostic role. It is mainly used for follow up of medullary carcinoma.

K. Biopsy: Due to low false –ve and false +ve rate of FNAC, open biopsy of thyroid is rarely required except in some conditions like:

1. Riedel's thyroiditis: as gland is fibrotic, FNAC is inadequate and biopsy is required.
2. Anaplastic carcinoma
3. Lymphoma: diagnosis can be suspected on FNAC, but for confirmation and typing of lymphoma, biopsy is required.

Open biopsy in reidel's thyroiditis and anaplastic carcinoma also serves purpose of respiratory decompression. Generally a wedge resection of isthmus is done.

Advantage of open biopsy is high diagnostic accuracy but complications like pain, bleeding etc are associated with it.

Suggested Reading:

1) **Brunicardi FC, Bell RH Jr., Saluja AK, Fisher WE, Anderson DK editors. Schwartz's principles of surgery. 9th edition. New York: McGraw-Hill;2010**
2) **Townsend CM, Beauchamp RD, Evers BM, Mattox KL editors. Sabiston's textbook of surgery. 19th edition. Philadelphia: Elsevier;2012**
3) **Williams NS, Bulstrode CJK, O'Connell PR. Bailey's & Love's Short Practice Of General surgery. 25th edition. London: Hodder Arnold;2008**
4) **Browse's NL, Black J, Burnand KC, Thomas WEG. Browse's Introduction to The Symptoms and Signs of Surgical Disease.4th edition.**
5) **Braverman LE, Cooper DS. Werner and Ingban's The Thyroid: A fundamental and Clinical Text.10th edition. Philadelphia: CRC press.**
6) **Lumley JSC, D'cruz AKD, Waballah JJ, ScottCEL. Hamilton Bailey's Demonstration of Physical Signs in Clinical Surgery. 19th edition.**
7) **Fauci AS,Braunwald E, Kasper DL. Harrison's Principles of Internal Medicine. 17th edition. New York: Mcgraw-Hill:2008.**
8) **Melmed S, Polonsky KS, Larsen PR, Kronenberg HM. Williams Textbook of Endocrinology. 13th edition.**
9) **Orlo H, Clark MD, Quan Yang D, Kebebew E. Textbook of endocrine surgery. 2nd edition.**

Management of thyroid diseases

Chandra Bhushan Singh

HYPOTHYROIDISM

Thyroid hormones are secreted from the thyroid gland at a molar T3:T4 secretion ratio of approximately 1:14. T4 conversion accounts for roughly 80% of T3 production in response to decreased T3 concentration by intracellular tissue deiodinases. Small changes in T4 are reflected as large inverse changes in TSH. Accordingly, TSH is a sensitive and early biochemical marker of thyroid gland failure and is elevated in face of normal FT4 and FT3 in subclinical hypothyroidism.[1] Iodine deficiency is the commonest cause of hypothyroidism worldwide. In countries where iodine deficiency does not exist, most cases are due to atrophic or goitrous Hashimoto's thyroiditis characterized by presence of autoreactive thyroid antibodies, namely thyroid peroxidase (TPOAb) and thyroglobulin antibodies (TgAb).[2] A third of pregnant women who develop postpartum thyroiditis (occurs in 5–9% of postpartum women) develop permanent hypothyroidism.[3] Hypothyroidism is also seen following thyroidectomy or after radioactive iodine therapy. Congenital hypothyroidism occurs in 1 in 3500 newborns and is one of the leading preventable causes of mental retardation. Less common causes of hypothyroidism include acute and subacute thyroiditis, drugs that interfere with thyroid hormone synthesis and secondary hypothyroidism due to pituitary disease. Hypothyroidism is more common in other autoimmune conditions such as type 1 diabetes and Addison's disease, family history of thyroid disease and in Down's syndrome and Turner's syndrome patients.[4]

TOXIC NODULAR THYROID ENLARGEMENT

Nodular thyroid diseases with autonomous hyperfunction can occur in two clinical situations. First is Toxic multinodular goiter , which presents as large multinodular goiter. It predominantly afflicts elderly people. The goiter and autonomous function often precede the onset of hyperthyroidism by many years. Second is Goetsch's disease or solitary autonomous thyroid nodule which is characterized by a single thyroid adenoma showing autonomous function independent of pituitary stimulation or any other extrathyroidal stimulator. It has preserved negative feedback on the production of thyroid-stimulating hormone (TSH) by the pituitary gland which suppresses the function of TSH-dependent extranodular tissue to a variable degree.[5] Many patients with a solitary autonomously functioning thyroid nodule are euthyroid with only small number of patients progressing to persisting hyperthyroidism . Spontaneous degeneration of the nodule is also described.

THYROIDITIS

Thyroiditis means inflammatory thyroid disorders. Thyroid inflammatory disorders are of various types . Commonest among them is chronic lymphocytic thyroiditis (Hashimoto's thyroiditis) which presents with hypothyroidism, goiter, or both. Measurement of serum thyroid autoantibodies and thyroglobulin confirms the diagnosis. Subacute granulomatous thyroiditis (de Quervain's disease - self-limited but painful disorder) can be diagnosed by physical examination, elevated ESR, elevated thyroglobulin level and depressed radioactive iodine uptake (RAIU). Subacute lymphocytic thyroiditis (silent thyroiditis) is autoimmune in origin and commonly occurs in postpartum period. It shows symptoms of hyperthyroidism and also a depressed RAIU. Acute (suppurative) thyroiditis is a rare, infectious disorder caused by bacteria and other microbes. Invasive fibrous thyroiditis (Riedel's thyroiditis) is also rare and shows slowly enlarging thyroid mass resembling malignancy.[6]

Chronic lymphocytic thyroiditis (Hashimoto's thyroiditis)

is the most common inflammatory condition of the thyroid gland and the most common cause of goiter and hypothyroidism in the United States.It is caused by an autoimmune process and is marked by high titers of thyroid peroxidase antibodies and thyroglobulin.3 Euthyroid patients with Hashimoto's disease develop hypothyroidism at a rate of approximately 5 percent per year.Usual age at presentation is 30 to 50 years and up to 95 percent of patients are women. It is also the most common cause of sporadic goiter in children. A genetic predisposition has been found which is inherited as a dominant trait. Other autoimmune diseases are also common in these patients , including systemic lupus erythematosus, rheumatoid arthritis, pernicious anemia, diabetes mellitus and Sjögren's syndrome. A rare but serious complication of Hashimoto's thyroiditis is localized thyroid lymphoma of B cell origin generally belonging to non-Hodgkin's type, with typical patient being women of 50 to 80 years of age.[7]

Hashimoto's thyroiditis is usually asymptomatic, though some patients may complain of a feeling of tightness or fullness in the neck. Pain in neck or tenderness is rarely seen. 20% patients present with symptoms of hypothyroidism in 20 percent at diagnosis. On examination the thyroid is firm, irregular,diffusely enlarged and nontender. The erythrocyte sedimentation rate (ESR) and white blood cell count(TLC) are normal. Definitive diagnosis can be made by the presence of thyroid-specific autoantibodies against thyroglobulin, thyroid microsomal antigen (also called thyroid peroxidase) and the thyroid-stimulating hormone (TSH) receptor. Antithyroid microsomal antibodies in titers greater than 1:6,400 or antithyroid peroxidase antibodies in excess of 200 IU per mL are diagnostic. Radioactive iodine uptake (RAIU) is variable and patchy while ultrasonography

shows diffusely hypoechogenic thyromegaly and therefore not essential in workup. A dominant nodule in a patient with Hashimoto's disease requires a fine-needle aspiration biopsy to exclude malignancy.[6]

Subacute Lymphocytic Thyroiditis

Subacute lymphocytic thyroiditis can occurs most commonly in the postpartum women (postpartum thyroiditis) or as sporadic disease (sporadic painless subacute lymphocytic thyroiditis).[7] It comprises of 29 to 50 percent of all cases of thyroiditis. Antimicrosomal antibodies are present in 50 to 80% of patients (postpartum form showing 80 % positivity and sporadic form 50% positivity), while antithyroid peroxidase antibodies are present in nearly all patients. It starts as an initial hyperthyroid phase, followed by subsequent hypothyroidism and, finally, a return to the euthyroid state. Postpartum patients, present with thyrotoxicosis usually with in first three months and illness lasts for one or two months before coming to a euthyroid state. There is high risk of recurrence in subsequent pregnancies. Serum TSH levels are done in all symptomatic patients. Most commonly women between 30 and 50 years of age are affected. A family history of autoimmune thyroid disease is found in 50 percent of patients with the postpartum form of thyroiditis. Severe hypothyroidism is seen when antimicrosomal antibody titers are high (esp. 1:1,600 or greater). 10 Approximately 6 percent of patients who have the postpartum form develop chronic hypothyroidism.[6] Patients have acute symptoms of hyperthyroidism, a small painless goiter (in 50 %). RAIU is decreased in the hyperthyroid phase of the disease and is almost always less than 3 % and contrasts markedly from elevated RAIU of Graves' disease.

Subacute Granulomatous Thyroiditis

Subacute granulomatous thyroiditis is the most common cause of a painful thyroid gland which is firm and nodular. It is mostly caused by a viral infection from preceeding upper respiratory tract infection. Viruses implicated are mumps virus, echovirus, coxsackie virus, Epstein-Barr virus, influenza and adenovirus. Female to male ratio of 3-5:1 with average age of onset is 30 to 50 years and occurrence in season of mostly summer and autumn. It presents with acute onset of pain in the thyroid region, exacerbated by turning the head or swallowing, and may radiate to the jaw, ear or chest. There are symptoms of hypermetabolism along with markedly elevated ESR and normal ESR essentially rules out the diagnosis.[6]Thyrotoxicosis is present in 50 percent of patients in acute phase, and elevation of T4 ,T3 and thyroglobulin and low or undetectable levels of serum TSH. A normal thyroglobulin level essentially rules out the diagnosis. The RAIU is notably low, often less than 2 percent at 24 hours.

Microbial Inflammatory Thyroiditis

Microbial inflammatory thyroiditis is also known as acute suppurative thyroiditis, is a rare Gram-positive bacterial infection of thyroid gland. Staphylococcus aureus is the most common infectious agent, but other organisms have also been implicated. There is normally inherent resistance of thyroid gland to infection. It mostly occurs in women 20 to 40 years of age having pre-existing thyroid disorder usually like nodular goiter. The pain is typically worse during swallowing and radiates locally. Tachycardia along with leukocytosis and an elevated ESR level is seen. TSH, T4 and T3 levels are typically normal. Culture and sensitivity of samples obtained through fine-needle aspiration can direct antibiotic treatment .

Invasive Fibrous Thyroiditis

This was first described by Riedel in 1898 and is rarest type of thyroiditis. It is characterized by dense fibrosis of thyroid gland presenting as stony hard or woody thyroid gland with inflammatory fibrosclerotic processes affecting extracervical sites in the form sclerosing cholangitis, retroperitoneal fibrosis and orbital pseudotumor. Multifocal fibrosclerosis is seen in one third of patients. 83% of all cases occur in females. Dyspnea, dysphagia and, occasionally, stridor can also be present.[6] The thyroid mass is usually unilateral.

SOLITARY THYROID NODULE

Presence of nodules in thyroid is a common clinical occurrence and has been observed in 50% of autopsied patients. An annual incidence rate of 0.1% has been found on the ultrasonography. Detection of presence of malignancy in a thyroid nodule is very essential as 1 of 20 (5% with range of 7-15 %) clinically identified nodules are malignant.[8] Thyroid nodules are more commonly found in women and (in women 6.4 to 10% as compared to 1.5 to 2% of men).Chances of malignancy are high in males, age group <15-20years or in old patients.[9]{During childhood and adolescence ,the malignancy rate is 3- to 4-fold higher than in adult patients. History of radiation exposure (increased risk of both benign and malignant thyroid lesions for at least 3 decades after exposure) and family history of malignancy(medullary thyroid cancer in family) increases chances of malignancy independent of the size of nodules.[10] Sometimes nodules are incidentally detected on USG or other imaging studies and are clinically nonpalpable. They are termed as ‘‘incidentalomas.’’ These nonpalpable nodules have the same risk of malignancy as do sonographically confirmed palpable nodules of the same size. Only nodules of size >1cm should be evaluated, since they have a greater potential to be clinically significant cancers. Occasionally, nodules <1cm present with local symptoms and require further evaluation especially when associated lymphadenopathy is detected. [11]On USG evaluation of palpable solitary nodule 20% to 48% of patients are found to have additional nodules. Chances of malignancy in a palpable nodule in a patient with previous irradiation are 20%–50%.

Malignancy can be part of multiple endocrine neoplasia (MEN - 2 or 2B)syndrome and then present along with pheochromocytoma, hypertension, chronic diarrhea and hyperparathyroidism.

Thyroid gland Nodule can be classified as:

1. Benign (90%)
   - A. Cysts
   - B. Neoplastic Adenomas
     - Papillary
     - Follicular (Common)
       - Fetal
       - Colloid
       - Embryonic
     - Hurthle Cell type
   - C. Toxic adenoma: solitary hyper-functioning thyroid nodule
   - D. Non toxic adenoma: solitary nonfunctioning thyroid nodule
2. Malignant

Amongst thyroid malignancy primary thyroid carcinomas are the commonest. Far less common are: lymphomas or metastatic tumor disease. Papillary carcinomas is the most common of thyroid malignancy, accounting for 80-90% of all thyroid cancers, but only represent 1% of all malignancies. Thyroid cancer has a favorable prognosis and accounts for less than 0.5% of cancer deaths.

Childhood STN has a higher incidence of Thyroid Cancer i.e. 15-20% as compared to adults. Thyroid malignant nodules develop as monoclonal neoplasms that arise from a single mutated cell. Nontoxic solitary adenomas probably arise from somatic mutations of genes that stimulate signaling cascades involved in cell proliferation. Most toxic adenomas arise from mutations that lead to stimulation of TSH receptor signaling pathway mainly due to acquired somatic activating mutations in TSH receptor. These mutations through stimulation of c-AMP cascade, cause enhanced thyroid follicular cell proliferation and function.

Nontoxic adenomas, if large, present as thyromegaly . Otherwise smaller adenomas are typically asymptomatic. Mild symptoms of thyrotoxicosis can be seen in toxic adenoma. The sensitivity and specificity rates for detecting thyroid malignancy by history and physical examination are around 60% and 80% respectively. About 20% of all patients of thyroid malignancy are asymptomatic clinically.

RESISTANCE TO THYROID HORMONE (RTH)

is a rare autosomal dominant syndrome of reduced end-organ responsiveness to thyroid hormone. In1967 Refetoff described the first cases of resistance to thyroid hormone in two siblings born to consanguineous parents who had signs suggestive of hypothyroidism, including deaf-mutism, goitres and delayed bone age.4 Familial occurrence of RTH has been documented in approximately 75% of cases. The true incidence of sporadic cases is 21.3%. Patients with RTH show elevated serum free thyroxine (FT_4) and free triiodothyronine (FT_3) concentrations and normal or slightly increased serum TSH levels. Clinical presentation is variable, though commonly goitre with absence of symptoms of thyrotoxicosis is seen . Clinically they are classified either as generalized resistance to thyroid hormone (GRTH), pituitary resistance (PRTH) or combined. Pathological basis of this condition is mutations in thyroid hormone receptor (TR) b gene. With the exception of one family of mutation which show complete deletion of the TRb gene, all others have been demonstrated to have minor alterations at the DNA level. There is great variation in severity of RTH but the clinical defect or deficiency is always partial. The magnitude of the hormonal resistance is dependent on the nature of the underlying defect. Invariably there is a mutation in one allele of the TRb gene which interferes with the capacity of that TRb receptor to respond normally to T3, usually by reducing its binding affinity to T3. Determination of TSH in neonates rarely identifies RTH. The TSH secreting pituitary adenoma and the presence of endogenous antibodies directed against thyroxine (T4) and triiodothyronine (T3) can mimic its presentation. No specific treatment is available for RTH though the diagnosis allows appropriate genetic counselling.

Adults most commonly present with a goitre or recurrent goitre following inappropriate treatment. Children show growth retardation with delayed bone age. Goitre is the most common reason prompting further investigation of the key family member (38%). The majority of untreated subjects maintain a normal metabolic state despite high circulating thyroid hormone concentrations. This happens due to compensation of tissue hyposensitivity to the hormone and coexisting clinical and laboratory evidence of thyroid hormone deficiency and excess. One-half of affected children have some degree of learning disability with or without attention deficit hyperactivity disorder (ADHD). One-quarter have intellectual quotients (IQ) less than 85%.[12]

THYROID MALIGNANCY

Thyroid carcinomas are classified according to the cell type from which they develop . The majority arise from the thyroid epithelial cells and account for approximately 95% of tumors and are divided into four histologic subtypes: papillary (85%), follicular (11%), Hurthle cell (3%), and anaplastic (1%) . Of these, 95% are sporadic tumors and the rest 5% represent familial nonmedullary thyroid cancer (FNMTC). Medullary thyroid cancers (MTCs) arise from the calcitonin-producing parafollicular cells of the thyroid and account for about 5% of all thyroid malignancies.

They are familial in 20% and occur as part of the multiple endocrine neoplasia (MEN) syndromes with associated pheochromocytomas of MEN II syndrome.[10] {ART10 Differentiated thyroid carcinoma (particularly papillary carcinoma) involves cervical lymph node metastases in 20%–50% of patients.[13] These cervical metastasis can also be present even when the primary tumor is small and intrathyroidal . The frequency of micrometastases (< 2mm) may approach 90%, depending on the sensitivity of the detection method . However, the clinical implications of micrometastases are likely less significant compared to macrometastases. Preoperative US identifies suspicious cervical adenopathy in 20%–31% of cases, potentially altering the surgical approach in as many as 20% of patients. [14].However,preoperative US identifies only half of the lymph nodes found at surgery, due to the presence of the overlying thyroid gland.

Pathology of follicular variant of papillary thyroid carcinoma (FVPTC)

The pathological appearance of a follicular-patterned tumor with the nuclear features of classical papillary thyroid carcinoma (cPTC) suggests that FVPTC is a hybrid. However, the heterogeneous nature of the disease and the mutational profile of FVPTC strongly suggest that it is a mixture of two diseases (2) . 30% of all PTCs are now FVPTCs (3) Therefore today >50% of malignancies are FVPTC (2). The annual incidence of FTC has been constant over recent decades (4), though the percentage of follicular-patterned thyroid malignancies are rising and FVPTC makes upto 85% of all follicular-patterned thyroid carcinomas (5). Pathological diagnosis of FVPTC is somewhat elusive and is identified by mutations, most common being mutation in cPTC is $BRAF^{V600E}$ (9). Follicular adenomas and follicular thyroid carcinoma (FTC) most commonly show RAS mutation but do not harbor $BRAF^{V600E}$ mutation (9). RAS mutations are virtually never found in cPTC. The distinction between a follicular adenoma and a FTC depends upon the presence or absence of capsular or vascular invasion.[15]

Familial follicular cell–derived DTC

It is suggested that when two first-degree family members are affected by FTC, the probability of FTC being familial is 38 %. This probability increases when the number of affected family members are three or more. Even when only two family members are affected, the disease displays the features of ‘‘genetic anticipation’’ (occurrence of the disease at an earlier age and more aggressive presentation when it occurs in subsequent generations after the first generation). The frequency of multicentricity is more than usual, though disease-free and overall survival are similar to sporadic cases. Many other syndromes are seen in patients or first degree relatives of familial DTC. These include PTEN [phosphatase and tensin homolog] hamartoma tumor syndrome [Cowden’s disease], familial adenomatous polyposis [FAP], Carney complex, multiple endocrine neoplasia 2, Werner syndrome[16]

Low risk papillary thyroid microcarcinomas (PMCs)

PMC is defined as small papillary thyroid carcinomas measuring 10mm or less. Ultrasound is capable of detecting thyroid nodules measuring at least 3mm, and ultrasound-guided FNABs can diagnose PTCs of this size. PMCs can present as lymph node or distant metastasis from a occult lesion , as incidentally lesion in resected thyroid gland , as incident lesion on imaging or as autopsy finding (latent PMCs). Biologically symptomatic PMCs or those with clinical lymph node metastasis have poor prognosis. The dormant clinical behaviour is evident from the fact that in autopsy studies, the incidence of latent PTCs measuring 3–9.9mm ranged from 0.5 to 5.2% while a mass screening study showed small thyroid cancer, in 3.5% of otherwise healthy women aged 30 years or older, most (84 %) of these being 15mm or less. As this incidence is about 1000 times the prevalence of clinical PTC (1.9–11.7 per 100000 women) it suggests that most PMCs detected incidentally by ultrasound do not grow or grow very slowly and are harmless clinically. It is believed that all PTCs start as a small carcinoma and only a small minority of PMCs grow significantly. At present it is impossible to identify those PMCs which will be slow-growing and non-growing lesions except by active observation.

Immediate surgery for all PMCs may be an overtreatment as it can later be performed when signs of disease progression appear . PMCs in older patients are less likely to progress than those in young or middle aged patients . Active surveillance is still suitable for both groups of patients. In contrast, pathologically incidental PMCs in resected thyroids have an excellent prognosis and only 2.2% show a recurrence when no additional surgery was done. Patients of papillary thyroid microcarcinoma suitable for active observation are monitored by ultrasound-guided FNABs for the nodules and explaining the diagnoses to the patients. High-risk features include tall cell variant or poorly differentiated carcinoma. Active follow up is done only in incidentally detected lesion by ultrasound once or twice per year. Progression in size by 3mm or more or appearance of lymph node metastasis means need to discontinue active surveillance. For suspicious lymph nodes, an FNAB and thyroglobulin measurement of the washout of the needles used for FNAB are indicated. Ultrasound follow up has limitation while evaluating the dorsal side tumors with strong echoes (need CECT then) . Additionally there can be a bias due **to** observers’ interpretations . Size enlargement rates at 5-year and 10-year are 6.4 and 15.9% while node metastasis rates are 1.4% and 3.4% respectively [17]. Role of TSH suppression towards lower limit of normal range of TSH in preventing PMC progression is unclear . During pregnancy human chorionic gonadotropin has a weak ability to stimulate the thyroid gland, possibly promoting the growth of PMC under surveillance . It still remains unknown whether pregnancy specifically affects the progression of low-risk PMC . Active observation for low-risk PMC is a well tolerated therapeutic strategy, and this strategy was also adopted in Japanese guidelines for the management of thyroid tumors in 2010

RETROSTERNAL GOITRE

Retrosternal goitre (RG) was first described by Albrecht von Haller in 1749 . Most commonly accepted definition of RG describes a goitre as substernal or retrosternal when a ≥ 50% portion of the mass is located in the mediastinum. RG is seen in 2-19% of all patients undergoing thyroidectomies. It most commonly presents in the fifth or sixth decade of life, with a female/male rate of 4:1. RGs can be classified as either primary or secondary. Primary intra-thoracic goitres arise from aberrant thyroid tissue which is ectopically located in the mediastinum, receives its blood supply from mediastinal vessels and is not connected to the cervical thyroid. They are rare, representing less than 1% of all RGs. Secondary RGs develop from the thyroid located in its normal cervical site. Downward migration of thyroid occurs towards mediastinum due to negative intra-thoracic pressure, gravity, traction forces during swallowing and the presence of anatomical barriers preventing the enlargement in other directions (thyroid cartilage, vertebral bodies, strap muscles, especially in patients with a short, large neck). They receive their blood supply, almost always from inferior thyroid artery, very commonly compress airways or oesophagus, and present with dyspnoea, choking, inability to sleep comfortably, dysphagia and hoarseness. Less commonly, they compress superior vena cava (superior vena cava syndrome) or sympathetic chain (Horner's syndrome). Computed tomography (CT) is most valuable for assessment of the extent of goitre and compression effects on adjacent anatomical structures. Magnetic resonance imaging (MRI) adds little and is not routinely used.[18]

EVALUATION OF THYROID DISEASES

Whenever the diagnosis of primary hypothyroidism is suspected it should always be confirmed by elevation of serum thyroid stimulating hormone (TSH) concentration.4 In overt hypothyroidism cases, serum TSH concentration is raised alongwith a low serum free thyroxine (FT4), while subclinical hypothyroidism, shows serum TSH is rise with normal serum FT4 and free triiodothyronine (FT3) concentrations.Positive thyroid antibodies are helpful in confirming autoimmunity. Mildly abnormal tests in patients with atypical or non-specific symptoms should be re-checked after six weeks as such abnormalities are commonly due to non-thyroidal illness rather than to intrinsic thyroid disease and will normalize with time.[19]

High-resolution US is the most sensitive test available to image and detect thyroid lesions, measure their dimensions, identify their structure, and evaluate diffuse changes in the thyroid gland. A lesion is highly suspicious if it is a solid hypoechoic nodule or solid hypoechoic component of a partially cystic nodule with one or more of the following features: irregular margins (infiltrative, microlobulated), microcalcifications, taller than wide shape, rim calcifications with small extrusive soft tissue component, evidence of extrathyroid extension . Such lesions should undergo FNAC when ≥ 1cm as risk of malignancy is >70–90%.

Evaluation of solitary thyroid nodule

Evaluation of solitary thyroid nodule consists of 2 components. First one should determine whether it is hyperfunctioning (autonomous) and causing hyperthyroidism and whether it is malignant . Malignant nodules require surgical removal . Evaluation of thyroid nodule consists of Serum TSH measurement followed by imaging studies and FNA biopsy. For patients with clinically or incidentally discovered thyroid nodules serum thyrotropin measurement is the initial and mandatory investigation . If the serum TSH is subnormal, a radionuclide (preferably ^{123}I) thyroid scan should be performed. If the serum TSH is normal or elevated, a radionuclide scan should not be performed as the initial imaging evaluation. The use of high-resolution ultrasonography (US), sensitive thyrotropin (TSH) assay, and fine-needle aspiration (FNA) biopsy is the basis for management of thyroid nodules. Measurement of serum TSH is the best initial laboratory test of thyroid function and should be followed by measurement of free thyroxine and triiodothyronine if the TSH value is decreased, and measurement of anti–thyroid peroxidase antibodies (TPOAb) if the TSH value is above the reference range. {ART10 Routine measurement of serum thyroglobulin (Tg) for initial evaluation of thyroid nodules is not recommended as it can be elevated in most thyroid diseases and are an insensitive and nonspecific test for thyroid cancer.[20] According to American thyroid association (ATA) there is no recommendation for or against routine serum calcitonin measurement in patients with thyroid nodules. Routine serum calcitonin for screening may detect C-cell hyperplasia and MTC at an earlier stage, and overall survival consequently may be improved. This may lead to earliest detection of C-cell hyperplasia and microMTC, though the clinical significance is uncertain. A single, nonstimulated (by pentagastrin) serum calcitonin measurement can be used in the initial workup of thyroid nodules and may be recommended before thyroid nodule surgery by some in the subgroup of patients in whom an elevated calcitonin may change the diagnostic or surgical approach (i.e., patients considered for less than total thyroidectomy, patients with suspicious cytology not consistent with PTC). If the unstimulated serum calcitonin level is greater than 50–100pg/mL, a diagnosis of MTC is common. There is emerging evidence that a calcitonin measurement from a thyroid nodule fine-needle aspiration (FNA) washout may be helpful in the preoperative evaluation of patients with a modestly elevated basal serum calcitonin (20–100pg/mL).

Serum calcitonin levels are increased in medullary thyroid cancer and in MEN –IIb. DNA analysis can show mutations in the RET- Proto-oncogenes in medullary carcinoma of Thyroid (MTC) & MEN syndromes. Serum carcinoembryonic antigen (CEA) levels are increased in MTC .

Serum anti - TPO antibody and anti- Tg (thyroglobulin) antibody levels are done to diagnose chronic autoimmune thyroiditis and is usually associated with serum TSH elevation.

Thyroid scintigraphy (^{123}iodine or ^{99m}technetium) in patients of solitary nodules is done when TSH level is low to detect autonomously functioning nodules (~5% of all).It is unnecessary when TSH is normal .Nodules with increased uptake (hot) are toxic adenomas and almost never malignant (1- 4% chance). Nodules with warm or cold uptake are often benign (~80%) but may be malignant in 20 -25% . All the patients of warm or cold nodules and/or hypo or euthyroid status require FNA Biopsy.

Ultrasonography can detect multiple nodules in patient with clinically solitary thyroid nodule. A dominant palpable nodule should be managed as solitary thyroid nodule even if ultrasonography reveals additional non-palpable nodular disease. Even a 1 mm size nodule could be detected with a high resolution ultrasonography. Non-palpable nodules greater than 1.0 to 1.5 cm represent an absolute indication to perform an ultrasound-guided fine needle biopsy. It can also help in differentiating malignant from benign nodules by detecting hypoechogenicity in solid nodules(up to 55% of benign nodules are hypoechoic compared to thyroid parenchyma, making nodule hypoechogenicity less specific), presence of microcalcifications, irregularity in shape, intranodular vascular spots, absence of halo & cystic elements, which suggests high chance of malignancy. On the other hand comet tail sign and coarse calcification suggests lower risk of malignancy. A nodule that has interrupted peripheral calcifications, in association with a soft tissue rim outside the calcification, is highly likely to be malignant, and the associated pathology may demonstrate tumor invasion in the area of disrupted calcification.[21] Features with the highest specificities (median >90%) for thyroid cancer are microcalcifications, irregular margins, and tall shape together although the sensitivities are significantly lower for any single feature. All patients with a palpable thyroid nodule or with clinical risk factors should undergo USG examination. It should also assess for the presence or absence of any suspicious cervical lymph nodes in the central or lateral compartments along with nodule size (in three dimensions) and exact location in the gland or lobe , composition (solid, cystic proportion, or spongiform – latter defined as the aggregation of multiple microcystic components in more than 50% of the volume of the nodule), echogenicity, margins, presence and type of calcifications, shape and vascularity. In patients with low serum TSH levels and nodularity on radionuclide thyroid scintigraphy , USG can detect associated other nonfunctioning nodules for need of FNAB.[22]

USG GUIDED FNA BIOPSY

allows accurate sampling & reducing false-negative rate. It is especially useful when nodule/s are difficult to palpate , during repeat FNAC after previous non diagnostic specimen, in nodules that are > 50% cystic and in lesions situated posteriorly. Thyroid nodule diagnostic FNA is recommended for : (A) Nodules ≥ 1cm in greatest dimension with high suspicion sonographic pattern. (B) Nodules ≥1cm in greatest dimension with intermediate suspicion sonographic pattern. (C) Nodules ≥1.5cm in greatest dimension with low suspicion sonographic pattern. Thyroid nodule diagnostic FNA may be considered for nodules ≥ 2cm in greatest dimension with very low suspicion sonographic pattern (e.g., spongiform) though observation without FNA is also a reasonable option. US-guided FNA biopsy is recommended for nodules smaller than 10 mm if clinical information or US features are suspicious. Findings are reported in either of 5 cytologic diagnostic categories as: nondiagnostic, benign, follicular lesion, suspicious, or malignant. The risk of cancer is not significantly higher for palpable solitary thyroid nodules than for multinodular glands or nodules embedded in diffuse goiters. For MNGs, the cytologic sampling should be focused on lesions with suspicious USG features rather than on larger or clinically dominant nodules. The coexistence of 2 or more suspicious USG criteria greatly increases the risk of thyroid cancer in that lesion.[23] Although most complex thyroid nodules with a dominant fluid component are benign, USG guided FNA biopsy should always be performed because papillary thyroid carcinoma (PTC) can be partially cystic. The USG characteristics suggestive of malignant involvement in impalpable thyroid nodules are the same as in palpable nodules. Thyroid nodule diagnostic FNA is not recommended for nodules that are purely cystic .

THYROID CYTOLOGY

Thyroid nodule FNA cytology should be reported using diagnostic groups outlined in the Bethesda System for Reporting Thyroid Cytopathology. The Bethesda system recognizes six diagnostic categories and provides an estimation of cancer risk within each category.

(1)Nondiagnostic or unsatisfactory: 1–4% cancer risk predicted and 20% (9–32%) Actual cancer post resection
(2)Benign : 0–3% cancer risk predicted and 2.5% (1–10%) Actual cancer post resection
(3) Atypia of undetermined significance or follicular lesion of undetermined significance (AUS/ FLUS): 5–15% cancer risk predicted and 14% (6–48%) Actual cancer post resection
(4) Follicular neoplasm or suspicious for a follicular neoplasm (FN/SFN) : 15–30% cancer risk predicted and 25% (14–34%) Actual cancer post resection
(5) Suspicious for malignancy : 60–75% cancer risk predicted and 70% (53–97%) Actual cancer post resection
(6) Malignant : 97–99% cancer risk predicted 99% and (94–100%) Actual cancer post resection[24]

US ELASTOGRAPHY

A thyroid nodule with firm or hard consistency is associated with an increased risk of malignancy. Elastography has recently been applied in the diagnostic approach to nodular thyroid disease and has shown a high sensitivity and specificity in selected patients. The predictive value of US-elastographic measurement seems to be independent of nodule size and is maintained for lesions that are indeterminate on FNA biopsy. Cystic nodules and nodules shown to have a calcified shell by USG are not suitable for US-elastographic evaluation. Because the

nodule to be examined must be clearly distinguishable from other nodules, MNGs with coalescent nodules are not suitable for this analysis.[25] Larger prospective studies are needed to establish the diagnostic accuracy of this technique

CT SCAN / MRI
have role in detecting local neck or upper thoracic spread & compression of neighbouring structures.

PET- SCAN
with ^{18}FDG imaging is not routinely recommended for the evaluation of thyroid nodules with indeterminate cytology and in other thyroid diseases. PET can identify thyroid incidentallomas during staging and surveillance for other malignancy in a patient. These PET detected nodules have been shown to have higher risk of malignancy.{ART10 ^{18}FDG-PET is not recommended for the evaluation of patients with newly detected thyroid nodules or thyroidal illness, the incidental detection of abnormal thyroid uptake may nonetheless be encountered when it was done for some other indication. Focal thyroid uptake most often corresponds to a clinically relevant thyroid nodule, and US examination is thus recommended to define thyroid anatomy alongwith FNAB of nodules which are ≥1cm as approximately one in three (~35%) ^{18}FDG-PET positive thyroid nodules proved to be cancerous. [26] In contrast, diffuse thyroid uptake most often represents benign disease corresponding to inflammatory uptake(chronic lymphocytic thyroiditis) .

FNAB / FNAC
is most accurate test for histological evaluation of thyroid nodules. Specimen adequacy requires ≥ 2 slides showing ≥ 6-8 cell clusters or 5 or 6 groups of 10 - 15 well preserved cells. False-positive rate is ~1.1% and false-negative rate is ~2.3% . Overall accuracy > 95%, sensitivity is 83 % and specificity is 92%. It is unable to distinguish follicular adenomas from follicular carcinomas, as carcinomas requires to reveal vascular or capsular invasion of the adenoma. Adequate sampling is difficult in cases of cystic lesions. Large needle biopsy can diagnose follicular carcinoma, though complications are more. Core biopsy (with or without USG guidance) should be considered after two futile aspirations.

Contrast-enhanced ultrasonography (CEUS) – can be done for the differentiation of benign and malignant thyroid nodules as there is a significant difference in enhancement between benign and malignant nodules. CEUS demonstrates sensitivity of 76.9%, specificity of 84.8% and accuracy of 82.6%. Quantitative analysis of CEUS using a microbubble contrast agent allows the differentiation of benign and malignant thyroid nodules as it is highly sensitive method for the detection of the microvascularization and may potentially serve, in addition to grey-scale and doppler ultrasound, as an adjunctive tool in the assessment of patients with thyroid nodules.[27]
Ultrasound is done using contrast pulse sequencing (CPS) ultrasound imaging mode. It uses a suspension of stabilized microbubble preparation containing sulfur hexafluoride with an average diameter of 2.5 μm made by 25 mg of lyophilized powder and 5 ml of 0.9% sodium chloride solution. Regular USG of thyroid is done including doppler flow signals. CEUS looks for most abundant blood flow signals within the lesion by power doppler. Trailing edge of the lesion is focussed , and the gain is adjusted to display only the boundaries of the lesion. Then, CPS is started and 2.5 ml of US contrast agent is injected intravenously through the ulnar vein, followed by injection of 5 ml of normal saline flush. Microbubble can flow in the microcirculation and resonate at a low mechanical index. The microvascular perfusion of the tumor can be displayed clearly by using low energy acoustic emission and pulse inversion harmonic imaging. The real-time dynamic images are stored over next 3 min. The contrast-enhancement patterns of the lesions show six aspects:

Degree of enhancement:
Category 1: enhancement is lower than the surrounding gland;
Category 2: similar to the surrounding gland;
Category 3: greater than in the surrounding gland)

Pattern of enhancement: centripetal enhancement and non-concentric (diffuse, eccentric) enhancement
(3) Homogeneity of enhancement: inhomogeneous or homogeneous
(4) Completeness of enhancement: incomplete (some area of lesion without contrast) or complete(entire lesion filled with contrast)
(5) Boundary of the enhanced lesions: blurred or well-defined
(6) Shape of enhanced lesions: irregular or regular

Most of malignant lesions show contrast-enhancement patterns of irregular (94.59%), blurred (86.49%), no significant enhancement (78.38% of malignant vs 95.12% of benign nodules show significant enhancement), inhomogeneous enhancement (78.38%) and incomplete enhancement (70.27%). Malignant nodules enhance less than benign nodules due to three reasons : (1) Inspite of neovascularization in cancerous tissue, its malignant invasive growth would undermine the organizational structure and blood vessels thereby causing necrotic blood vessel neovascularization. (2) Micro-thrombus and consequent stenosis and occlusion in malignant lesions, (3) Most malignant blood vessels are in low efficacy state (nonfunctional or nonopen) . Results of CEUS are very promising though it has not been included in clinical practice. ART 4. Currently, use of CEUS should be restricted to definition of the size and limits of necrotic zones after USG-guided ablation procedures.

THYROID SCAN

Technetium-99m-pertechnate is widely used for imaging the thyroid gland. ^{99m}Tc is trapped by thyroid, but unlike iodine, it does not undergo organification and remains in the gland for a relatively short period. Imaging is done 30 min after administration of radiotracer. ^{123}Iodine has a short physical half-life of 13 h. Both tracers are pure gamma emitters. ^{131}Iodine is worse for imaging (except metastases in thyroid differentiated cancer) because it gives a high absorbed radiation dose related to the long physical half-life of 8 days and beta emissions. It is ideal for the treatment of thyroid disease, and is used in the management of differentiated thyroid cancer, Graves' disease, and toxic nodular goitre.

Indications for thyroid scintigraphy and RAI uptake are: differential diagnosis of thyrotoxicosis, before treatment with radioiodine ^{131}I, measuring of goitre volume, ectopic goitre, congenital hypothyroidism. Other indications are metastases of well-differentiated thyroid cancer (eg. papillary or follicular cancer). Very rarely, ovarian goitre is present. Nuclear imaging of Graves' disease is characterized by an enlarged gland and increased tracer uptake (usually more than 55%) that is distributed homogenously. Toxic multinodular goitre shows irregular distribution of tracer and a normal or slightly elevated ^{131}I uptake. The irregular tracer distribution is consistent with heterogeneity in cell function and growth, and the presence of micro- and macronodules. Large and discrete hyperfunctioning nodules may be associated with poor uptake in the extranodular thyroid tissue. The latter consists of suppressed normal tissue with less tracer accumulation. After ^{131}I treatment, the areas that were cold may appear warm. Thyroid scanning is used in the follow-up of thyroid cancer . Whole body scans using 2-5 mCi (74-185 MBq) ^{131}I are performed after thyroid hormone withdrawal to raise the TSH concentration or after the administration of rhTSH.[28]

Evaluation of thyroid recurrent or metastatic DTC cancer

Recently, Gulec et al. presented the results of ^{124}I positron emission tomography/computed tomography (PET/CT) in patients with differentiated thyroid cancer (DTC) and found that it is a valuable clinical imaging tool in finding extent of disease and it should be used in patients suspected of recurrent disease based on increased thyroglobulin (Tg) levels but with a negative neck ultrasound. This group is of special interest, as currently no diagnostic modality is able to predict adequate uptake and benefit of treatment with radioactive iodine in tumor locations reliably. Diagnostic ^{131}I wholebody scintigraphy (WBS) has a low sensitivity and is therefore no longer recommended. ^{124}I PET/CT shows false negative results in comparison with post-treatment ^{131}I whole body scan (WBS). The sensitivity of ^{124}I PET/CT remains around 44%.[29]

For a patient of with metastatic or recurrent DTC it is very crucial to know whether he can be treated with ^{131}I, or the patient is iodine refractory, because ^{131}I is the most potent treatment modality for these patients. The use of ^{124}I PET/CT to make this decision, with an estimated patient-based sensitivity of 44–57%, would result in excluding about half of the patients from a potentially beneficial treatment. In conclusion, ^{124}I PET/CT as applied in the study by Gulec et al. and in other studies can lead to false negative results for patients with suspected recurrent DTC, and should therefore not yet be applied for treatment decisions in regular care.[29]

STAGING OF THYROID MALIGNANCY

Preoperative neck USG for cervical (central and especially lateral neck compartments) lymph nodes is recommended for all patients undergoing thyroidectomy for malignant or cytological and molecular suspicious lesions . USG guided FNA of sonographically suspicious lymph nodes ≥ 8–10 mm in the smallest diameter should be performed to confirm malignancy . The addition of FNA-Tg washout(thyroglobulin in FNA washout) in the evaluation of suspicious cervical lymph nodes is appropriate in select patients, but its interpretation may be difficult in patients with an intact thyroid gland. Sonographic features suggestive of abnormal metastatic lymph nodes include enlargement, loss of the fatty hilum, a rounded rather than oval shape, hyperechogenicity, cystic change, calcifications, and peripheral vascularity . No single sonographic feature is adequately sensitive for detection of lymph nodes with metastatic thyroid cancer . [24]

Neck imaging by CT/MRI/PET -- Preoperative cross-sectional imaging studies (CT, MRI) with intravenous (IV) contrast is recommended as an adjunct to US for patients with clinical suspicion for advanced disease, including invasive primary tumor, or clinically apparent multiple or bulky lymph node involvement. Routine preoperative ^{18}FDG-PET scanning is not recommended. CT can also visualize nodal regions beyond typical cervical regions like mediastinum, infraclavicular, retropharyngeal, and parapharyngeal regions. Neck CT with contrast can therefore be useful in delineating the extent of laryngeal, tracheal, and/or esophageal involvement in tumors displaying aggressive local invasion, as well as delineating bulky nodal disease, which may harbor significant extranodal extension that involves muscle and/or blood vessels. [30] Following IV contrast iodine is generally cleared within 4–8 weeks in most patients, so concern about iodine burden from IV contrast causing a clinically significant delay in subsequent whole-body scans (WBSs) or RAI treatment after the imaging followed by surgery is generally unfounded (315). The benefit gained from improved anatomic imaging generally outweighs any potential risk of a several week delay in RAI imaging or therapy. When there is concern, a urinary iodine to creatinine ratio can be measured.

Routine preoperative measurement of serum Tg or anti-Tg antibodies is not recommended.

TREATMENT

Benign Diffuse Goitre

The use of levothyroxine (LT4) to reduce the volume of the goiter is still a controversial treatment for large goiters, and the optimal surgical procedure for multinodular goiter is still debatable. Radioiodine is a safe and effective treatment option when used alone or in combination with recombinant human TSH. For non-toxic diffuse goiter or non-toxic nodular goiter , the following management goals should be considered:

a. Correct the underlying thyroid dysfunction, if present;
b. Verify if the goiter is growing or causing obstructive symptoms;
c. Exclude malignancy if one or more nodules are suspicious;
d. Determine whether the goiter requires therapy, and if so, weight the benefits and risks of medical and surgical interventions and discuss with the patient

The progressive and nodular increase in thyroid in non-toxic benign goiters is due to a combination of genetic and environmental factors, of which iodine deficiency is the most important . All individuals with benign non-toxic goiter must undergo serum TSH measurement and thyroid ultrasonography to diagnose existence of nodules and guide the selection of the nodule (or nodules) to be biopsied. After exclusion of malignancy, treatment should be considered for individuals with compression of local structures, cosmetic concerns, and/or thyroid hyperfunction. In patients with benign non-toxic goiter , the size of the goiter and the occurrence of symptoms often follow a non-linear association.

Non-Toxic Diffuse Goiter (NDG)

There is no ideal therapy for NDGs, but for patients requiring treatment, clinical management is the most frequent choice. It is unclear whether or not treatment for early NDGs can inhibit the development of nodular goiter. Prolonged TSH stimulation, which frequently occurs in association with iodine deficiency, has an important role in thyroid enlargement. In these circumstances, iodine supplementation would be an adequate approach (400 µg of iodine for 8–12 months). A significant reduction in goiter size has been observed in patients with NDG supplemented with iodine. In fact, supplementation with iodine 400 µg/day has been demonstrated to be as effective as suppressive therapy with LT_4 150 µg/day though iodine supplementation is not accepted as treatment in few European countries. In contrast, a beneficial effect of LT4 has been shown in NDG.[31] A volume reduction of 50% or more is achieved in 31% of patients after 6 months. If suppressive treatment is considered, then administration of thyroid hormone in enough doses to inhibit or reduce TSH secretion may be used. However, it should be considered that the volume of the goiter returns to pretreatment size after LT_4 withdrawal. The benefits of such therapy must be weighed against the potential risks of TSH suppression. Regarding radioiodine therapy in NDG, two small uncontrolled studies are available. In the first study comprising 11 patients the mean thyroid volume reduction achieved with a single dose of radioiodine within the first year was 62%, and 2 of the 11 patients (18%) developed hypothyroidism.[33] In another study on 10 patients the thyroid volume by ultrasonography declined by 50% within 12–18 months and one patient (10%) developed persistent hypothyroidism and another (who presented positive antithyroperoxidase levels) developed transient hypothyroidism.[34]

Non-Toxic Nodular Goiter (NNG)

The ideal treatment for NNG is controversial. The enlargement of goiter may become stable or reduce spontaneously with time in around 20% of the women and 5% of the men. Current alternatives for NNG treatment include

- Clinical observation for asymptomatic patients
- Thyroid hormone suppressive therapy
- Radioiodine therapy alone or preceded by recombinant human TSH (rhTSH)
- Surgery

Among these options, treatment is chosen individually for each patient in view of the risks, benefits, and availability of the various techniques, experience of the treating physician, and patient's personal preference

Clinical Observation

Clinical observation, including yearly clinical examination, thyroid function monitoring and ultrasonographic assessment at regular intervals, is an alternative in cases of small goiters not causing compressive symptoms and associated with normal thyroid function. If clinical observation is chosen, the possibility of malignancy should be excluded by fine-needle aspiration biopsy (FNAB) that is guided by ultrasonography. Asymptomatic euthyroid patients with benign non-toxic goiter and without cosmetic symptoms may be simply observed with clinical and laboratory evaluation and thyroid imaging tests. The American Thyroid Association recommends a standard follow-up interval of 6–18 months for patients with NNG, which may be gradually prolonged if no substantial changes are observed during the first 3–5 years.

Suppressive therapy with Levothyroxine

Although LT_4 is broadly used in the United States, Europe, and Latin America , the use of thyroid hormones to treat NNGs is controversial. Considering that NNG patients frequently have normal serum TSH levels, the enlargement of the thyroid in these patients is probably associated with the prolonged action of different growth factors (including TSH) on thyroid follicular cells with different synthetic and growth potentials. Advantages of this treatment modality include low cost, administration on an outpatient basis, and inhibition of the development of new nodules. In contrast, suppressive therapy has little effectiveness, as it delays permanent treatment and may have potential

undesirable effects on bone (demineralization) and heart (arrhythmias), especially in older individuals. There is chance of return to original volume after treatment withdrawal. A randomized trial comparing suppressive therapy with radioiodine highlights the dismal response potential of suppressive therapy as patients in radioiodine group showed a 35% reduction in goiter volume at 1 year and 44% at 2 years, whereas those who received LT_4 presented 7 and 1% reduction at 1 and 2 years, respectively. A response to the therapy was found in 97% of the individuals who received radioiodine and 43% of those undergoing LT_4 therapy.[35]

Also, about 22% of the individuals with NNG may harbor areas with functional autonomy, which increase the concerns with LT_4 therapy because of risks of bone loss and atrial fibrillation. Therefore, treatment with thyroid hormone should be avoided, especially in patients with prior serum TSH concentrations below the normal range. The reduction in goiter size with LT_4 seen in some individuals is probably due to decreased TSH secretion, especially in patients who live in areas with borderline or low iodine levels. Any decrease in NNG size that may occur with LT_4 suppression is lost when the treatment is interrupted, and the nodules and goiter may grow again in size. A LT_4 dose adjusted to obtain a non-suppressive level of serum TSH in the range of 0.5–0.8 μU/mL has been shown to significantly reduce the growth of nodules within multinodular goiters in 165 out of 356 female patients during a follow-up period of 9 years.[36]

Surgery

The best surgical procedure to treat patients with NNG is still controversial. The recurrence of goiter is lower in patients who undergo total thyroidectomy compared with those who undergo subtotal thyroidectomy, with rates of goiter recurrence of 8.4 % in patients undergoing subtotal thyroidectomy and 0.5 % in total thyroidectomy patients. No clear benefits or harms are observed with subtotal or total thyroidectomy in patients in terms of recurrence in goiter size, complications such as permanent recurrent laryngeal nerve palsy, or occurrence of thyroid carcinoma. Also the cancer detection rate is lower (6.1%) but insignificant in patients undergoing subtotal thyroidectomy compared with 7.3% of those undergoing total thyroidectomy. In most patients total thyroidectomy is preferable over subtotal thyroidectomy due to higher recurrence rates and 2.5–42% requiring a new intervention in case of latter. Rates of permanent complications, such as hypoparathyroidism and vocal palsy, are similar with both surgeries but new intervention if required will increase chance of these complication. [37] In patients with unilateral NNG, some authors recommend unilateral thyroidectomy based on a low rate of recurrence (2%) and high rate of maintenance of euthyroidism (73%). A cervical incision is often used to approach intrathoracic goiters; however, 10–30% of the patients require sternotomy or thoracotomy.

After total thyroidectomy, patients are started on LT_4 replacement at a dose of 1.4–2.2 μg/kg/day. However, in patients undergoing partial thyroidectomy, treatment with LT4 should be implemented after the establishment of hypothyroidism and not preventively against goiter recurrence, because this benefit has not been confirmed in randomized studies.

Therapy with radioiodine

Therapy with radioiodine may be recommended in cases of NNG affecting patients who refuse or have contraindications for surgery. Over the past years, this type of treatment has increased in patients with nodular goiter and is associated with a substantial decrease in glandular volume, reaching 30–40% in the first year, and 50–60% in the fourth year. Obstructive symptoms improve in most individuals, with reports of a single dose administered orally restoring euthyroidism over a period of 2–4 months. Patients receive 100 μCi of radioiodine per gram of thyroid tissue and show 100% uptake in 24 h with approximate reduction in goiter volume of 41% after 1 year of follow-up. The larger the volume of the gland and the lower the radioiodine uptake (RAIU), the higher should be the radioiodine activity to be administered.[38] In some European countries such as Denmark and the Netherlands (to some degree), radioiodine has currently replaced surgery as the treatment of choice for NNG. Some patients develop temporary mild thyrotoxicosis within the initial 2 weeks of treatment, and about 45% of them develop hypothyroidism, requiring thyroid hormone replacement for life. The occurrence of hyperthyroidism due to Graves' disease associated with increased serum concentrations of TSH receptor antibodies has also been described in patients with increased baseline levels of thyroid peroxidase antibodies after radioiodine treatment for NNG. Based on measurements of whole-body radiation exposure, the theoretical lifetime risk of development of cancer outside the thyroid gland has been calculated as 1.6%. Several studies have assessed the adjuvant role of rhTSH in the radioiodine treatment of NNG. Administration of rhTSH is associated with a twofold to fourfold increase in RAIU by the thyroid. Since patients with NNG often present low serum TSH, the radioiodine is only taken up by some "hot" areas encircled by suppressed thyroid tissue that is inactive on scintigraphy. Upon stimulation with rhTSH, these dormant areas, reactivate and eventually amplifies the effect of the radioiodine in the gland and better volume reduction. rhTSH has been shown to distribute the radioiodine more homogeneously in the goiter. One or two rhTSH doses range from 0.1 to 0.3 mg are administered 24 h prior to the radioiodine. However, the dose with ideal efficacy and safety is yet to be defined.[40] To avoid unintentional stimulation of the thyroid, a "modified-release rhTSH" (MRrhTSH) has been recently introduced.Both rhTSH and MRrhTSH are not approved by the US Food and Drug Administration or European Medicines Agency to treat NNG in association with radioiodine; so, their use for this purpose is currently off-label.

In summary, individuals with NDG should receive clinical rather than surgical treatment. Individuals with NDG should be thoroughly evaluated to exclude malignancy. They should then receive individualized therapy after assessment of risks and benefits of each treatment option and discussion with their physicians. The first therapeutic

option is total thyroidectomy, followed by treatment with radioiodine alone or after rhTSH stimulation to increase the radioiodine efficacy. It is unclear if suppressive therapy with thyroid hormone is effective in patients with NNG.

GRAVE'S DISEASE (GD)

is the most common cause of hyperthyroidism. There are three treatment modalities for GD: antithyroid drugs (ATD), radioactive iodine (RAI), and surgery. These options differ in their efficacy, safety, convenience, and cost. No treatment option is clearly superior to others for everyone. Clinicians in Europe and Asia prefer to prescribe ATDs, while clinicians in the United States prefer RAI. The extent to which clinician preferences translate into practice is unknown. The most common treatment of GD in commercially insured patients in the United States today is ATD. An increase of ATD use started in 2005 at the expense of RAI use. Preference to prescribe methimazole over propylthiouracil may reflect its ability to control thyrotoxicosis quickly and the recognition of propylthiouracil's adverse safety profile.

MANAGEMENT OF SOLITARY THYROID NODULE

Benign thyroid nodules -- Routine TSH suppression therapy for benign thyroid nodules in iodine sufficient populations is not recommended. Though modest responses to therapy can be detected, the potential harm outweighs benefit for most patients. Hyperthyroidism caused by TSH suppression has been significantly associated with an increased risk of cardiac arrhythmias and osteoporosis, as well as adverse symptomatology. If inadequate dietary intake is found or suspected, a daily supplement (containing 150 µg iodine) is recommended. Evidence suggests that surgery can help if they are large (>4cm) and causing compressive or structural symptoms, or based upon clinical concern and should be considered after counselling the patient. Most asymptomatic nodules demonstrating modest growth should be followed without intervention. There are no data to recommend use of thyroid hormone therapy in patients with growing benign nodules . Cystic nodules that are cytologically benign can be monitored for recurrence (fluid reaccumulation), which can be seen in 60%–90% of patients.[24]

Levothyroxine suppressive therapy, is only considered for small nodular goiters in young patients living in iodine-deficient regions. The effect of LT_4 suppression on bone metabolism, but this seems to be a problem predominantly among postmenopausal women, and not among premenopausal women. If treatment is aimed at reduced but not totally suppressed TSH values, there is less effect on the skeleton. Overall, the consequences of low level subclinical thyroid disease (serum TSH 0.1-0.45 mU/L) seem to be minimal. Low level LT_4 suppression will reduce the chance of malignancy by half.[41]

TOXIC SOLITARY THYROID NODULE

Oral administration of 20 mCi of radioiodine is a simple and highly effective method for the treatment of patients with a toxic autonomous thyroid nodule. A solitary autonomous thyroid nodule is treated with radioiodine only when it is clinically and biochemically hyperthyroid. Amongst the long-term effects of radioiodine treatment on thyroid function in patients with a toxic solitary autonomous thyroid nodule it is seen that following therapeutic dose of 20 mCi of iodine-131 (^{131}I) the failure rate (recurrent hyperthyroidism) is 2%. Higher recurrence rates occur when standard dose of 15-20 mCi is not used and it is adjusted according to the individual size of the nodule. The incidence of hypothyroidism is around 6% and is not related to the dose per gram of nodular tissue. The risk of development of hypothyroidism is low or almost prevented if extranodular uptake of ^{131} I prevented. This can be achieved by not treating euthyroid patients, by no longer using injections of exogenous thyroid stimulating hormone in the diagnostic work-up of the patients and by always performing radioiodine imaging shortly before treatment. Extranodular iodine uptake is, of course, frequently seen in patients with a solitary autonomous thyroid nodule who are not thyrotoxic and when the pretreatment radioiodine image reveals uptake of iodine in extranodular parenchyma, therapy has to be postponed or should be avoided. Patients become euthyroid within 0.5 yr after a standard dose of 20 mCi of ^{131}I. [42]

MALIGNANT NODULE

1. In pregnancy-- PTC discovered by cytology in early pregnancy should be monitored sonographically. If it grows substantially before 24–26 weeks gestation, or if USG reveals cervical lymph nodes that are suspicious for metastatic disease, surgery should be considered during pregnancy. However, if the disease remains stable by midgestation, or if it is diagnosed in the second half of pregnancy, surgery may be deferred until after delivery. Scientific data supporting this recommendation is weak . Utility of thyroid hormone therapy targeted to lower serum TSH levels to improve the prognosis of thyroid cancer diagnosed during gestation is not known. Most data confirm that the prognosis of women with well differentiated thyroid cancer identified but not treated during pregnancy is similar to that of non pregnant patients. When surgery is advised during pregnancy, it is most often because of high-risk clinical or sonographic findings, nodule growth, or change over short duration follow-up or it is based upon physician judgement. To minimize the risk of miscarriage, surgery during pregnancy should be done in the second trimester before 24 weeks gestation.[43]
2. Malignant Nodule with follicular cytology or those with size more than 1 cm or advanced symptoms and signs requires total thyroidectomy followed by possible ablative therapy with radioactive ^{131}iodine.
3. For solitary cytologically indeterminate thyroid nodules thyroid lobectomy is the recommended initial surgical approach. This approach may be modified based on clinical or sonographic characteristics, patient preference, and/or molecular testing when performed. Because of increased risk for malignancy, total thyroidectomy may be preferred in patients who are positive for known mutations specific for carcinoma, sonographically suspicious, or large (>4cm), or in patients with familial thyroid carcinoma or history of radiation exposure.[24]

4. Benign Nodule should be monitored for nodule size by periodic palpation and ultrasonography. Use of TSH suppression with levothyroxine, in the hope of shrinking the nodule, is now generally not recommended. Thyroidectomy should be done if a nodule enlarges or develops in a patient whose serum thyroglobulin rises in spite of TSH suppression with thyroxin. Risk of thyrotoxicosis must be considered If Levothyroxin is used. If instituted, use 0.05-0.1 mg/d, and monitor nodule size by ultrasonography. Serum TSH should be monitored with the goal of attaining a subnormal, but not immeasurable, TSH level (0.3-1 mU/L). Levothyroxin-suppressive therapy should be discontinued if there is no evidence of reduction in nodule size. It is contraindicated in patients > 60 years of age, postmenopausal women, and persons with a low TSH levels. Repeat FNA analysis of benign nodules that have not grown substantially is not warranted.
5. Toxic Adenoma is treated by radioactive ^{131}iodine ablation (most commonly). Surgical resection and Antithyroid drugs are less preferred. Percutaneous ethanol sclerotherapy has been described but not used in clinical practice.
6. Thyroid Cyst Aspiration will resolve 25-50% of cysts, but fluid reaccumulation is common. Aspiration could be repeated thrice. Surgery is indicated for growing or painful cysts, recurring after three aspirations, size > 4cm, or complex (both solid and cystic).Percutaneous ethanol sclerotherapy has been described.
7. Non toxic solitary thyroid nodule when shows rapid nodule growth or the original size is large (more than 5cm) requires surgical removal irrespective of FNAB results .

HASHIMOTOS THYROIDITIS

Thyroiditis is usually asymptomatic and the goiter is small, many patients do not require treatment.6 When hypothyroidism is present, treatment with thyroxine (T) is indicated.7 Thyroid hormone replacement therapy is also indicated in patients with a TSH level in the normal range, to reduce goiter size and prevent progression to overt hypothyroidism in high-risk patients.[7] Lifetime replacement of levothyroxine is indicated in hypothyroid patients, at a starting dosage of 25 to 50 µg per day, with gradual titration to an average daily dosage of 75 to 150 µg. A lower starting dosage (12.5 to 25 µg per day) and a more gradual titration are recommended in elderly patients and in patients with cardiovascular disease. The dosage may be increased in these patients 25 to 50 µg every four to six weeks until the TSH level is normal. In patients with an elevated TSH level and a normal thyroxine (T) level (subclinical hypothyroidism), indications for treatment are less clear. If the TSH level is greater than 20 mU per mL (20 mU per L) with a normal T level, there is a high probability that the patient will develop hypothyroidism. If the TSH level is elevated but is less than 20 mU per mL and the antimicrosomal antibody titer is greater than 1:1,600, hypothyroidism will develop in 80 percent of patients. Therefore, it is recommended that treatment be initiated in patients with symptoms of hypothyroidism, in patients with a serum TSH level greater than 10 mU per mL (10 mU per L) and in patients with a high risk of progression to hypothyroidism (e.g., those with high antibody titers).[7]Because of the risk of developing hypothyroidism, patients with a history of chronic lymphocytic thyroiditis require annual assessment of thyroid function.

SUBACUTE LYMPHOCYTIC THYROIDITIS

Acute symptoms of hyperthyroidism are managed primarily with beta blockers. Antithyroid drugs are not indicated in the management of patients with hyperthyroidism because symptoms are caused by the release of preformed thyroid hormones from damaged gland. Replacement of thyroid hormone in the hypothyroid phase is indicated if the patient's symptoms are severe or of long duration. If the hypothyroid phase lasts longer than six months, permanent hypothyroidism is likely.[6]

SUBACUTE GRANULOMATOUS THYROIDITIS

The natural history of subacute granulomatous thyroiditis involves four phases that generally unfold over four to six months. There is acute phase of thyroid pain and thyrotoxicosis lasting three to six weeks or longer. Transient asymptomatic euthyroidism follows. Hypothyroidism often ensues and may last weeks to months or may be permanent (in up to 5 percent of patients). The final phase is a recovery period, during which thyroid function tests normalize. Therapy with antithyroid drugs is not indicated. Therapy with beta blockers may be indicated for the symptomatic treatment of thyrotoxicosis. Nonsteroidal antiinflammatory drugs are generally effective in reducing thyroid pain in patients with mild cases. Patients with more severe disease require a tapering dosage of prednisone (20 to 40 mg per day) given over two to four weeks. Up to 20 percent of patients experience the recurrence of thyroid pain on discontinuation of prednisone.[7]

MICROBIAL INFLAMMATORY THYROIDITIS

When the cause of the infection is determined, appropriate parenteral antibiotics should be prescribed. Patients with abscesses require surgical drainage and, possibly, a thyroid lobectomy. Heat, rest and aspirin provide symptomatic relief; steroids may offer additional benefit.13The disease is usually self-limited, lasting weeks to months.

INVASIVE FIBROUS THYROIDITIS

Because of the similarity between fibrous thyroiditis and thyroid carcinoma, diagnosis must be made using open biopsy. The disease is usually self-limited, with surgical wedge resection of the thyroid isthmus being the mainstay of treatment in symptomatic patients.

THYROID MALIGNANCY

Accurate staging is important in determining the prognosis and tailoring treatment for patients with DTC. The presence of metastatic disease does not obviate the need for surgical excision of the primary tumor in DTC.

Because metastatic disease may respond to RAI therapy, removal of the thyroid as well as the primary tumor and accessible loco-regional disease remains an important component of initial treatment even in most patients with metastatic disease.[24]

The basic goals of initial therapy for patients with DTC are to improve overall and disease-specific survival, reduce the risk of persistent/recurrent disease and associated morbidity, and permit accurate disease staging and risk stratification, while minimizing treatment-related morbidity and unnecessary therapy. The specific goals of initial therapy are to

1. Removal of primary tumor and clinically significant lymph node metastases. Completeness of surgical resection is an important determinant of outcome, while residual metastatic lymph nodes represent the most common site of disease persistence/recurrence.
2. Adequate surgery is the most important treatment variable influencing prognosis, while RAI treatment, TSH suppression, and other treatments each play adjunctive roles in at least some patients.
3. Facilitate postoperative treatment with RAI, by removing all functional thyroid tissue so that RAI remnant ablation, or RAI treatment of presumed (adjuvant therapy) or known (therapy) residual or metastatic disease can be facilitated.
4. Permit accurate postoperative staging and risk stratification of the disease to guide initial prognostication, disease management, and follow-up strategies.
5. Accurate long-term surveillance for disease recurrence.
6. Minimum treatment-related morbidity which is determined by the extent of surgery and the experience of the surgeon both[24]

According to American Thyroid Association (ATA) guidelines 2015, lobectomy might be considered as the initial surgical approach for follicular cell-derived thyroid cancers from 1 to 4cm in size. For surgical management of thyroid cancer, total thyroidectomy is no longer mandatory for all patients with primary thyroid cancers >1cm.
For patients with thyroid cancer >4cm, or with gross extrathyroidal extension (clinical T_4), or clinically apparent metastatic disease to nodes (clinical N_1) or distant sites (clinical M_1), the initial surgical procedure should include a near-total or total thyroidectomy and gross removal of all primary tumor unless there are contraindications to this procedure . For patients with thyroid cancer >1cm and <4cm without extrathyroidal extension, and without clinical evidence of any lymph node metastases (cN0), the initial surgical procedure can be either a bilateral procedure (near total or total thyroidectomy) or a unilateral procedure (lobectomy). Thyroid lobectomy alone may be sufficient initial treatment for low-risk papillary and follicular carcinomas; however, the treatment team may choose total thyroidectomy to enable RAI therapy or to enhance follow up based upon disease features and/or patient preferences.

If surgery is chosen for patients with thyroid cancer <1cm without extrathyroidal extension andcN0, the initial surgical procedure should be a thyroid lobectomy unless there are clear indications to remove the contralateral lobe. Thyroid lobectomy alone is sufficient treatment for small, unifocal, intrathyroidal carcinomas in the absence of prior head and neck radiation, familial thyroid carcinoma, or clinically detectable cervical nodal metastases. Previous guidelines have endorsed total thyroidectomy as the primary initial surgical treatment option for nearly all DTCs >1cm with or without evidence of loco-regional or distant metastases. This was based on retrospective data suggesting that a bilateral surgical procedure would improve survival , decrease recurrence rates, allow for routine use of RAI remnant ablation, and facilitate detection of recurrent/persistent disease during follow-up. However, recent data have demonstrated that in properly selected patients, clinical outcomes are very similar following unilateral or bilateral thyroid surgery. In some patients, the presence of the remaining lobe of the gland may obviate the lifelong need for exogenous thyroid hormone therapy. Finally, follow-up management includes greater reliance on neck ultrasonography and serial serum Tg measurements (even in patients that did not receive RAI remnant ablation). [44]

Follicular variant of papillary thyroid carcinoma (FVPTC)
The prognosis of the follicular variant of papillary thyroid carcinoma (FVPTC) falls between that of classical papillary thyroid carcinoma (cPTC) and follicular thyroid carcinoma (FTC) (1). FVPTC has lower mortality and less frequent distant metastases than FTC, but higher mortality and more frequent distant metastases than cPTC .FVPTC has fewer lymph node metastases and less frequent infiltrative disease and extrathyroidal extension than cPTC , but more than FTC. But it is questionable whether it is hybrid disease or a mixture of two different thyroid malignancies . The initial operation for many of these patients is a hemi-thyroidectomy (given atypia of undetermined significance/follicular lesion of undetermined significance or follicular neoplasm cytopathology). Therefore, many of these patients are subjected to completion thyroidectomy and radioactive iodine therapy. Noninvasive encapsulated (or circumscribed) FVPTC behave in an indolent fashion, and therefore should not be considered malignant , rather they are benign.[15]

In differentiated thyroid cancer (DTC), the aim of thyroid hormone therapy is to correct postablative hormone deficiency as well as optimize outcomes via TSH suppression. TSH is a thyroid growth factor and high TSH levels stimulate malignant growth and may worsen prognoses in patients with DTC. It is recommend that serum TSH concentrations should be suppressed in all patients in the immediate postablative period and then subsequent targets determined according to the postablation risk stratification. Patients with a satisfactory treatment response can be maintained at a low-normal TSH concentration (0.3–2.0mU/L). A serum TSH concentration in the range

0.1–0.5mU/L is recommended for individuals with indeterminate response whereas patients with high risk or incomplete response should aim for serum TSH concentrations <0.1mU/L.[45]

RETROSTERNAL GOITRE

Retrosternal goitre is defined as a goitre with a portion of its mass ≥ 50% located in the mediastinum. Surgical removal is the treatment of choice and, in most cases, the goitre can be removed via a cervical approach. Surgical removal of a retrosternal goitre is a challenging procedure; it can be performed safely, in most cases, via a cervical approach, with a complication rate slightly higher than standard cervical disease only. Hypoparathyroidism and post-operative bleeding are the commonest concerns. The most significant criteria for selecting patients requiring sternotomy are computed tomography features, in particular the presence of an ectopic goitre, the thyroid gland volume and the extent of the goitre to or below the tracheae carina. Surgery is the only treatment whether the patient is symptomatic or not .There are numerous reasons for performing surgery in such cases:

Non-surgical treatment of RG with thyroid hormone or radioactive iodine ablation is very rarely successful .

In addition tissue edema following latter can cause life threatening compressive symptoms just like a sudden enlargement of the goitre, secondary to haemorrhage or malignant change

Chances of malignancy are 3-21 % of RGs, and it can be missed, it is difficult and potentially dangerous to perform FNA Biopsy from mediastinal portion of a RG.

Most RGs can be removed through a cervical approach, while a partial or total sternotomy is required in a minority of patients, ranging between 1 - 11% . Access to the goitre is obtained by vertical extension of the cervical incision downward, towards the sternal manubrium. The inferior pole of thyroid is dissected using fingers from the mediastinal tissues . The major risk of this manoeuvre is poor access and control of vascular structures, a higher risk of bleeding. Risk of rupture of the veins is less as due to cervical origin of the vessels, they usually descend in the mediastinum, behind the mediastinal extension of the goitre, thereby allowing the digital dissection of the thyroid and then its cervical dislocation before ligation or coagulation of the vessels. The ultrasonic instruments, can be very useful in the coagulation and resection of small thyroid vessels in the mediastinum. Four factors which can predict the need to perform sternotomy are :(1). the presence of malignancy(2). involvement of the posterior mediastinum (3). extension of the goitre below the aortic arch and (4). the presence of ectopic goitre.[18]

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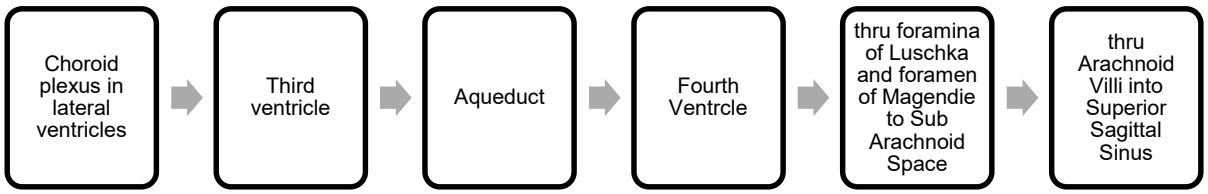
Hydrocephalus

S Bhaskar

CSF

1. Choroid plexus contributes 70-80% of daily CSF production. Brain parenchyma and ependymal lining produce a small proportion of CSF. It occurs by a combination of filtration across the endothelium and active secretion of sodium by the choroid epithelia. CSF is produced at the rate of 0.33 ml/min, around 500 ml per day. The total volume of CSF is around 100-150 ml in an adult. So the entire volume is circulated 3-4 times in 24 hours. The pathway of CSF, which is largely produced in the lateral ventricles, is it flows into the third ventricle thru the foramen of Monro and then into the fourth ventricle via the aqueduct. From the fourth ventricle it goes into the subarachnoid space by the two lateral (Foramina of Luschka) and one midline (Foramen of Magendie) foramen. The CSF passes into the subarachnoid spaces and from the parasagittal arachnoid granulations gets absorbed into the blood stream. The arachnoid villi are herniations of the arachnoidal tissue into the dural venous sinuses. There are two proposed mechanisms for absorption thru the villi- "closed" wherein the CSF is absorbed thru seepage across the endothelial lining. The "open" mechanism suggests the presence of channels acting like a one-way valve. Couple of other mechanisms is trans membrane transport by vacuoles carrying CSF across the endothelial layer and the role of the microcirculation of the CNS in absorption.



Hydrocephalus

The incidence of congenital hydrocephalus is 0.2-0.5/1000 live births. The incidence is higher in elderly primiparous mothers. It is classically divided into obstructive and non-obstructive hydrocephalus. Another classification is communicating and non-communicating hydrocephalus based on whether there is a block between the ventricular and subarachnoid CSF spaces.

The hydrocephalus may be classified into three categories

1. Over production of CSF
2. Obstructive: Level- Lateral ventricle, foramen of Monro, Third ventricle, Aqueduct of Sylvius, Fourth ventricle, subarachnoid spaces
3. Absorption defect

Classification based on aetiology:

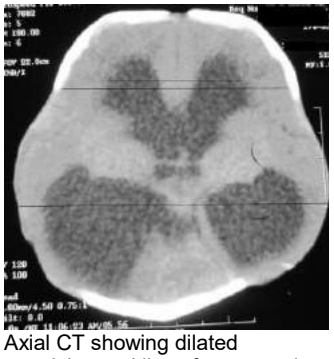
- Congenital- e.g.; aqueductal stenosis
- Traumatic- e.g.; post traumatic
- Inflammatory- e.g.; tuberculous meningitis hydrocephalus
- Neoplastic- e.g.; posterior fossa tumors

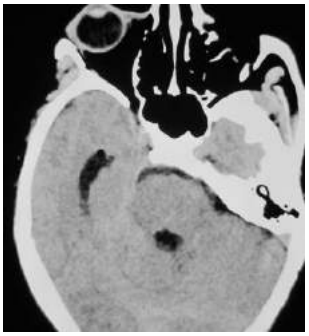
Clinical Features

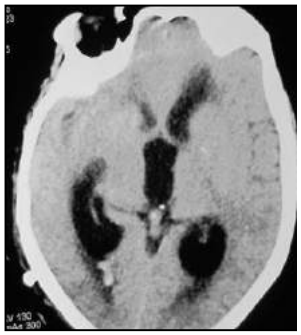
The clinical features are dependent on the age. In neonates as the sutures are open there is increase in the size of the head, bulging fontanelle, dilated veins over the scalp, sun-set sign. The child can present with irritability, refusal to accept feeds. Measuring the head circumference of the child at regular intervals and plotting it against centile chart is done to monitor it. In older children and adults the symptoms of raised ICP, headache, vomiting, and drowsiness is more likely to be seen as presenting features of hydrocephalus. In an entity called Normal Pressure Hydrocephalus seen in adults, especially older age group it presents as dementia, urinary incontinence and gait disturbance.

Investigations

Cranial ultrasonography can be used in neonates with open fontanelle to assess ventricular size and any hematoma or masses causing hydrocephalus. USG is a non-invasive method and can be used to monitor ventricular size. Plain X-rays are no longer used to diagnose or monitor hydrocephalus. In the current times CT and MRI are the two main modalities used to diagnose this condition. The obvious advantage of a MRI is the absence of radiation, better visualization of intracranial structures. The disadvantages include availability, cost in a country like ours, time taken to image and the need to sedate the children for doing the study. CT is more widely available, cheaper than a MRI but exposes the developing brain to radiation, which in the longer run might cause cumulative damage.
The ventricular size and shapes are studied to diagnose hydrocephalus. Radiological criteria used for diagnosis of hydrocephalus- Dilatation of temporal horns (>2 mm), Evans index, Frontal horn: Internal diameter ratio. Presence of periventricular ooze (due to seepage of CSF transependymally into the parenchyma), obliteration of sulci. This appears as a hypodensity on CT and T2 hyperintensity on MRI around the ventricles especially around the frontal horns.


Axial CT showing dilated ventricles and lines for measuring frontal horn: Internal Diameter & Evans ratio (Frontal horn: Biparietal diameter)


Axial CT showing dilated temporal horn


Axial CT showing dilated ventricles (lateral and third)

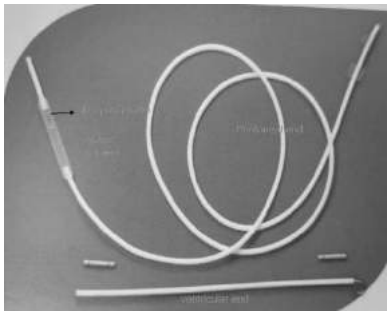
Treatment

Medical

Medical management includes diuretics like furosemide that reduce the production of CSF by decreasing the overall fluid status in the body. Acetazolamide inhibits carbonic anhydrase enzyme, which is present in the choroid plexus and is necessary for production of CSF. The medical management is helpful in cases where the hydrocephalus is mild and also temporary like for example in post-haemorrhagic hydrocephalus.

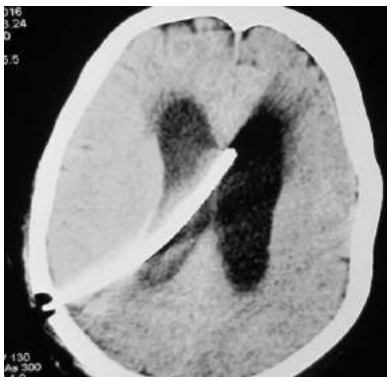
Surgical

The principle of surgery for hydrocephalus is bypassing the obstruction in the CSF pathway. This is done by placing a shunt from the ventricular space to peritoneal/pleural/atrial cavities. The ventriculoperitoneal shunt is one of the most commonly done procedures for hydrocephalus. In situations where this is not possible for e.g., adhesions, diseased peritoneal cavity etc., alternative sites for placement that have been successfully attempted are gallbladder, thoracic duct, ileum, ureter, and fallopian tube.



The same principle is used in placing shunts for communicating hydrocephalus wherein a shunt is placed from the lumbar subarachnoid space to the peritoneal cavity.

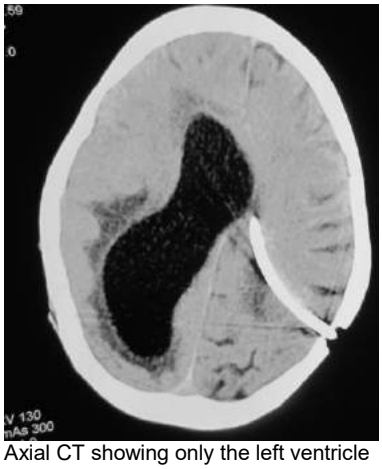
The shunt has a ventricular end that has a blind end with side holes for CSF flow. The distal end has a valve to allow CSF flow into the peritoneal cavity and prevent viscera to enter the shunt limen. There is a valve placed at the cranial end. The valve designs are based on differential pressures (fixed or programmable) or flow control type. The different valves used are slit and spring, ball and spring, mitre and diaphragm. The fixed valve shunts are available in low, medium and high pressure setting valves. These valves open and close at prefixed pressures. To overcome the drawbacks of these fixed pressure valves, programmable valves have been designed. In these devices an externally applied magnetic field is used to change the pressure setting in the valve. The disadvantage is the cost of these implants. The shunt system can have an anti-siphon device that will prevent the complication of over drainage due to siphon effect.



There are many commercial available shunt systems. There are two Indian fixed pressure shunt systems, Chhabra and Cere Drain (Sri Chitra shunt system). These are relatively cheaper as compared to the foreign shunt systems and have been equally effective.

Complications of shunts

These can be classified into mechanical- blockage, disconnection, migration, shortening. Flow related- over drainage causing subdural or extradural hematoma, intraventricular hemorrhage, low-pressure headache, secondary craniostenosis and cranial deformity (in children). The slit ventricular syndrome wherein the ventricular size is small on imaging but due to the non-compliance of the ventricular wall the pressure may be high.



Axial CT showing only the left ventricle being drained by the shunt

The complications at the sites of distal catheter placement include- peritoneal collections, symptomatic pleural effusion, cardiac failure. Perforations at various sites including stomach, small and large bowel, gall bladder etc. have been reported. Shunt infection is reported anywhere between 5-15 %. The commonest cause is contamination at the time of placement of shunt. Almost 70% of the shunt infections present within 2 months of the procedure and the rest by 6 months. Preoperative prophylactic antibiotics reduce the incidence of shunt related infections. The commonest organisms are coagulase negative staphylococcus (S.epidermidis). Staphylococcus aureus, enterococci, micrococci, coryneforms also constitute a significant proportion. The best technique to reduce shunt related infections is to maintain sterility in the OT, proper skin preparation, prophylactic antibiotics, minimal handling of the shunt components. Advances like antibiotic impregnated shunt tubes have been developed. These are expensive and are not freely available in our country.

Other complications include hematoma, seizures, focal neurological deficits, CSF leak.

Endoscopic Procedures

Due to the various complications associated with the shunt surgeries, endoscopic interventions for hydrocephalus has gained popularity. Endoscopic third ventriculostomy is done to bypass the obstruction to the CSF pathway. This communicates the third ventricle cavity to the prepontine cisterns. The success rate for this procedure is high (80-90%) in cases of aqueductal stenosis. This has been reported to be successful in cases of hydrocephalus due to tuberculous meningitis, normal pressure hydrocephalus also but not so high percentages.

Endoscopic septostomy can performed to make a communication between the two lateral ventricles where indicated. This obviates the need to place a biventricular shunt. In multiple loculated hydrocephalus endoscopic fenestrations can be done to make the shunt function better. Endoscopic placement of a stent across the aqueduct or aqueductoplasty is also done for hydrocephalus. Another advantage is that during the procedure a biopsy can be done from the obstructing lesion along with the ETV.

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Hypospadias: Basis of surgical repair

Satish Kumar Aggarwal

Incidence of hypospadias is increasing thanks to environmental changes, use of chemical fertilisers, anti androgen influences in the environment and an increasing genetic pool in the society. The current incidence is about 1 in 150 boys.

This article aims to present surgical decision making in a simplified way. Rather than delving upon described procedures, stress is on developing essential skills necessary for all techniques and the philosophy of designing an operation based on the abnormal anatomy. The discussion is limited to the more common anterior hypospadias.

Anatomical basis of repair

Hypospadias is an atresia / hypoplasia of the ventral part of the penis. The anatomical abnormality includes that of skin, dartos, spongy tissue, urethra, the glans and sometimes, the corpora cavernosa. The ventral skin is poorly developed and adherent to the urethra. The dartos is deficient. The corpus spongiosum fans out laterally on each side distal to the meatus and is sometimes atretic. The glans is rotated laterally, outwards and downwards – responsible for a false impression of Chordee. The foreskin is crowded dorsally giving ride to the appearance of a hood. Most chordee is due to skin, dartos and atretic spongy tissue. In some cases there is actual disproportion in the dorsal and ventral growth of corpora cavernosa. In such situation a Nesbit procedure is required to correct chordee. The urethral plate is the delicate urothelial strip running from the meatus to the glans. It is seldom a cause of chordee. The glans anatomy and projection of the urethral plate on the glans varies a lot from patient to patient and determines the design of the operation.

Seventy percent of cases have anterior hypospadias – distal and mid penile, depending on the location of the meatus. The location of the meatus does not, however, indicate the magnitude of the defect. The true level is defined by the level at which the corpus spongiosum starts deviating to fan out on each side of the urethral plate immediately beneath the skin.

Aims of repair

Reconstruct a penis that is structurally and functionally normal.

1. Correction of chordee
2. Reconstruction of good and uniform caliber urethra till the tip of glans. There should be no potential for hair growth in the neourethra.
3. Restoration of slit like meatus at the tip of the glans
4. Normally configured and cosmetically pleasing glans and frenulum

5. Rearrangement of the skin to provide cover to the ventral repair and excise redundant skin from the dorsum.

Principles of modern hypospadias repair

A. ***Chordee***: The old belief that correction of Chordee requires division of urethral plate, led to the classical Asopa and Duckett repairs incorporating tubularised inner prepuce to form the entire neourethra – because these procedures required the native urethral plate to be divided in order to correct curvature. The modern concept is that the urethral plate itself seldom contributes to Chordee. Most Chordee is caused by hypoplastic ventral skin, deficient or fibrotic dartos, and atretic /hypoplastic spongiosum. Therefore most Chordee can be corrected by skin take down (degloving) alone. In a small subset of patients chordee persists after skin take down because of disproportionate ventral and dorsal growth of the corpora cavernosa. Such cases require Nesbit procedure.

B. ***The native urethral plate:*** Preservation of the native urethral plate is the cornerstone of modern management of anterior and mid hypospadias. The quality and width of the urethral plate determines the choice of operation. The native urethral plate can be used in the following ways:

a. **Simple tubularisation (Duplay)**: the plate should be wide and supple.

b. **TIP repair (Snodgras):** The plate is not wide enough for simple tubularisation but with a mid line axial incision in the plate, it can be tubularised without tension. The midline defect resulting from the incision epithelialises quickly.

c. **Midline incision with free graft**: In the so called "**Snodgraft**" procedure the urethral plate is incised in the midline and the resultant defect is covered by a free graft from inner prepucial skin. This is a very useful technique when the incision in the urethral plate extends beyond the distal limit of the urethral plate (Hinging of urethral plate).

d. **Island Onlay prepucial flap**: If the native urethral plate is very narrow and not very supple it can be augmented by putting an onlay flap on it. The dorsal half of the future urethra is contributed by the native plate and the ventral half by the on- laid inner prepucial skin.

e. **Mathieu meatal based flap**: This is another way to supplement urethral plate. Instead of a prepucial onlay flap, a flap of infra meatal shaft skin is flipped on to the native urethral plate.

C. ***Anatomy of the glans and projection of the urethral plate on the glans***

This is a vital but often neglected aspect of the operation because proper understanding of the anatomy determines the design of the operation. The normal glans is shaped like a cone with the urethra nested within its substance and the meatus positioned at the tip like a vertical slit. In hypospadias the plate width and projection on to the glans dictates the depth of the glans groove:

- **Wide healthy and pliable urethral plate** – Good clefting, deep groove. Easy to repair by Snodgras type repair.
- **Narrow plate not well projected** – Flat glans or shallow groove. Not suitable for Snodgras type repair. Probably better for Island Onlay Flap repair. Glans repair difficult.
- **Very narrow and dysplastic plate projecting on to the glans**- Conical glans. Very difficult to repair. May require deep clefting to nest the urethra within the glans. Staged Bracka repair may be better.

A close look at the glans in hypospadias will always identify the apex and the base of the ventral glansplasty. The width of the urethral plate between the right and the left apices forms the circumference of the meatus. Hence the length of the ventral glansplasty and the meatal circumference is always imprinted on the glans. In a well grooved glans the length of the ventral glansplasty is good thereby allowing good nesting of the urethra within the glans. The meatus also will be good sized. As the degree of clefting decreases the circumference of the future meatus also decreases. Since the length of the ventral glansplasty is fixed, meatal caliber can be improved only by working dorsal to the apex. This can be achieved by **Hinging of the urethral plate** – extending the Snodgras cut distally beyond the urethral plate on the glans.

Essential skills for Hypospadias surgeon

Rather than remembering different operations it is good to master some essential skills that are needed for all cases. Depending on the design there application may vary from patient to patient.

1. **Placing the holding stitch** on glans: Midline in sagittal plane – less bleeding, better cosmetically as leaves less marks on glans. Take suture within the future meatus- the mark will be within the meatus hence better cosmetically. Use prolene and leave long to tie the catheter at the end.

2. **Marking for design**: Mark the landmarks on glans. Outline the urethral plate. Mark the level of healthy ventral skin. Check for the length of dysplastic urethra proximal to the meatus. Mark circumferential incision to save a good mucosal collar at corona.
3. **Degloving**: Start on the ventrum by incising along the margins of urethral plate. Use scissors instead of the knife for better control. Don't go deep, otherwise you will injure the corpus spongiosum and the field will become bloody. Incise the skin proximally to reach the level of healthy spongy tissue. After defining the deviant spongy tissue proceed to deglove dorsally. Remain superficial to the Buck's fascia. The neurovascular bundles will be visible through the Buck's fascia. Deglove up to the suspensory ligament.
4. **Artificial erection test**: Tie a tourniquet at the base (I use a glove finger – tight enough to allow a urethral catheter to move to and fro easily). Using a 26 needle inject saline into the corpora cavernosum. Observe for chordee. Mark the site of maximum bend. Loosen the tourniquet. Remove the needle. Press the shaft to decompress the corpora.
5. **Nesbit procedure**: If chordee persists after erection test- proceed for Nesbit. At the site of maximum bend incise Buck's fascia on each side of the neurovascular bundles on the dorsum. Lift the neurovascular bundles off the tunica albuginea. Excise a diamond shaped area of tunica albuginea from the dorsum. Close the defect by PDS. Close the incision in Buck's fascia. Check for correction by artificial erection.
6. **Raising Dartos Flap**: Dartos flap can be raised with (for onlay flap procedure) or without (to provide soft tissue cover to repair) the inner prepucial skin. Leave the intrinsic blood supply to the outer skin intact to avoid necrosis. Separation of the dartos from inner prepuce is difficult but at the shaft skin it becomes easy. Mobilise enough to rotate it to the ventrum without causing twist. If glans substitution is planned raise the flap including a strip of inner prepucial skin.
   Incision of the urethral plate and hinging of urethral plate has been described above.
7. **Raising glans wings and mobilization of corpus spongiosum:** Incise Buck's fascia lateral to the spongy tissue near the glans. Develop a plain just superficial to the tunica albuginea. Raise glans flaps off the tunica albuginea till the apex of the glansplasty. Mobilise laterally to allow medial and inward rotation without tension. Lift the deviated corpus spongiosum off the corpora to shift it medially.
8. **Urethroplasty**: Tubularise the plate using vicryl or monocryl fine sutures. Ensure adequate caliber. Invert the epithelium. Close spongy tissue over the repair as second layer.
9. **Glansplasty**:Transpose dartos fascia to cover the repair. The portion lying under the glans should be kept thin to prevent tension in glans closure. Close glans with PDS in a horizontal mattress fashion. Check meatal caliber. Include refashioning of coronal collar with glans closure. If glans not favourable: use glans substitution and frenuloplasty.
10. **Skin cover**: Cut back on the dorsal skin in the midline to a suitable level. Take the dorsal midline stitch with the coronal collar. Transpose the rest of the skin to ventrum. Excise redundant skin. Aim for a midline raphe.
11. **Dressing**: Should provide gentle uniform compression all around. The author uses a gauge dressing over a paraffin sheet, kept in place by elastic tape. Others: Foam dressing – costly. Glove finger dressing, tegaderm dressing.

Operations to master

1. Snodgras TIP repair
2. Duckett Island Onlay flap repair
3. Dorsal free graft with hinging of urethral plate - SNODGRAFT
4. Bracka staged repair

Further tips for exams

- Define hypospadias: see above
- Anatomy: See diagrams in Campbell Urology.
- Blood supply of Dartos: superficial external pudendal vessels
- Blood supply of glans: Dual supply from artery to bulb via corpus spongiosum, and from dorsal vessels of penis.
- Fascial anatomy: Buck's fascia – two layers, Dartos fascia, tunica albuginea
- Plane of dartos flap and degloving: Superficial to Buck's.
- Historical: Remember contributions from Asopa, Ducket, Snyder, Duplay, Denise Brown, Aivor Bracka, Snodgras. Their full names, affiliations, contribution, interesting aspects about them and their life.
- Fistula: how, why, where, what to do, when to repair, simple repair or complete re do. Prevention: mobilise glans wings, glans closure without tension, glans substitution and frenuloplasty
- Techniques of repair: local transposition of dartos flap, de-epithelialised skin flap etc.
- Meatal stenosis: techniques to prevent: glans substitution, frenuloplasty.
- Other associations: scrotal transposition, bifid scrotum
- Severe hypospadias special problems – vaginal diverticulum, staged repair, DSD associations.

Ten Commandments of Safe and Optimum Neck Dissections

Chintamani

Neck nodes are the best predictors of outcome in head and neck cancers, and the survival drops by 50 % in node-positive necks. Neck dissections are therefore an essential aspect of management of head and neck cancers. Most surgeons dedicated to head and neck surgery must have a thorough understanding of surgical anatomy of this region and steps essential for performing this surgery optimally and safely.

History and evolution[1-3]

The first neck dissection was performed by GW Crile in the year 1906 (he preserved the spinal accessory nerve for some reason). Subsequently, various other surgeons like Martin made it more and more radical and insisted on removal of spinal accessory nerve to make it optimum. The better understanding of the lymphatic drainage of head and neck region by Rouviere et al. made it possible to predict the pattern of lymphatic drainage in a cancer involving a particular region, and neck dissections thus became more and more conservative/selective. Bocca provided the first classification of modified radical neck dissections (MRND), and preservation of any one structure made it MRND I, while if all the three extra-lymphatic structures were preserved, it was called MRND III or functional neck dissections (FND).

These commandments are by no means the only way to perform this surgery but “one correct way” of doing it. There is no rigidity in these steps, and these are merely recommendations to achieve an optimal outcome safely.

Commandment 1. **Not to operate by clock**

A surgeon operating by clock has no business to be in this region that has too many vital structures packed closely together. A thorough understanding of surgical anatomy is mandatory to avoid lethal injuries. Fortunately, on most occasions, the surgical anatomy is by and large fixed, and it amounts to cutting on the dotted line. One has to only follow the “holy bloodless planes” in order to achieve an optimal clearance.

Commandment 2. **Positioning correctly and making the right incision**

The classical position for most head and neck surgeries is reverse Trendelenberg with extension at the neck to have maximum access. The head is turned away to the opposite side in order to expose all the triangles of the neck adequately (Fig.1,2)

Raising the head end of the table by 15° reduces venous congestion in the region but also adds to the risk of air embolism by creating negative pressure in the veins. The recommended method to avoid this catastrophe is to ligate these veins in continuity, i.e. ligating before cutting them.


Fig. 1, 2: Positioning: reverse Trendelenburg with neck extended and turned to the opposite side exposes all triangles optimally

There are numerous incisions for neck dissections, but the most common and the one used by the author is “modified Schobinger’s incision”. The incision has two limbs, one horizontal and the other one comes down vertically as a lazy “s” (*in order to prevent scar contracture later*). The horizontal limb typically lies at least about 2 cm below the mandible to avoid injury to the *ramus mandibularis*, and the vertical limb starts at a point that is at least 2 cm behind the point where the carotid pulsations are felt. This is to avoid the trisection from lying directly over the carotids (*in the event of the dehiscence of incision at this trisection, the carotids may lie exposed leading to a blow out, especially following radiotherapy)*. This also allows the posterior flap to be as short as possible as it is devoid of platysma, which is vital for the survival of these flaps. There are some other popular incisions in use like the “Mcfee incision” which is in the form of a step ladder [*it is particularly useful in the irradiated necks where flap failure rates are “expectedly” higher owing to poor blood supply*]. The “utility incision” is frequently used when surgery is being performed for thyroid cancer, and neck dissection is also contemplated.

Commandment 3: Raising the flaps adequately and finding the "Holy planes" and Ramus Mandibularis

The next step is to raise the sub-platysmal flaps (anterior and posterior). As the access to all parts is limited, one has to rely on well-raised platysmal flaps to reach all end points of dissection. While raising the superior flap, one has to be very cautious in order to preserve the marginal mandibular nerve or "ramus mandibularis" which is a branch of facial nerve that supplies the angle of mouth. The morbidity following injury to this nerve is severe in terms of poor oral competence, drooling of saliva and difficulty in speech. There are various techniques to protect this nerve, and the author likes to use the "Hayes Martin" technique that involves dissecting the common facial vein in the neck and transecting after ligating it. The upper cut end is hitched up to get the nerve *out of harm's way* (fig 3,4,5)

Flaps: the ramus mandibularis and the spinal accessory nerves may be seen

Hayes Martin technique of safeguarding the ramus mandibularis. The common facial vein is dissected, ligated and transected, and the upper end is hitched out of harm's way.

Commandment 4: Not to Look for Aberrations and Sticking to the Established Plan

Surgery in this region amounts to cutting on the dotted line as the anatomy is usually fixed and aberrations are rare (*and are often only in the mind of the surgeon*). One has to be absolutely thorough with the surgical anatomy in order to avoid bleeding and/or injury to vital structures. The dissection now proceeds in a predictable way in a bloodless field demonstrating each structure to the assistants. This is made possible by following the basic surgical principles of neat dissection in a bloodless field and sticking to "God's planes" from level V or the posterior triangle upwards and medially dissecting levels IV, III, II, Ib and Ia and preferably removing the primary lesion en bloc to conclude the surgery. Some surgeons prefer to take an antero-posterior (i.e. level I to level V) approach, which is equally good.

Commandment 5: Searching for the Anatomical Lighthouses

Each step is taken in a direction to reach an end point or what the author would like to call a "lighthouse". These lighthouses make the entire dissection fairly predictable and reproducible ensuring an optimum clearance each time.

Lighthouses in the posterior triangle

- Erb's point: where the greater auricular nerve winds around the sternocleidomastoid muscle in the posterior triangle. The spinal accessory nerve (SAN) enters the posterior triangle approximately 2 cm superior to this point
- Safety layer: this prevertebral layer of deep fascia that covers the phrenic nerve and the brachial plexus is also called the "Holy layer". If not infiltrated by cancer itself, one can avoid injury to the phrenic nerve and the brachial plexus by staying superficial to it during dissection of level V or the posterior triangle (Figs. 6 and 7)
- Phrenic nerve: this is the only structure that traverses lateral to medial in the neck, all other structures travel either medial to lateral or from above downwards (Fig. 7). By dissecting and staying superficial to this layer, injury to the brachial plexus and the phrenic nerve is avoided, and unless directly involved by the disease, all these structures must be protected (Fig. 7).
- Omohyoid (Figs. 8 and 9): This muscle serves as a very important lighthouse that traverses from posterior to anterior triangle crossing the internal jugular vein (IJV). Many surgeons including the author would retract rather than cut this muscle and look for a level IV lymph node (*rather than routinely dissect level IV as there is a risk of injury to vital structures like a thoracic duct on the left side*). Moreover, level IV is not very commonly involved in most head and neck cancers, routine level IV dissection is therefore not recommended except in scenarios like cancers of tongue where skip metastases to this level are known or poor grade cancers.

Lighthouses in the anterior triangle

The dissection proceeds along the IJV, and carotid sheath is routinely removed along with levels II, III and IV nodes. This step exposes the common carotid artery and the vagus nerve that lies between the IJV and the common carotid artery.

- Facial vein: this is the last tributary of the IJV that would need to be ligated, and this also guides one to the facio-jugular node (level IIa), which may serve as the "sentinel lymph node" in certain oral cavity lesions. The vein crosses the common carotid artery to drain in to the IJV. This last tributary may need to be ligated before the IJV is ligated and transected as close to the skull base as possible if one is performing the classical radical neck dissection (RND).
- **Posterior belly of digastric**: This lighthouse can be used as a guide to move towards level I after the dissection at level II is complete. The hypoglossal nerve crosses in to the submandibular triangle or level I (b) under this muscle.



Commandment 6: Identify Internal and External Carotid Vessels and the Hypoglossal Nerve

As mentioned above, the carotid sheath is opened, and levels II and III are dissected along with the sheath. The external carotid artery is actually "internal" in anatomical location and gives off branches in the neck, the first one being the "superior thyroid artery". About 2 cm superior to the bifurcation of the "common carotid artery", the "hypoglossal nerve" can be seen crossing the carotids and ascending towards level I.

[While dissecting close to the carotid bifurcation, it is mandatory to alert the anesthesiologist, as there may be bradycardia or even cardiac arrest due to stimulation of baroreceptors that can be corrected/prevented by infiltrating 1 % lignocaine].

Commandment 7: Always Find the "Facio-jugular Lymph Node"

The dissection now proceeds upwards and medially, and the facio-jugular lymph node (or level II (a)) is dissected. The common facial vein may be ligated and transected at this point, and one may proceed along this vein to reach level I or one may also trace the posterior belly of digastric to reach level I as mentioned previously.

Commandment 8: Find the Digastric to Reach Level I (b) and I (a)

One may now dissect along the posterior belly of the digastric muscle to reach level I. The facial vessels (artery and vein) both would need to be ligated and transected or may be preserved if not directly involved to utilize them as recipient vessels for a "free flap".

Commandment 9: Aim to Preserve Extra-Lymphatic Structures [SAN, IJV, SCM] but not at the Cost of Oncological Safety

The classical radical neck dissection (RND) involves removal of lymph nodes from levels I to V along with three extra-lymphatic structures spinal accessory nerve (SAN), internal jugular vein (IJV) and sternocleidomastoid muscle (SCM). Over the years, it has been extensively studied that these structures may be preserved unless directly involved by the disease. Depending on the number of structures preserved, it may be called as modified radical neck dissection (MRND I) if only one is preserved or (MRND II) if two are preserved or MRND III if three structures are preserved. In the order of importance, SAN gets a preference over IJV, and SCM preservation is the last but not the least priority.

Commandment 10: Shall Preserve the Internal Jugular Vein at Least on One Side

If bilateral neck dissections are contemplated, IJV must be preserved at least on one side in order to avoid the morbidity of facial edema and high mortality.

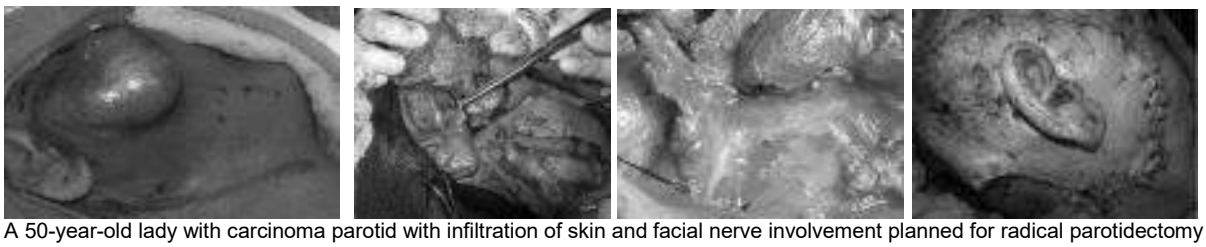
Selective Neck Dissections

There are occasions when neck dissections may not follow this conventional approach, and one may have to select and remove only limited neck node basins, based on the predicted map of lymphatic spread in the head and neck

region. These are called selective neck dissections (SND), and one may simply mention the levels removed along with SND as a prefix. For example, in a classical supra-omohyoid neck dissection, levels I–III are removed; this may be described as SND I, II and III. Similarly, in certain scenarios like thyroid cancers, one may end up removing levels II, III and VI in view of the high probability of lymphatic spread to these regions, and the same may be described as SND II, III and VI.

Extended Neck Dissections

Extended neck dissections may involve removal of more levels than the conventional levels I–V in one particular case, e.g. in cancers of parotid. A fungating carcinoma involving the classical site for an Indian oral cancer (lower gingiva-buccal sulcus) and extending on to either side of midline. A bilateral neck dissection along with extensive composite resection of the lesion has been performed. In case of thyroid cancers, in addition to MRND III, level VI may also have to be removed.



A 50-year-old lady with carcinoma parotid with infiltration of skin and facial nerve involvement planned for radical parotidectomy and right-sided MRND type III. The radical parotidectomy in progress, the facial nerve is resected flush at the point of exit from the foramina. The MRND III and reconstruction performed using a local axial transposition flap based on occipital artery.

In certain cases (like in this case), the level VI dissection may have to combine with MRND III using the utility incision. The sternocleidomastoid muscle may be retracted to dissect level V. The spinal accessory nerve, common carotid, vagus nerve.

The inferior thyroid artery (ITA) has been hooked on a sling to clear off all the lymphatics. The recurrent laryngeal nerve may be seen crossing through the capsular branches of ITA. The main trunk of ITA is never ligated unless injured; only the capsular.

Extended neck dissection completed. The levels I, II, III, IV, and VI have been removed in a medullary thyroid cancer. The spinal accessory is being pointed at. It actually amounts to MRND III and clearance of level VI.

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Cytoreductive Surgery and Hyperthermic Intraperitoneal Chemotherapy

Durgatosh Pandey, Saqib Sahab, Pankaj Kumar Garg

Introduction

Most cancers that occur within the abdomen or pelvis disseminate by three different routes. These are: Haematogenous metastases, Lymphatic metastases, and Implants on peritoneal surfaces.[1] The dependent peritoneal surfaces, such as the right retro-hepatic space, paracolic sulcus, and pelvis, are involved as a result of gravitational forces. The under surfaces of the diaphragm and omentum are involved because of major peritoneal fluid resorption at these anatomic sites.[2] Peritoneal surface malignancy (PSM), the presence of cancer cells on the surface of the peritoneum can be - Primary or Metastatic. Tumours that primarily originate from the peritoneum are rare and include mesothelioma and primary peritoneal serous carcinoma. In vast majority, the PSM are metastatic that originate from malignancies of intra-abdominal organs including: appendix, colon, rectum, stomach, and ovaries.[3] Extra-abdominal organ malignancies such as Breast cancer can also extend to the peritoneum, though rare[4,5].

For a long time, PSM was classified as a non-surgical advanced stage of the cancer. The possibility of complete surgical debulking through a long complex surgery was traditionally aborted as per the high risk of such approach with limited benefits. Similarly, systemic intravenous chemotherapy had little peritoneal penetration and effect on the peritoneal tumours, as the peritoneal membrane anatomically constitutes a compartment separate from the vascular compartment.

Cytoreductive surgery (CRS) and hyperthermic intraperitoneal chemotherapy (HIPEC) is a multimodality procedure performed for the treatment of peritoneal neoplasm, with the aim of removing all peritoneal tumour deposits.[6] Parietal peritonectemy along with removal of involved abdominal organs as necessary is done in order to achieve complete cytoreduction. HIPEC involves perfusing the abdominal cavity with heated (41 - 43°C) fluid containing a chemotherapeutic agent for about 90 mins (60 – 120 mins) after complete cytoreduction but before the joining of anastomoses. This multimodality treatment was first described by Paul Sugarbaker, and is frequently referred to as the 'Sugarbaker technique' and has shown promising results in peritoneal surface malignancies.[2]

Indications

Total peritonectomy with perioperative chemotherapy is being tried in following scenarios. However, tumor biology and patient characteristics are the primary factor deciding the benefit of this approach.

Current indications for cytoreductive surgery and perioperative intraperitoneal Chemotherapy

1. Large volume of noninvasive peritoneal carcinomatosis or sarcomatosis.
2. Pseudomyxoma peritonei
3. Peritoneal mesothelioma.
4. Low volume peritoneal seeding from invasive cancer.
5. Perforated gastrointestinal cancers.
6. Cancer adherent to adjacent organs or structures.
7. Gastrointestinal cancer with positive peritoneal cytology.
8. Gastrointestinal cancer with ovarian involvement.
9. Positive margins or tumour spill intraoperatively (especially large rectal cancers).
10. Systemic chemotherapy for recurrent ovarian cancer after a long disease-free interval.
11. Palliation of patients with malignant ascites.
12. Documented PSM in the absence of extra-abdominal or liver parenchymal metastases.

CRS with HIPEC should not be considered in the presence of distant metastasis, multiple liver metastases where anticipated liver resection would cause hepatic decompensation, and extensive small bowel involvement where anticipated resection may lead to small bowel syndrome. Radiological investigations such as computed tomography (CT), positron emission Tomography (PET) and magnetic resonance imaging (MRI) scans have been used, as has diagnostic laparoscopy, to select the patients who may benefit from this aggressive procedure. A consensus was reached at the Fifth International Workshop on Peritoneal Surface Malignancy, stating that contrast-enhanced multi-sliced CT remains the fundamental imaging modality, whilst MRI, PET, laparoscopy and serum tumour markers were helpful but non-essential.[7]

Techniques of Cytoreductive Surgery

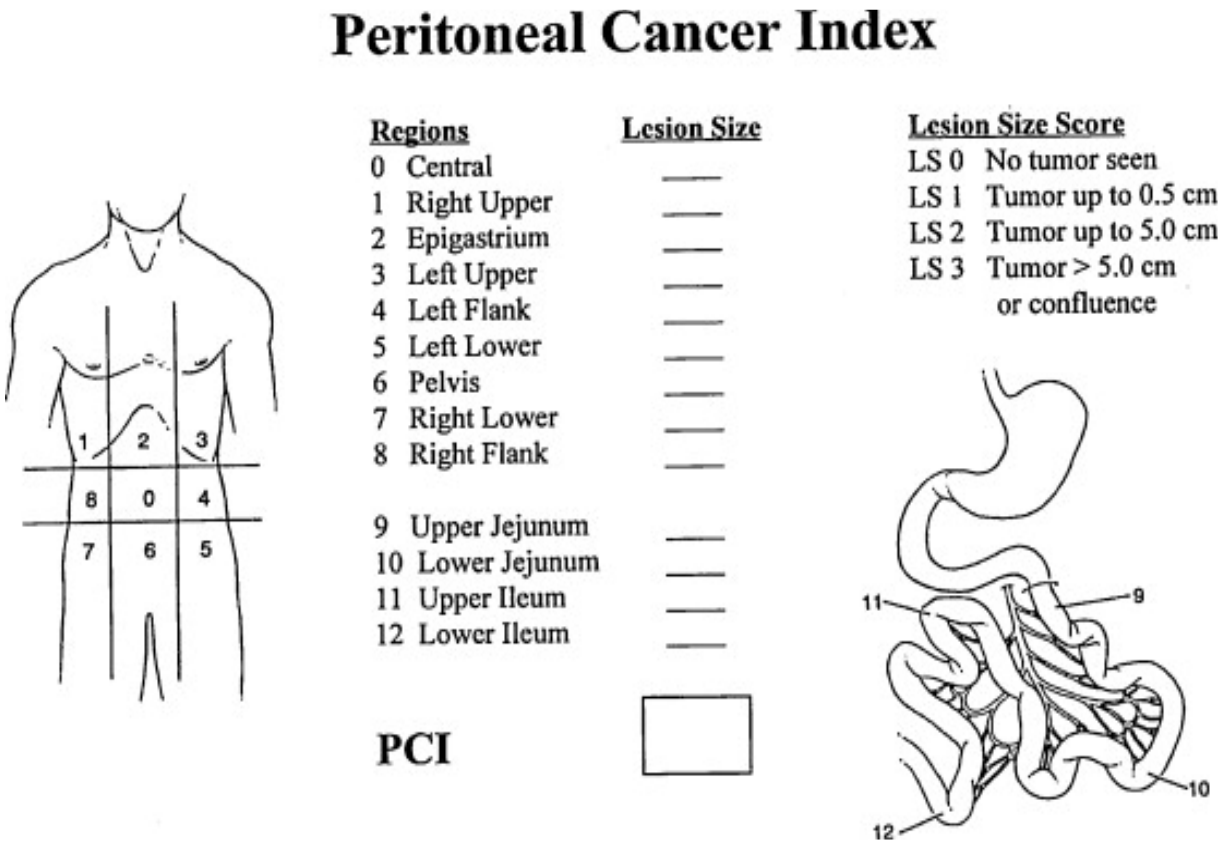
The goal of aggressive CRS is to remove all macroscopic peritoneal disease. Different grading tools were suggested to report the extent of Peritoneal carcinomatosis such as:-

Peritoneal Cancer Index (PCI)

It is based on two variables – lesion size and distribution of peritoneal surface malignancy (Fig 1). The number of nodules is not scored, only the size of the largest nodule is taken. For each of the 13 regions, a lesion size score is determined. The summation of the lesion size score in each of the 13 abdominopelvic regions is the Peritoneal Cancer Index for that patient. A maximal score is 39 (13x3).

There are some caveats to the Peritoneal Cancer Index (PCI):

1. Noninvasive malignancies such as pseudomyxoma peritonei, grade I sarcoma and cystic peritoneal mesothelioma may have very high preoperative PCI yet are amenable to complete cytoreduction
2.
3. Invasive cancers at crucial anatomic sites carry poor prognosis despite low PCI. For example – unresectable cancer on the common bile duct, diffuse small bowel involvement, lymph node metastases unrelated to the primary tumour



The score of the Peritoneal Cancer Index compatible with benefit using combined treatment will vary with the type of peritoneal surface malignancy treated. Berthet, et al in a study of sarcomatosis found an index of < 13 associated with a 74% five-year survival; an index of > 13 was associated with an 11% five-year survival. For colon cancer with carcinomatosis, Sugarbaker reported a Peritoneal Cancer Index of < 10 associated with a 50% five year survival; an index of 11-20 was associated with a 20% five-year survival; and an index of > 20 was associated with a 0% five-year survival.[1]

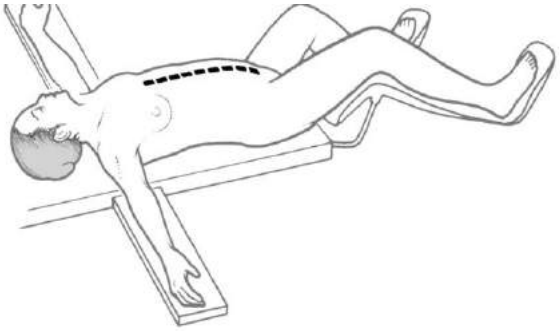
Completeness of Cytoreduction Score (CC score)

It is a postoperative prognostic indicator in both invasive and non-invasive PSM. It is defined as follows:-

- CC 0 – score indicates that no visible peritoneal carcinomatosis remain after cytoreduction
- CC 1 – score indicates that tumour nodules persisting after cytoreduction are less than 2.5 mm. This nodule size is penetrable by intraperitoneal chemotherapy.
- CC 3 – score indicates tumour nodule between 2.5 mm to 2.5 cm
- CC 4 – score indicates tumour nodules greater than 2.5 cm or confluence of unresected tumour nodules at any site within the abdomen and pelvis

A complete cytoreduction for noninvasive malignancy such as pseudomyxoma peritonei includes CC 0 and CC 1 resection. For invasive cancers such as colorectal or gastric carcinomatosis only CC 0 is considered complete cytoreduction[1,7].

Peritonectomy Procedure

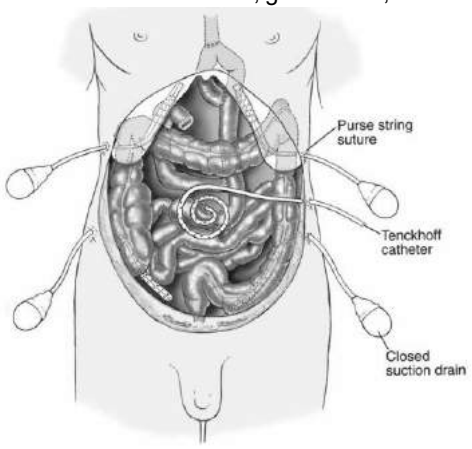


The goal of cytoreduction is to remove as much macroscopic tumour as possible so as to leave minimal possible disease for chemotherapy treatments.

The patient is positioned in supine position with gluetal folds advanced to the break in the operating table in order to provide full access to perineum during the surgical procedure. Vertical midline incision is made from the xiphoid to the pubis (Figure 2) Xiphoid may be excised, if required, using electrosurgical dissection.

Intra-abdominal dissections are facilitated by electrosurgical unit using a 3mm ball tip diathermy. During re-operations old surgical scars from the skin to the peritoneum is excised to prevent recurrence. A thorough lysis of adhesions from prior surgeries is necessary for full exploration. Frequently, complete liver mobilization is also needed to evaluate the disease extension behind the liver. The peritoneum with wide visible disease is surgically resected, while limited disease can be destroyed by electro fulguration. The peritoneal stripping proceeds in a centripetal fashion starting at the edge of the incision and proceeding to the attachments of the peritoneum to the viscera.

The procedure can be categorised into 1) total anterior parietal peritonectomy 2) right subdiaphragmatic and parietal peritonectomy, 3) left subdiaphragmatic and parietal peritonectomy, 4) greater omentectomy with splenectomy, 5) lesser omentectomy and stripping of the omental bursa, 6) pelvic peritonectomy with salpingo-oopherectomy in women, and resection of other involved organs, such as uterus and ovaries, gallbladder, stomach, distal pancreas, colon and limited small bowel if necessary (8). Multi-visceral resection does not appear to affect the morbidity of the procedure and should be performed if a complete cytoreduction can be achieved as a result (9). All anastomoses are done after intraoperative intraperitoneal chemotherapy in order to reduce the rate of anastomotic recurrences. Closed suction drains are placed in the dependant portion of the abdomen. This includes the right subhepatic space, the left subdiaphragmatic space and the pelvis A Tenckhoff catheter may be placed through the abdominal wall in order to administer heated intraoperative intraperitoneal chemotherapy. All transabdominal drains and tubes are secured in a watertight fashion with a purse string suture at the skin. If subphrenic peritonectomy was performed, right angle thoracostomy tubes are inserted in order to prevent fluid accumulation in the chest as a result of intraperitoneal chemotherapy and diaphragm stripping.



Hyperthermic Intraperitoneal Chemotherapy (HIPEC)

Benefits of intraperitoneal hyperthermia and of intraoperative timing of Intraperitoneal chemotherapy (1,10,11) are

- Heat increases drug penetration into tissue.
- Heat increases the cytotoxicity of selected chemotherapy agents.
- Heat has anti-tumour effects by itself.
- Heat at the peritoneal surface causes increased cytotoxicity of systemic chemotherapy to small cancer nodules.
- Intraoperative chemotherapy allows manual distribution of drug and heat uniformly to all surfaces of the abdomen and pelvis.
- Renal toxicities of chemotherapy can be avoided by careful monitoring of urine output during chemotherapy perfusion.
- Nausea and vomiting are avoided because the patient is under general anaesthesia.
- The time that elapses during the heated perfusion allows a normalization of many functional parameters (temperature, blood clotting, hemodynamics , etc)

HIPEC involves two conceptual changes with regard to chemotherapy administration in peritoneal carcinomatosis – route and timing.

Route

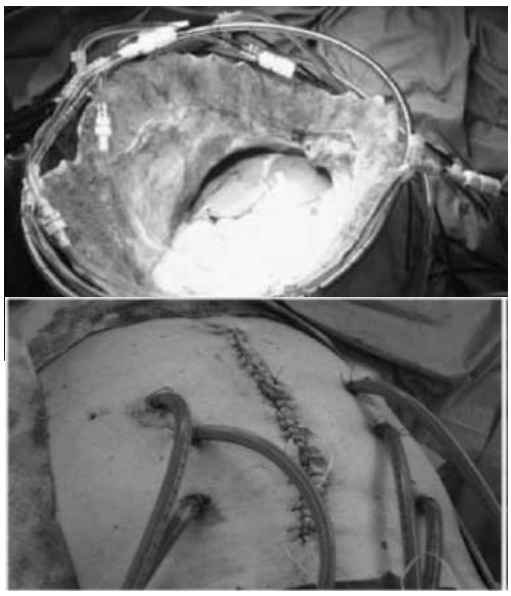
Intraperitoneal chemotherapy gives high response rates within the abdomen because the peritoneal space to plasma barrier provides dose intensive therapy with minimal systemic absorption and side effects. This means that

the exposure of peritoneal surfaces to pharmacologically active molecules can be increased considerably by giving the drugs via the intraperitoneal as opposed to intravenous route.

Timing

Intra peritoneal chemotherapy is administered in the intraoperative and early postoperative period. Immediate application of intraperitoneal chemotherapy after cytoreductive surgery controls the sub-millimetric disease and diffuses through two or three layers of cells before the formation of early physiologic postoperative adhesions where these cells can be trapped away from the reach of the chemotherapy.

Technique of Intraoperative Chemotherapy



The chemotherapeutic agents can be administered intraoperatively by the open or closed method. In the open technique, the abdominal wall is elevated on the Sugarbaker retractor to create a funnel to accommodate the heated chemotherapy that circulates through inflow and outflow lines attached to a pump and heating unit (Fig 4).

In the closed method, the skin is temporary closed after placing the inflow and outflow tubing through separated incisions (Fig 5).

After cytoreductive surgery is complete, the Tenckhoff inflow catheter and outflow drains are placed. Temperature probes are secured to the skin edge and temperature is monitored at inflow catheter and remote site within the abdomen and pelvis. The abdominal cavity is then filled with the chemotherapy solution that circulates using a pump with a heating unit. The HIPEC part of the procedure usually last about 90 minutes (60-120 minutes) with continuous cycling of chemotherapeutic agent so that all anatomic structures within the peritoneal cavity are uniformly exposed to heat and chemotherapy. The perfusate is externally heated to a temp of 44-46 degree C to achieve a core intraperitoneal temp of 41 – 43 degree ^{0}C.

Chemotherapeutics

Majority of the centres use Mitomycin C patients with peritoneal carcinomatosis of colorectal and appendiceal origin, and in a subset of patients with mesothelioma. The most widely applied doses range from 12.5 mg/m^2 to 35 mg/m^2 over 90 min. Oxaliplatin and irinotecan have more recently been explored as HIPEC in PC from colorectal and appendix adenocarcinoma. Cisplatin HIPEC has been used in mesothelioma, ovarian and gastric cancer. Cisplatin is a platinum salt, which has shown improved survival when combined with CRS, however is associated with increased toxicity and complications, which has resulted in slow acceptance of this treatment modality within the scientific community. Cisplatin HIPEC is associated with an increased incidence of nephrotoxicity (12).

Complications

CRS carries significant morbidity and mortality in the range of 40% to 60% and 5% to10%, respectively. Surgical complications include anastomotic breakdown, abscess, prolonged ileus, deep vein thrombosis, pulmonary embolism, cardiac and cerebrovascular events. Adverse events have been shown to be related to the stage of peritoneal disease, duration of the operation, number of bowel anastomoses and blood loss. Morbidity can ensue from intraperitoneal Chemotherapy and in-dwelling catheters and surgical drains and is dependent on the type of chemotherapeutic agent used. Common side effects include nausea and vomiting, myelosuppression, chemical peritonitis with abdominal pain and distension and leakage of chemotherapy, which may require additional suturing over catheter or drain exit sites. Median intensive care unit stay, blood transfusion requirement, time to feeding, and total hospitalisation duration of 1 day, 1 unit, 4 days and 12 days, respectively, have been reported.

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Head Injury

Daljit Singh

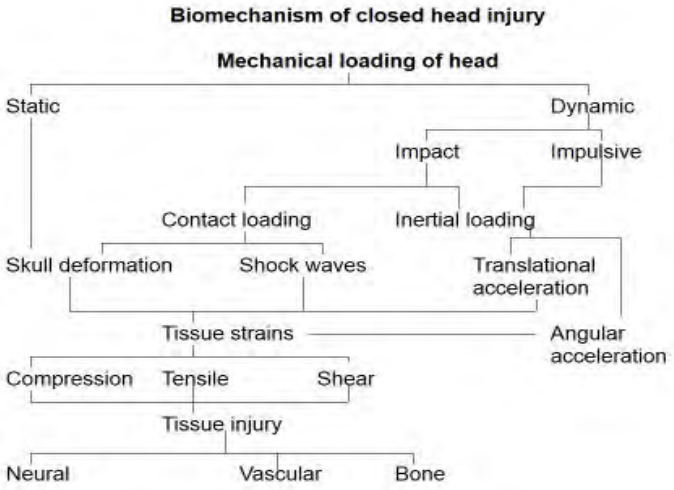
No head injury is minor to be neglected nor serious enough to be given up.

Introduction & Epidemiology of head injury

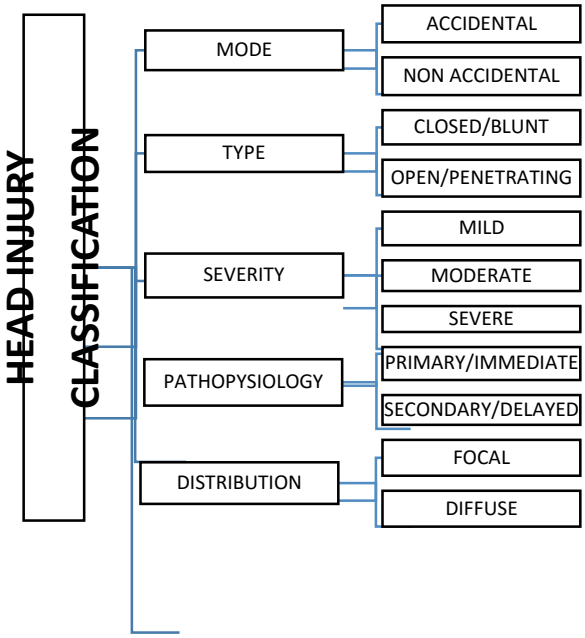
Head injury continues to be a nightmare, not only for the public but also for the neurosurgeon, because of high morbidity and mortality. Head injury defines an injury to the head and brain. Traumatic brain injury (TBI) is a nondegenerative, noncongenital insult to the brain from an external mechanical force, possibly leading to permanent or temporary impairment of cognitive, physical, and psychosocial functions, with an associated diminished or altered state of consciousness.

World incidence is 106/100,000/year. 10 million people are affected every year worldwide. Approximately 1.5 million head injuries occur every year in the United States, with 250,000 patients requiring hospitalization and 52,000 dying of the injury. TBI is the leading cause of death and disability in children and adults 1 to 44 years of age. Incidence in India is 1.5 to 2 million/yr. and mortality is 0.2 million.

Biomechanics of head injury



Classification of Head injury



Mechanistic Types of Head Injuries

Contact Injuries	**Head Motion Injuries**
Skull Deformation injuries	
- Local Skull bending	Subdural Hematoma
- Skull fracture	Contre coup contusion
- EDH	Intermediate contusion
- Coup contusion	
Skull volume change	
- Vault, basilar fracture	Brain deformation
- Contrecoup contusion	Concussion Syndromes
	DAI
	Intracerebral Bleed

Marshall's CT Classification of head injury

Category	**Definition**
Diffuse injury I (no visible pathology)	No visible intracranial pathology seen on CT scan.
Diffuse injury II	Cisterns are present with midline shift 0-5 mm and/or lesions densities present: no high or mixed density lesion> 25cc may include bone fragments and foreign bodies.
Diffuse injury III (swelling)	Cisterns compressed or absent with midline shift 0-5mm; no high or mixed density lesion> 25cc.
Diffuse injury IV (shift)	Midline shift > 5mm; no high or mixed density lesion > 25cc
Evacuated mass lesion	Any lesion surgically evacuated
Non evacuated mass lesion	High or mixed density lesion> 25cc; not surgically evacuated.

Pathophysiological classification of head injury

Primary traumatic head injury	Secondary brain injury
Focal • Fractures • Axonal injury • Contusion • Laceration • Vascular injuries resulting in EDH, SDH, SAH, intraparenchymal bleed	1) Disturbance of cerebral metabolism 2) Disturbance of cerebral blood flow 3) Intracranial hypertension 4) Secondary displacement of brain 5) Hypotension 6) Hypoxia 7) Pyrexia 8) Anaemia 9) Hyperglycemia 10) Seizures
Diffuse ▪ Diffuse axonal injury ▪ Diffuse vascular injury	

Modified Glasgow coma scale

Glasgow coma scale was developed by Teasdale and Jennett in 1974, for assessment of coma & impaired consciousness. Head injury is categorized into mild, moderate and severe based on the GCS scale. Patient's prognosis is also quantified based on GCS scale.

	Adult	1-5 years*	0-1 years**
Eye Opening			
4	spontaneously	spontaneously	spontaneously
3	to command	to command	to shout
2	to pain	to pain	to pain
1	no response	no response	no response
Best Verbal Response			
5	oriented	appropriate words, phrases	coos, babbles, smiles
4	confused	inappropriate words	cries
3	inappropriate words	cries, screams	inappropriate cries, screams
2	incomprehensible	grunts	grunts
1	no response	no response	no response
Best Motor Response			
6	obeys commands	spontaneous	spontaneous
5	localizes pain	localizes pain	localizes pain
4	withdraws from pain	flexion withdrawal	flexion withdrawal
3	abnormal flexion	abnormal flexion	abnormal flexion
2	extension	extension	extension
1	no response	no response	no response

Head injury severity scale

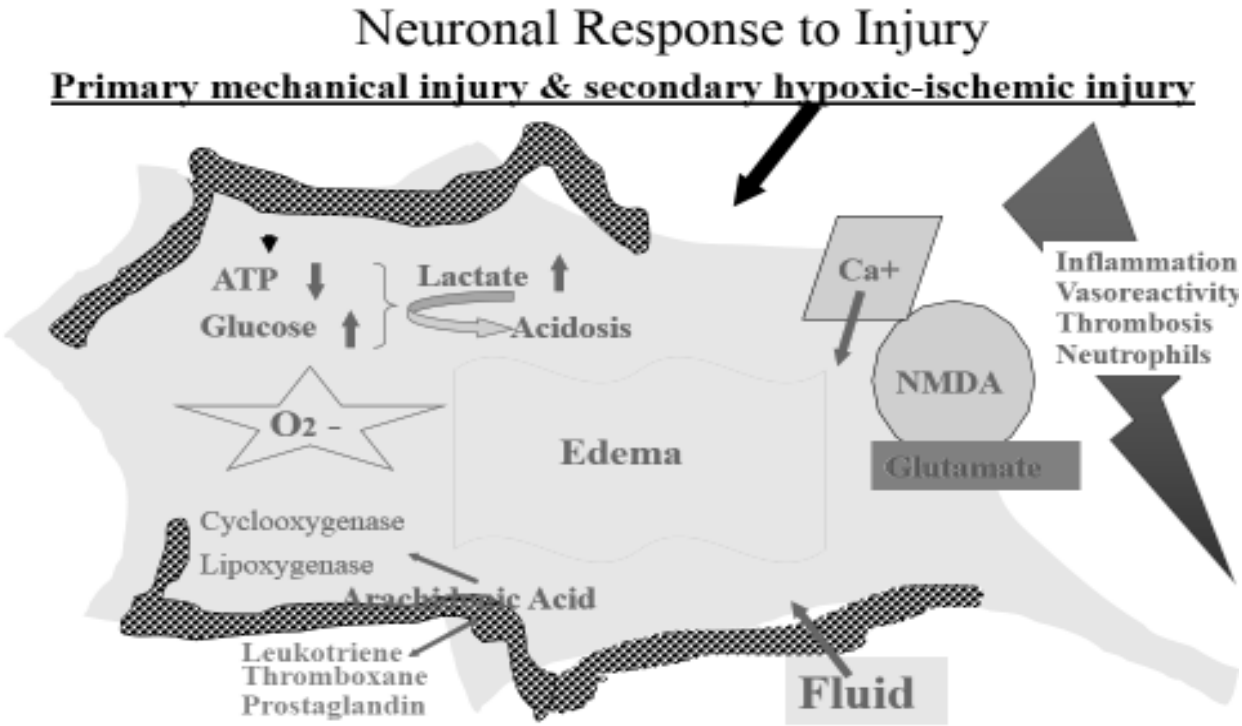
Injury category	GCS score
Minimal	15, No LOC or amnesia
Mild	13, 14, or 15 plus amnesia or brief LOC or impaired alertness or memory
Moderate	9 –12 or LOC >5min or focal deficit
Severe	5 - 8
Critical	3-4

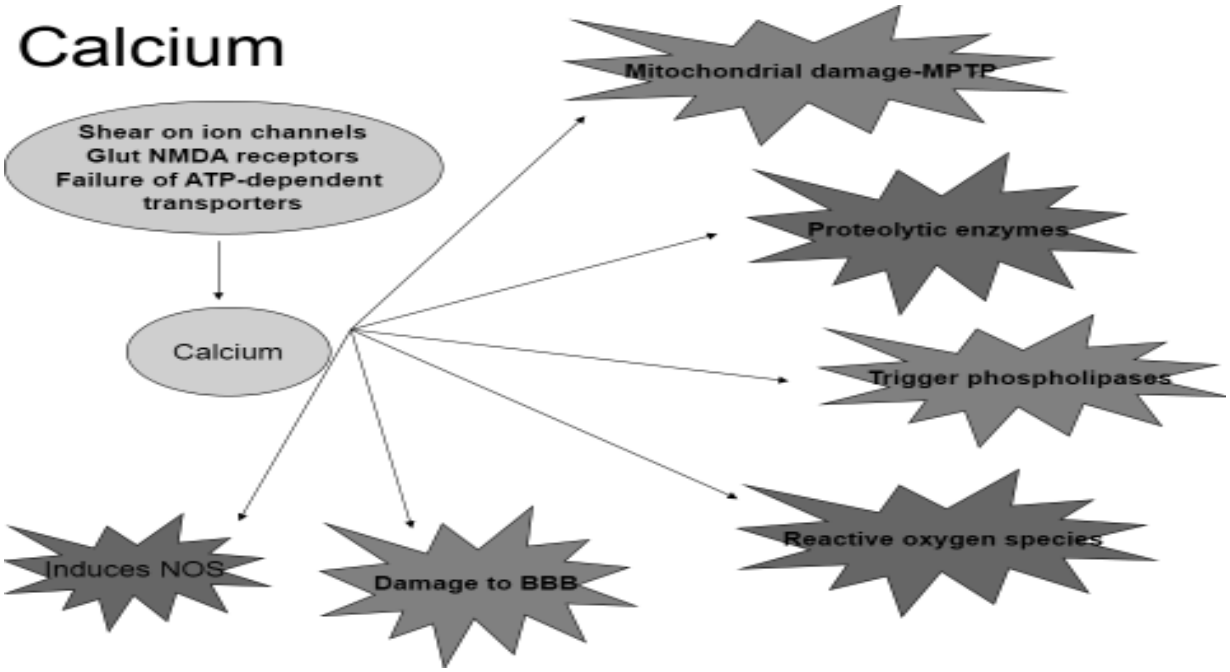
Pathophysiology of traumatic brain injury

The following events occur in sequence:

1. Injury to neurons, vessels, glial cells, axons
2. Alteration in brain metabolism
3. Raised ICP.
4. Disruption of cerebral blood flow
5. Vasogenic and cytotoxic edema
6. Further rise in ICP
7. Deranged cerebral auto regulation
8. Hypoxia and cerebral ischemia

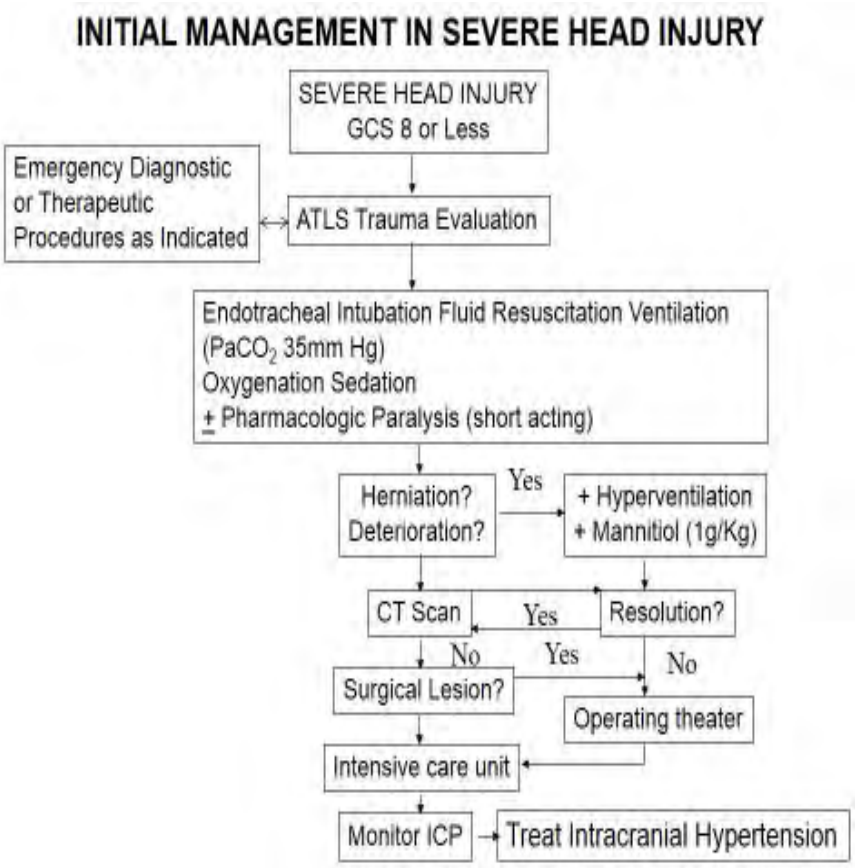
Trauma to brain results in altered neuronal membrane potential, which alters Na^+ and K^+ transmembrane ratio and releases excitatory amino acids. This causes increase in intracellular Na+ and Cl^- leading to cell swelling. This effects the release of free fatty acids and generation of prostaglandins, leukotrienes and thromboxanes, resulting in breakdown of blood brain barrier and cerebral edema. Increase in mitochondrial calcium results from these effects thereby causing mithochondrial swelling, disruption of inner mitochondrial membrane and electron transport system, producing active oxygen species and DNA breakdown. So the abnormal calcium homeostasis is the main cause for neuronal cell death.





Emergency room management of head injury patients

The primary survey of the patient includes airway, breathing and circulation management, looking for neurological disabilities and other injuries. The secondary survey includes detailed history and neurological examination. Severe head injury requires quick assessment, diagnosis and resuscitation.



Neurosurgical examination of head injured patients:

The following describes some features that should be assessed under certain circumstances with the understanding that this must be individualized.

General physical examination (oriented towards neuro assessment)

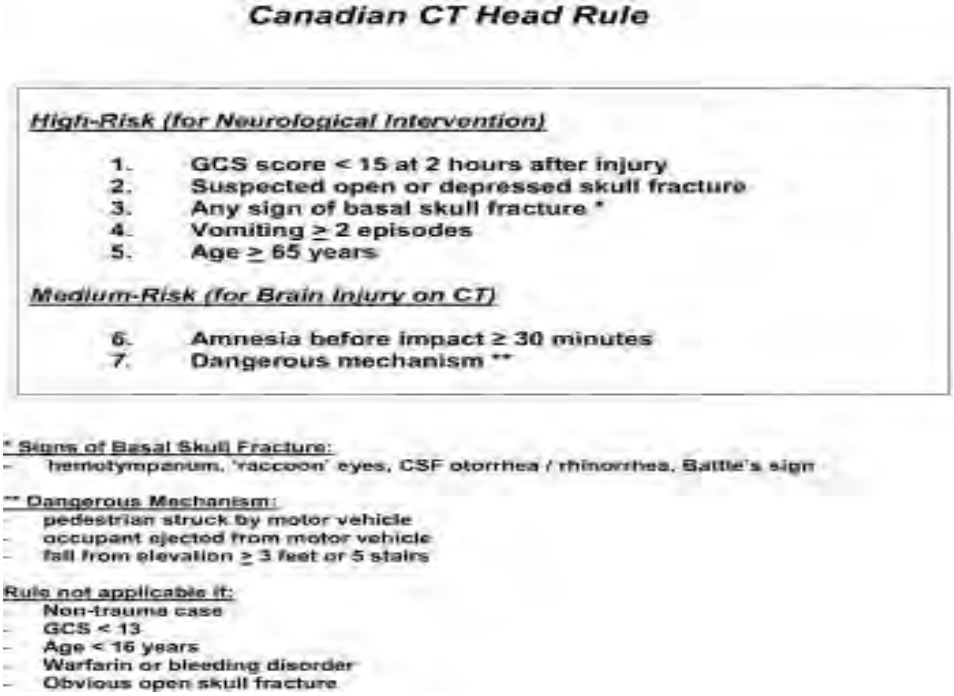
1) Visual inspection of cranium :
   A) Evidence of basal skull fractures – periorbital ecchymoses (Raccoon's eyes), post auricular ecchymoses (Battle's sign), CSF rhinorrhea/ otorrhea, haemotympanum or laceration of external auditory canal.
   B) Check for facial fractures
   C) Periorbital edema , proptosis.
2) Cranio cervical auscultation –
   Auscultate over carotid arteries for dissection and over globe of eye for traumatic carotid-cavernous fistulas.
3) Physical signs of trauma to spine – bruising, deformity

Neurologic Examination

1) Cranial nerve examination:-
   A) Optic nerve function : If conscious, serial quantitation of vision in each eye is important. If unconscious , check for afferent pupillary defect , best demonstrated with swinging flashlight test (indicates optic nerve injury). Fundoscopic examination for papilledema, pre retinal haemorrhages, retinal detachment, which are suggestive of anterior optic nerve injury.
   B) Pupil size and reaction to light (direct & consensual)
   C) Check for 6^{th} and 7^{th} cranial nerve palsy.
2) Level of consciousness and orientation :
   Glasgow coma scale is used to quantify level of consciousness in poorlr responsive patient.
3) Motor examination
   If patient is cooperative, check for motor strength in all 4 extremities. If patient is uncooperative, check for movements of all the 4 extremities to noxious stimulus. If any doubt about the integrity of spinal cord, check for resting anal sphincter tone on rectal examination and assess bulbocavernous reflex
4) Sensory examination : In cooperative patients, check pinprick on trunk and in all 4 extremities, also check for joint position sense in lower extremities. In uncooperative patients, check for central response to noxious stimulis.
5) Reflexes: Check deep tendon reflexes and plantar reflex for upgoing toes (Babinski sign). In suspected spinal cord injury check for anal wink and bulbocavernous reflex.

Imaging in head injury

An unenhanced (non contrast) CT scans of the brain usually suffices for patients presenting in emergency department with head injury. Indication for CT scans include: 1) All patients with moderate and severe head injury (GCS<13) 2) Patients having mild head injury fulfilling the Canadian criteria described below:



The emergent conditions that are needed to be ruled in initial CT scans are:-

1) Haemotomas: Extradural, subdural, subarachnoid, intracerebral, and intra ventricular.
2) Hydrocephalus.
3) Cerebral swelling: Obliteration of basal cisterns, compression of ventricles and sulci.
4) Cerebral anoxia : Loss of grey-white interface.
5) Skull fractures : Basal skull fractures, calvarial fracture.
6) Ischemic infarction
7) Pneumocephalus
8) Shift of midline structures.

MRI scans may be useful later after the patient is stabilized to evaluate brainstem injuries and small white matter changes as seen in diffuse axonal injury.

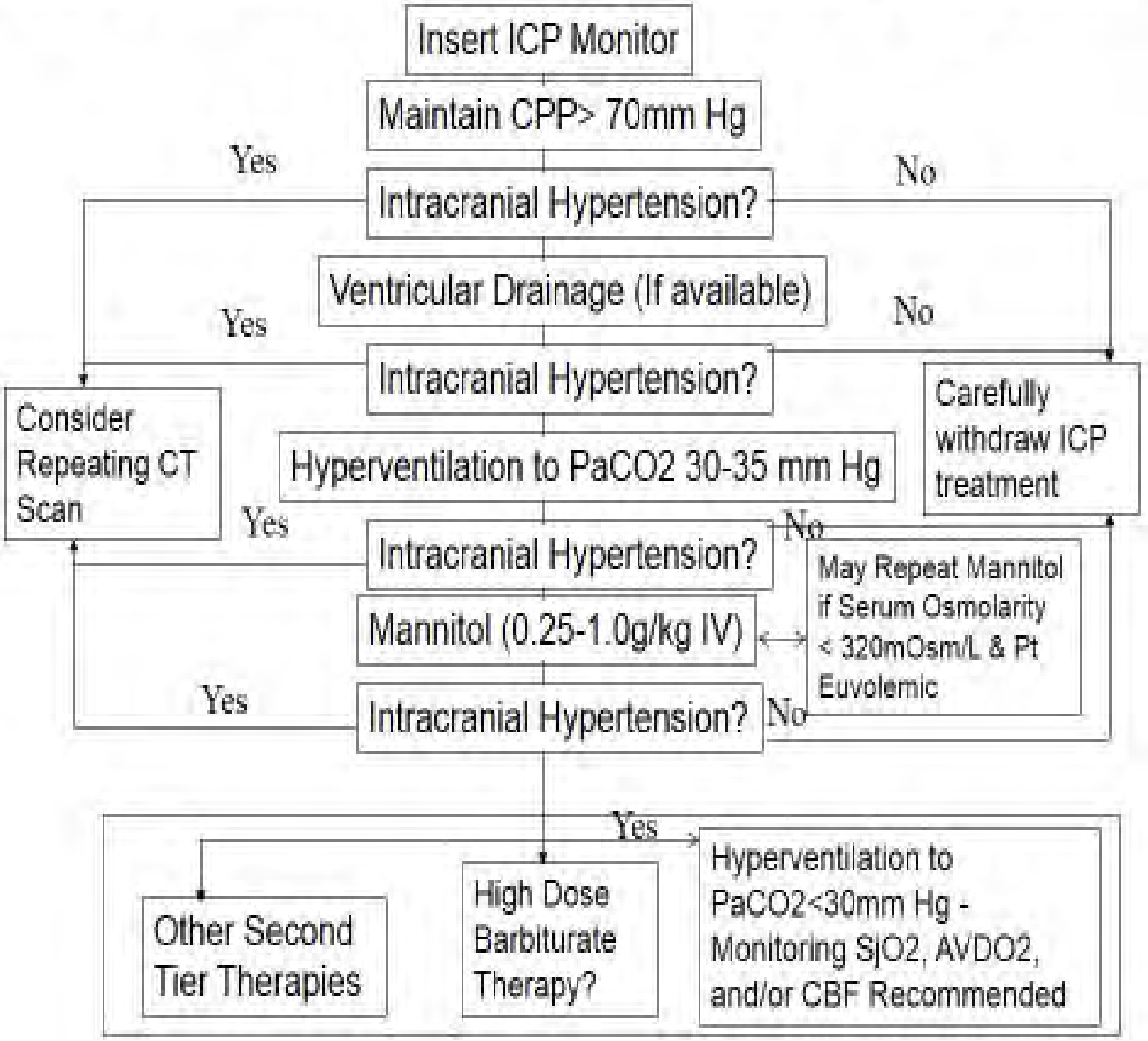
Monitoring in head injury

1) Clinical monitoring :-
   a) Level of consciousness.
   b) Focal deficits.
   c) Respiratory pattern, BP, pulse, blood glucose, electrolytes.
   d) Blood gas analysis.
2) Neuro monitoring:-
   a) ICP monitoring.
   b) Cerebral perfusion pressures.
   c) Evoked potential monitoring.
   d) CT scan monitoring.
   e) Transcranial Doppler monitoring
   f) Microdialysis of brain.

Indications for intracranial pressure monitoring

1) Patients with GCS - 3-8 after cardiopulmonary resuscitation with abnormal CT scan.
2) Patients with GCS, 3-8, with normal CT scan but if two or more of the following features are noted:
   a. Age > 40 years
   b. Unilateral or bilateral motor posturing
   c. Systolic B.P< 90mm Hg

CRITICAL PATHWAY FOR TREATMENT OF INTRACRANIAL HYPETENSION



Concussion (Mild traumatic brain injury)

Definition: Concussion is a complex pathophysiological process affecting the brain resulting in alteration of brain function, that is induced by nonpenetrating biomechanical forces, without identifiable abnormality in standard structural imaging.

Results in a graded set of neurological symptoms that may or may not involve loss of consciousness (LOC). Symptom on set is usually rapid, short-lived and resolves spontaneously. Alteration of consciousness may include confusion, amnesia (hallmark of concussion) or loss of consciousness. Patients themselves may be unaware whether or not they have experienced loss of consciousness. The alteration should be brief, but there is no consensus on the length of time considered to be brief. Resolution of the clinical and cognitive features typically follows a sequential course.

There are no gross or microscopic parenchymal abnormalities. Levels of glutamate rise after concussion and brain enters hyperglycotic and hypermetabolic state, which may persist up to 7-10 days.
Ct is normal or significant only for mild swelling which may represent hyperemia. MRI will demonstrate abnormalities in 25% of the cases, where CT is normal.

Concussion grading: Glasgow coma scale is too insensitive for use in patients with concussion. Two widely used concussion grading systems are those of Cantu and that of American Academy of Neurology (AAN)

	Grade 1	Grade 2	Grade 3
Cantu Guidelines	Post-traumatic amnesia <30 minutes, no loss of consciousness	Loss of consciousness <5 minutes or amnesia lasting 30 minutes -24 hours	Loss of consciousness >5 minutes or amnesia >24 hours
Colorado Medical Society Guidelines	Confusion, no loss of consciousness	Confusion, post traumatic amnesia, no loss of consciousness	Any loss of consciousness
American Academy of Neurology guidelines	Confusion, symptoms last <15 min. no loss of consciousness	Symptoms last >15 minutes no loss of consciousness	Loss of consciousness (3a, coma lasts seconds, 3b for minutes)

Guidelines for management of Minor Head injury

***Classification*:**
Group 0 - GCS 15 with dizziness or pain in impact zone and scalp contusion.
Group 1 - GCS 15 with LOC or amnesia, vomiting or diffuse headache.
Group 2 - GCS 14.

***Management*:**
Group 0: No radiological examination required. Can be sent home after 6 hrs of observation. Patients with risk factors (infants, alcoholic, and elders) need CT scan.
Group 1: CT examination is necessary and if CT is negative, then discharge the patient.
Group 2: CT is always necessary and observation till neurologically intact.

Post-concussion syndrome (PCS)

Post-concussion syndrome, also known as post concussive syndrome or PCS, is a set of symptoms that may continue for weeks, months, or years after a concussion. These symptoms include headache, dizziness, fatigability, irritability, anxiety, insomnia, loss of concentration and memory, noise and light sensitivity. At least 80-100% patients with concussion experience at least one PCS symptom in first month of post injury. Most recover within 1-3 months but in 10-20%, there will be persistence of symptoms.

The majority of experts believe that PCS results from a mix of factors, including preexisting psychological factors and those directly relating to the physical injury.

Conventional neuroimaging studies of the brain following a concussion are typically normal. However, studies have found some subtle physiological changes associated with PCS using more novel imaging modalities. Studies using positron emission tomography have linked PCS to a reduction in glucose use by the brain. Changes in cerebral blood flow have also been observed as long as three years after a concussion in studies using single photon emission computed tomography (SPECT).

Management of post-concussion syndrome typically involves treatments addressing specific symptoms. Painkillers for headaches and antidepressants for depression are usually prescribed. Psychotherapy in form of cognitive behavioral therapy is found to be useful in few patients.

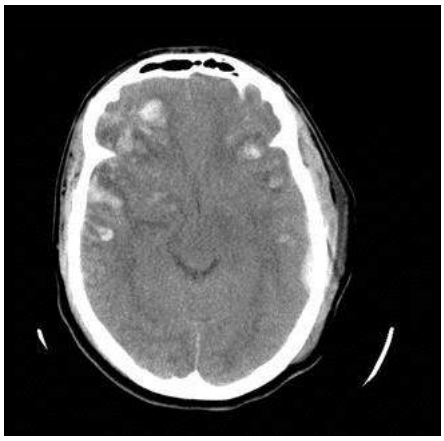
Hemorrhagic contusion (Traumatic intracerebral hemorrhage)

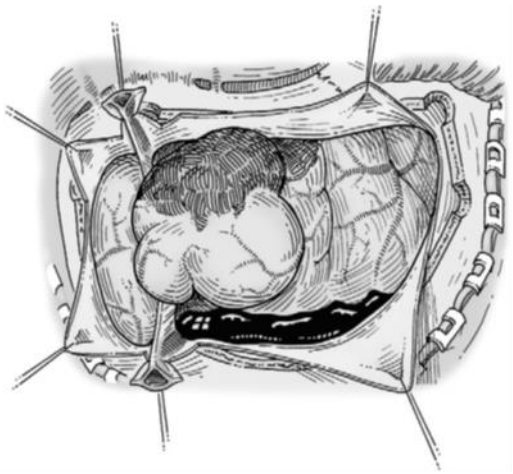
Most commonly occur in areas where sudden deceleration of the head causes the brain to impact on bony prominences (e.g. temporal, frontal and occipital poles) in coup or contre coup fashion.
Often considered as high density areas on CT (some exclude areas <1 cm diameter), contusions often enlarge and/or coalesce with time as seen on serial CTs. They also may appear in a delayed fashion. Surrounding low density may represent associated cerebral edema.
Indications for surgical evacuation for contusion:

- Progressive neurological deterioration referable to the contusion, medically srefractory IC-HTN, or signs of mass effect on CT
- contusion volume >50 cm^3 or ml
- GCS = 6–8 with frontal or temporal contusion volume >20 cm^3 with midline shift (MLS) ≥5 mm
- compressed basal cisterns on CT.

Nonoperative management with intensive monitoring and serial imaging, may be used for contusion without neurologic compromise and no significant mass effect on CT and controlled ICP.

Surgical treatment may range from craniotomy and evacuation of intraparenchymal haematoma to a decompressive craniectomy depending on the mass effect and size of haematoma. Traumatic intracerebral hematomas are also known to develop in areas previously devoid of radiographic injury within 24 to 72 hours after the initial injury. This phenomenon is commonly referred to as delayed traumatic intracerebral hemorrhage, seen in 5% of head injury cases.





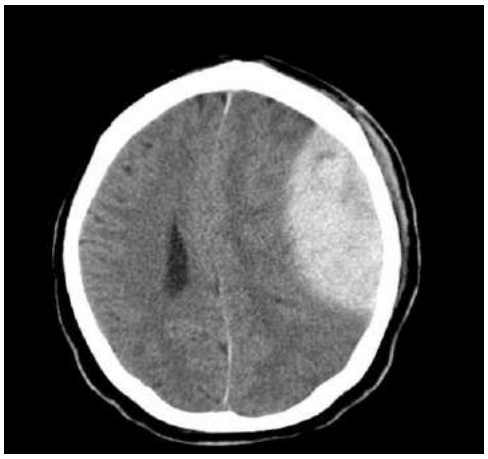
Extradural / Epidural hematoma (EDH)

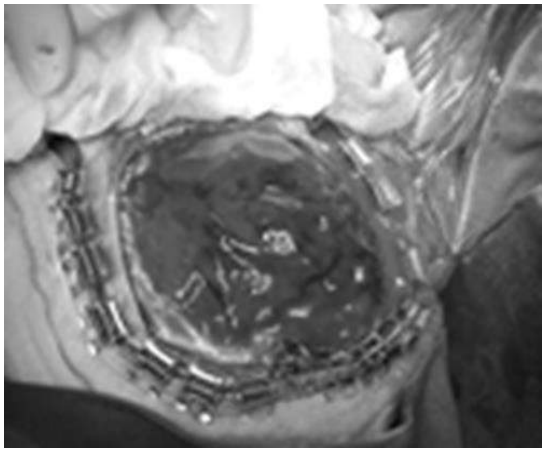
Epidural hematoma (EDH) is seen in 1% of head trauma admissions Ratio of male:female is 4:1. Usually occurs in young adults, and is rare before age 2 yrs or after age 60 (perhaps because the dura is more adherent to the inner table in these g Source of bleeding in 85% of cases is arterial (the middle meningeal artery is the most common source of middle fossa EDHs). Many of the remainder of cases are due to bleeding from middle meningeal vein or dural sinus. 70% occur laterally over the hemispheres with their epicenter at the pterion, the rest occur in thefrontal, occipital, and posterior fossa (5–10% each).

Pathophysiology of formation of EDH involves temporoparietal skull fracture that disrupts the middle meningeal artery as it exits its bony groove to enter the skull at the pterion, causing arterial bleeding that gradually dissects the dura from the inner table result ing in a delayed deteriorat ion.

Classic presentation is of brief posttraumatic loss of consciousness (LOC) from initial impact, followed by a “lucid interval” for several hours, then obtundation, contralateral hemiparesis, ipsilateral pupillary dilatation as a result of mass effect from hematoma.

Classic CT scan appearance of EDH is of high density biconvex (lenticular) shape bleed adjacent to the skull(84%). In 11% the side against the skull is convex and that along the brain is straight, and in 5% it is crescent shaped (resembling subdural hematoma). An EDH may cross the falx (distinct from SDH which is limited to one side of the falx) but is usually limited by skull sutures. EDH usually has uniformly density, sharply defined edges on multiple cuts, high attenuation (undiluted blood), contiguous with inner table, usually confined to small segment of calvaria. Mass effect is frequent.





Management

- EDH volume >30 cm^3 should be evacuated regardless of GCS
- EDH with the all of the following characteristics can be managed nonsurgically with serial CTscans and close neurological observation in a neurosurgical center: a) volume <30 cm^3 b) thickness <15 mm c) midline shift (MLS) <5 mm d) GCS>8 e) no focal neurologic deficit.

Although medical management of p-fossa EDHs has been reported, these are more dangerous and surgery is recommended.

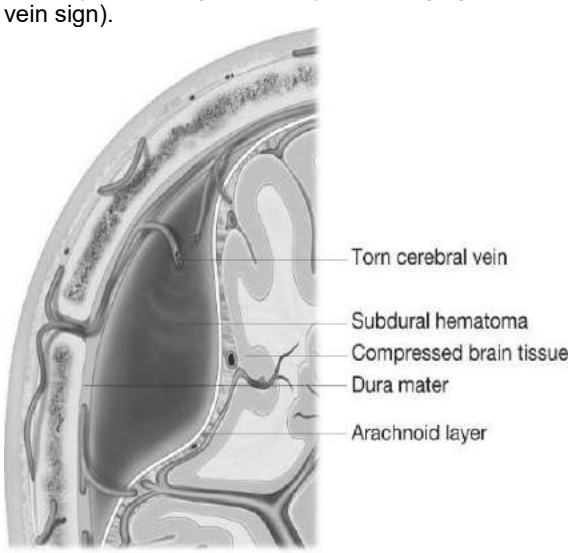
Acute subdural hematomas (ASDH)

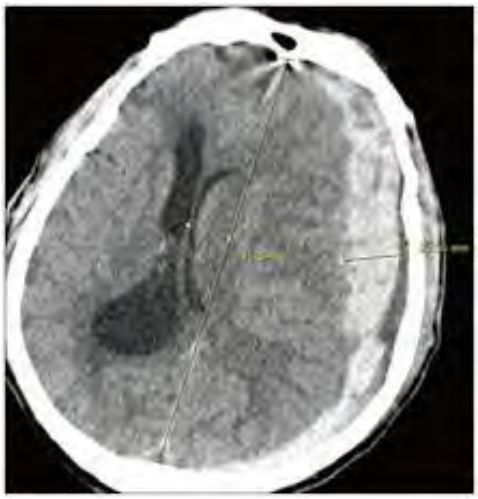
Acute subdural hematomas are more common than EDH and are commonly associated with underlying brain injuries (impact damage). Two common causes of traumatic ASDH are:-

- Accumulation around parenchymal laceration (usually frontal or temporal lobe). There is usually severe underlying primary brain injury. Often no "lucid interval." Focal signs usually occur later and are less prominent than with EDH
- Surface or bridging vessel torn from cerebral acceleration-deceleration during violent head motion. With this etiology, primary brain damage may be less severe, a lucid interval may occur with later rapid deterioration.

Symptoms may be due to compression of the underlying brain with midline shift, in addition to parenchymal brain injury and possibly cerebral edema. Receiving anticoagulation therapy increases the risk of ASDH 7-fold in males and 26-fold in females.

CT scan in ASDH: Crescentic mass of increased density adjacent to inner table. Edema is often present. Differences from EDH includes, SDH is more diffuse, less uniform, usually concave over brain surface, often less dense (from mixing with CSF), and bridging subdural veins (from brain surface to the skull) may be seen (cortical vein sign).



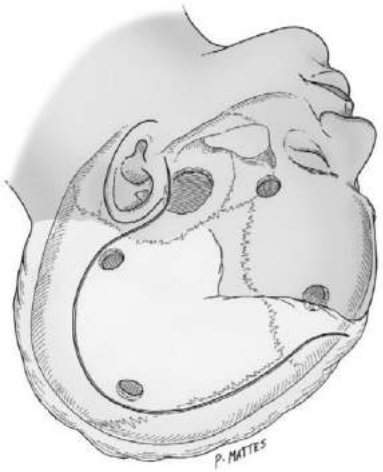


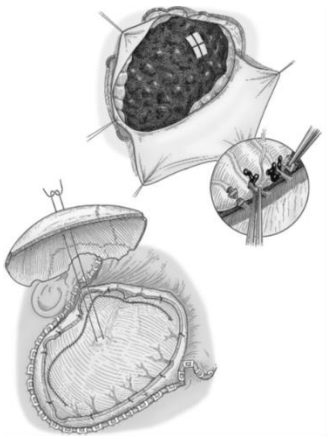
Management

Indications for surgery

1. ASDH with thickness >10 mm or midline shift (MLS) >5 mm (on CT) should be evacuated regardless of GCS
2. ASDH with thickness <10 mm and MLS<5 mm should undergo surgical evacuation if:
    a. GCS drops by ≥ 2 points from injury to admission
    b. the pupils are asymmetric or fixed and dilated
    c. ICP is >20 mm Hg (monitor ICP in all patients with ASDH and GCS<9)

ASDH meeting the above criteria for surgery should be evacuated via craniotomy with or without bone flap removal and duraplasty (a large craniotomy flap is often required to evacuate the thick coagulum and to gain access to possible bleeding sites).



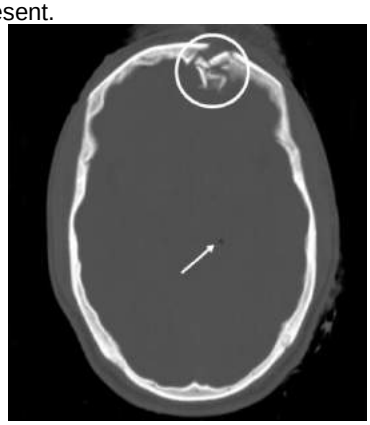


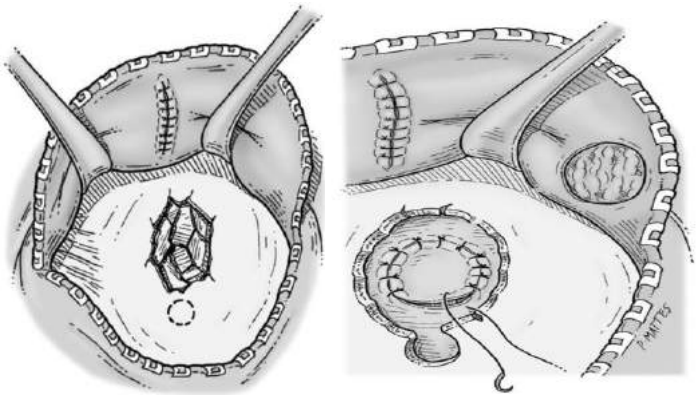
Depressed skull fractures

Indications for surgery:-

1. Open (compound) fractures.
2. The depth of the depressed fragments of the fracture is equal to or greater than the width of the surrounding bone.
3. The fracture occurs over cosmetic areas such as the forehead.
4. There is a significant underlying contusion that requires surgery.
5. Compound air sinus injury.

A depressed skull fracture that is closed, is not exerting a mass effect, and does not require repair for cosmetic reasons should not be elevated if overlying a venous sinus.
Surgical treatment includes elevation of the depressed segment and repair of dura/ evacuation of hematoma if present.





Posterior fossa hemorrhages

Most posterior fossa mass hemorrhages less than 3cm in diameter are managed conservatively.
Surgical indications include:-

1. All symptomatic patients
2. Mass effect on CT scans that include distortion, dislocation or obliteration of the 4th ventricle, basal cisterns compression and presence of obstructive hydrocephalus.

Diffuse axonal injury

First described by Strich in 1956, DAI occurs in 50% of severely head injured patients and accounts for 35% of all death from Head injury. Diffuse axonal injury (DAI) is defined as the presence of diffuse damage to axons in the cerebral hemispheres, corpus callosum, brain stem and cerebellum. Shear and tensile forces acting on the axons during acceleration and deceleration in the coronal plane cause this type of injury.

The triad of DAI consists of : a) axonal swelling in the white matter, b) haemorrhagic lesion in corpus callosum, c) lesion in dorsolateral quadrant of brainstem.

Clinical classification of DAI:
MILD - coma of 6-24 hours.
MODERATE-coma of >24 hrs without decerebrate posturing
SEVERE-coma >24 hrs with decerebrate posturing or flaccidity

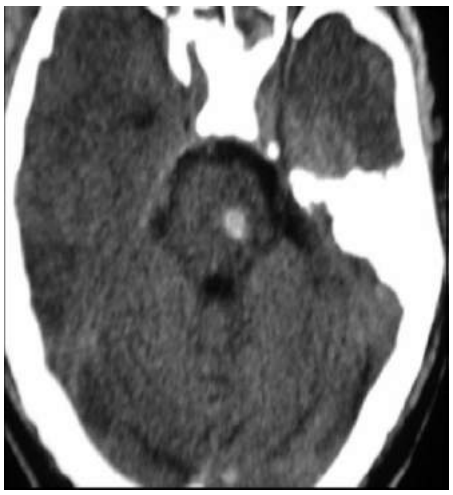
Grading of DAI:

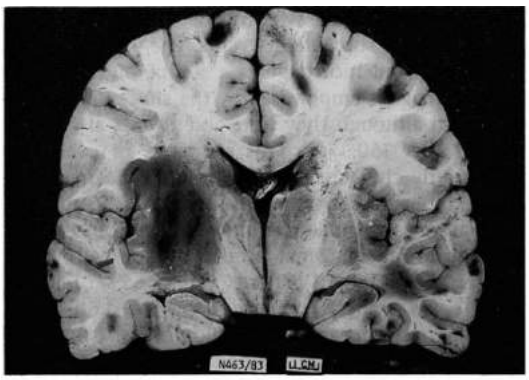
I. Microscopic axonal damage in the white matter, corpus callosum, brain stem or cerebellum without any macroscopic evidence.
II. Macroscopic or Microscopic detected focal lesions in the Corpus callosum and diffuse axonal damage.
III. Macroscopic or microscopic injury, focal injury to corpus collosum with dorsolateral quadrant of rostral brain stem.

Axonal retraction balls are the characterstic microscopic finding in DAI and it can be recognised in the first 12 hours using silver impregnation techniques. Amyloid precursor protein (APP) is the marker of choice for detecting DAI.

DAI is readily picked up by MRI images and are usually occult on CT scans

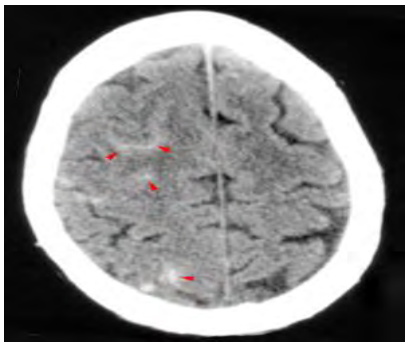
These patients are usually managed in neurosurgery ICU's with adequate monitoring and medications to lower the intracranial pressure. Mortality rate is 50% and around 30% who survive persist in vegetative state.





Diffuse axonal injury - 32 hours survival. Coronal slice that shows haemorrhagic lesions concentrated in midline structures viz. corpus callosum, parasagittal white matter (so-called gliding contusions), and basal ganglia.

Traumatic Subarachnoid haemorrhage



Head injury is the common cause of SAH. It is seen in 26-53% of patients who have sustained severe traumatic head injury. There is a two fold increase in mortality in patients having SAH. Severe headaches, mental status depression, and focal deficits are common. Grading - Greene et al

Grade I - < 5mm
Grade II - > 5mm
Grade III - < 5mm with mass lesion
Grade IV - Grade 2 + mass lesion

Treatment involves maintenance of intravascular volume (hypervolemia), mean arterial pressure (MAP) to ensure adequate cerebral perfusion pressure (CPP; hypertension), and hemodilution ("triple H" therapy).There is some evidence that nimodipine may improve outcome in head injured patients with subarachnoid hemorrhage.

Post traumatic epilepsy

Posttraumatic epilepsy (PTE) is a recurrent seizure disorder that apparently results from injury to the brain. This injury may be due to traumatic brain injury (TBI) or to an operation on the brain. Seizures that occur within 24 hours after brain injury are called immediate post traumatic seizures(PTS). PTS that occur within 1 week after injury are termed early PTS, and seizures that occur more than 1 week after injury are termed late PTS. About 20% of people who have a single late posttraumatic seizure never have any further seizures, and these people should not be labeled as having PTE. Approximately 80% of first PTS occur within 2 years of the injury.

Cortical lesions seem important in the genesis of the epileptic activity. The PTE kindling model of epilepsy postulates that iron deposition from extravasated blood leads to damage by free radicals, and the accumulation of glutamate leads to damage by excitotoxicity.

Antiepileptic drugs may be given to prevent further seizures; these drugs completely eliminate seizures for about 35% of people with PTE. However, antiepileptics only prevent seizures while they are being taken; they do not reduce the occurrence once the patient stops taking the drugs. Medication may be stopped after seizures have been controlled for two years. The antiepileptics carbamazepine and valproate are the most common drugs used to treat PTE; phenytoin may also be used but may increase risk of cognitive side effects such as impaired thinking.

Nutritional management of head injury

Severe head injuries tend to be associated with hypermetabolism and hypercatabolism resulting in negative nitrogen balances which may exceed 30 grams on day1 of injury. Enteral feeding should begin as soon as the patient is hemodynamically stable, attempting to reach a non-protein caloric intake of at least 30-35 kcal/kg/day and a protein intake of 2.0-2.5 g/kg/day as soon as possible.

With severe head injuries (Glasgow Coma Scale < 8), there is an increased tendency for gastric feeding to regurgitate into the upper airway. Keeping the patient upright and checking residuals is important in such patients. Jejunal feedings are less apt to be aspirated. If it is apparent that the gastro-intestinal tract cannot be used to reach the nutritional goals within three days, total parental nutrition is begun within 24-48 h so as to reach these nutrition goals by either one or both routes by the third or fourth day.

Blood glucose levels exceeding 150-200 mg/dl tend to increase the severity of the neurologic problems and efforts should be made to prevent hyperglycemia by carefully regulating the glucose and insulin intake. To determine N2 balance, urinary urea nitrogen should be measured in 24h specimens. These tests should be performed once or twice weekly until it is clear that the nutrition is adequate.

Rehabilitation in head injury

Traumatic brain injury (TBI) commonly affects younger people and causes life-long impairments in physical, cognitive, behavioural and social function. The cognitive, behavioural and personality deficits are usually more disabling than the residual physical deficits. Recovery from TBI can continue for at least 5 years after injury.

Rehabilitation is effective using an interdisciplinary approach, and close liaison with the patient, family and carers. The focus is on issues such as retraining in activities of daily living, pain management, cognitive and behavioural therapies, and pharmacological management.

The social burden of TBI is significant, and therefore family education and counselling, and support of patient and carers, is important.

General practitioners play an important role in providing ongoing support in the community, monitoring for medical complications, behavioural and personality issues, social reintegration, carer coping skills and return-to-work issues.

Cushing’s Disease

Sunil Chumber, Pratyusha Priyadarshini

Introduction

Harvey W. Cushing, first described patients with a peculiar fat deposition, amenorrhea, impotence (in men), hirsutism, purple striae, hypertension, diabetes, and other features resulting from hypercortisolism. He also discovered that these patients had basophilic tumors of the pituitary which lead to adrenocortical hyperplasia, thus resulting in the manifestations of the syndrome. The term Cushing's syndrome refers to a complex of symptoms and signs resulting from hypersecretion of cortisol regardless of etiology. However, Cushing's disease refers to a pituitary tumor which leads to bilateral adrenal hyperplasia and hypercortisolism.

Cushing's syndrome is a rare disease, affecting 10 in 1 million individuals. It is more common in adults but may occur in children. Women are more commonly affected (male:female ratio 1:8).

This disease has significant long term morbidity and mortality. If left untreated it may result in 5 year survival of 50%. Patients who are incompletely controlled have 11-fold increased mortality as compared to normal population.

Etiology

By far, the most common cause of Cushing's syndrome is prolonged exogenous administration of excess glucocorticoids. Endogenous cause of Cushing's can be divided into ACTH-dependent or ACTH independent. The ACTH dependent cause accounts for 80-85% of the Cushing syndrome and rest of the 15-20% are ACTH independent Cushing's syndrome. ACTH dependent Cushing's syndrome can be further divided into pituitary origin or ectopic origin, of which pituitary origin (Cushing's disease) is most common comprising 70% of Cushing's syndrome. Primary adrenal sources (adenoma, hyperplasia, and carcinoma) account for about 20% of cases and ectopic ACTH-secreting tumors account for <10% of cases. Table no-1 summarizes the etiology of Cushing's.

Table 1: Etiology of Cushing's syndrome

Exogenous	**Endogenous**	
Most common cause Due to prolonged exogenous administration of glucocorticoids	**ACTH dependent**	**80-85%**
	• Cushing's disease	70%
	• Ectopic ACTH syndrome	10%
	• Unknown source of ACTH	5%
	ACTH independent	**20%**
	• Adrenal adenoma	10%
	• Adrenal carcinoma	5%
	• Macronodular adrenal hyperplasia	<2%
	• Others	<4%

Clinical features

Metabolic effects of excessive glucocorticoids leads to a variety of signs and symptoms, table 2 summarizes these clinical features. These patients exhibit peculiar pattern of fat deposition due to lipogenic action of excessive corticosteroids centrally and catabolic effects peripherally, along with peripheral muscle wasting. Patients typically have truncal obesity with "moon face" and fullness of supraclavicular fat pads ("buffalo hump"). Endocrine abnormalities include glucose intolerance, amenorrhea, and decreased libido or impotence. In children, Cushing's syndrome is characterized by obesity and stunted growth. Patients with Cushing's disease may present with headaches, visual field defects, and panhypopituitarism. Hyperpigmentation of the skin may be seen in patients with ectopic ACTH-producing tumor due to high levels of circulating ACTH.

Table 2: Clinical features of Cushing's syndrome

Signs and symptoms	**%**	**Signs and symptoms**	**%**
Obesity or weight gain	95	Hirsutism	75
Facial plethora	90	Depression/emotional lability	70
Rounded face	90	Easy bruising	65
Decreased libido	90	Glucose intolerance	60
Thin skin	85	Weakness	60
Decreased linear growth in children	70-80	Osteopenia or fracture	50
Menstrual irregularity	80	Nephrolithiasis	50
Hypertension	75		

Investigations

Work up of patients with suspected Cushing's syndrome have two main objectives, first to confirm the diagnosis of Cushing's syndrome ,second to determine the etiology of the disease and localize the culprit lesion.

Investigations to confirm the diagnosis

Cushing's syndrome is characterized by elevated glucocorticoid level not suppressible by exogenous hormone administration and loss of diurnal variation. This phenomenon is used to screen patients using the overnight low-

dose dexamethasone suppression test. In this test, 1 mg of dexamethasone is given at 11 P.M. and plasma cortisol levels are measured at 8 A.M. the following morning. In Physiologically normal adults cortisol levels are suppressed to <2mcg/dL, while patients with serum cortisol >2mcg/dl are considered to be positive. Overnight dexamethasone is a simple screening tool, however it has high false positive rate of 30%. Hence patients with positive test undergo further testing with standard low dose dexamethasone test (LDDST) to confirm the diagnosis of Cushing's syndrome. In this test, 0.5 mg of Dexamethasone is administered every 6 hourly for 48 hours (10 µgm/kg/dose) and blood sample for serum cortisol is collected at 6 hours after the last dose. Serum cortisol levels of > 5 µgm/dl confirms presence of hypercotisolism while, serum cortisol < 5 µgm/dl rules out hypercotisolism.

Measurement of 24-hour urinary cortisol levels is also a very sensitive (95 to 100%) and specific (98%) modality of diagnosing Cushing's syndrome. A urinary cortisol excretion of < 135 nmol/24 hr rules out the diagnosis of hypercortisolism. While more than threefold rise in the 24-hour urinary cortisol confirms the diagnosis. Recently, late night (11:00 P.M.) salivary cortisol measurements using commercially available kits are being increasingly used. This test has high sensitivity and specificity as salivary cortisol levels highly correlates with plasma cortisol levels.

Evaluation of the etiology of Cushing's syndrome

Once a diagnosis of Cushing's syndrome is established, further testing is needed to determine whether it is ACTH-dependent or ACTH independent. The first step is measurement of plasma ACTH levels (normal value 10 to 100 pg/mL). Elevated ACTH levels are found in patients with Cushing's disease (15 to 500 pg/mL), but the highest levels are found in patients with ectopic sources of ACTH (>1000 pg/mL). In contrast, ACTH levels are suppressed (<5 pg/mL) in patients with primary cortisol-secreting adrenal tumors.

Next, the high-dose dexamethasone suppression test is used to distinguish between the causes of ACTH-dependent Cushing's syndrome (pituitary vs. ectopic). Started immediately after LDDST, 2 mg of dexamethasone is administered orally every 6 hourly for 48 hours (40 µgm/kg/dose) and blood sample for serum cortisol is collected 6 hours after last dose. In patients with pituitary adenoma, serum cortisol shows 50-90% suppression. However, patients with ectopic ACTH production exhibit no suppression in serum cortisol after HDDST.

For patients with equivocal ACTH and high-dose dexamethasone-suppression test results further evaluation with corticotrophin releasing hormone (CRH) stimulation test might be useful. Patients with pituitary tumors will have raised serum cortisol after receiving an intravenous bolus of CRH. However, CRH stimulation test is not routinely done at our center due to its limited availability and also it is not 100% specific.

Localization

If ACTH dependent Cushing's syndrome is suspected, however, the source of ACTH remains unknown despite above mentioned biochemical evaluations; the next investigation of choice is pituitary MRI. In patients with clinical features and biochemical parameters highly suggestive of ACTH dependent Cushing's syndrome, pituitary lesion of 6mm or more on MRI is diagnostic of Cushing's disease. However, up to 40% of patients with Cushing's disease may have normal pituitary MRI scan, these patients will require bilateral selective inferior petrosal vein sampling to discriminate between pituitary and non-pituitary source of ACTH. But, venous sampling is an operator dependent, technically demanding, skilled and invasive procedure. This procedure is not done at AIIMS, however, sampling from the internal jugular veins, a more simplified procedure is used to distinguish between the sources of ACTH.

In patients diagnosed with ACTH –independent Cushing's syndrome, a fine cut CT scan or MRI is ordered to look for the adrenal lesion. Patients with ectopic ACTH Cushing's syndrome undergo axial imaging with thin-cut multi slice CT of thorax and abdomen, which has a high detection rate for primary tumors.
In patients with small neuroendocrine tumors not visualized on CT scan, further imaging options include somatostatin-receptor scintigraphy, whole body FDG-PET and (11) C-5-hydroxytryptophan-PET.

Treatment

Surgery remains the mainstay of treatment for patients with Cushing's syndrome, while patients not amenable for surgery are offered medical therapy.
The treatment of choice in Cushing's disease is transsphenoidal excision of the pituitary adenoma (TSS), which has disease remission rate of 50-80%. In patients with failed TSS, stereotactic radiosurgery (CT guidance to deliver high doses of radiotherapy to the tumor (photon or gamma knife)) is now increasingly being used and another option is bilateral laparoscopic adrenalectomy. Pituitary irradiation which was used earlier for patients with persistent or recurrent disease is not favored now due to high rate of panhypopituitarism and other complications.

Patients with ectopic ACTH production are best managed by excision of the primary tumor, including recurrences, if possible. Bilateral laparoscopic adrenalectomy has been used to palliate patients with unresectable disease and those whose ectopic ACTH secreting tumor cannot be localized.

Laparoscopic adrenalectomy is the treatment of choice for patients with adrenal adenomas. Open adrenalectomy is reserved for patients with very large adrenal tumors and patients suspected with adrenal cancers. Patients with adrenal hyperplasia are cured by bilateral laparoscopic adrenalectomy.

Patients with disease not amenable for surgery are candidates for pharmacologic therapy with adrenal inhibitors (medical adrenalectomy) such as ketoconazole, metyrapone, and mitotane.

All patients undergoing surgery for Cushing's syndrome require stress dose of steroids in perioperative period. Patients undergoing bilateral adrenalectomy require lifelong glucocorticoid and mineralocorticoid in replacement dose. Patients with unilateral adrenalectomy will also require steroid supplementation for 6-24 months for hypothalamo-pituitary-adrenal axis of contralateral suppressed adrenal gland to recover.

Table 3: Preferred surgical options for Cushing's syndrome and their outcomes

Etiology	**Preferred surgical option**	**Outcome**
ACTH-dependent		
Pituitary adenoma	Transsphenoidal surgery(TSS)	50-60% remission rate
	Bilateral laparoscopic adrenalectomy (failed TSS)	Low morbidity and mortality Improved quality of life Nelson's syndrome (upto 10%)
Ectopic ACTH syndrome	Resection of localized primary tumors	Good immediate recovery
	Bilateral laparoscopic adrenalectomy (source not localized)	Poor prognosis Effective palliation
ACTH- independent		
Adrenal adenoma	Laparoscopic adrenalectomy	Excellent
Adrenal carcinoma	Open radical adrenalectomy	Poor
Adrenal hyperplasia	Bilateral laparoscopic adrenalectomy	Excellent

Conclusions

Cushing's syndrome is a rare disease with characteristic clinical features. The diagnosis and exact anatomical localization is challenging and requires systematic evaluation and high index of suspicion. Surgical excision of causative pathology is primary modality of treatment and has the potential to offer long term care. However, patients with adrenocortical carcinoma and ectopic ACTH dependent Cushing's with source not localized have poor prognosis.

Suggested reading

1. **Chapter 38. Thyroid, Parathyroid and Adrenal in Schwartz's Principle of Surgery 9th edition.**
2. **Chapter 41. The Adrenal Glands in Sabiston Textbook of Surgery- The Biological Basis of Modern Surgical Practice, 19th edition**
3. **Chapter 28. Cushing's Disease and Syndrome in Endocrine surgery- Principles and Practice**

Liver Abscesses

Nikhil Talwar, Rigved Gupta

Liver abscess refers to a potentially life threatening condition with single or multiple foci of pus collection within the liver parenchyma. Based on etiopathogenesis liver abscesses can be classified into two types,

1. **Pyogenic Liver Abscesses (PLA):** Caused mostly by aerobic & anaerobic bacterial infection (both gram positive & gram negative) & rarely by fungal & tubercular involvement.
2. **Amebic Liver Abscesses (ALA):** Caused by protozoan *Entamoeba histolytica* (the causative organism of intestinal & extra intestinal amebiasis)

This differentiation is important as the management of both these conditions differs significantly. Although worldwide ALA is more common, PLA constitutes most cases in western hemisphere.

PYOGENIC LIVER ABSCESSES (PLA)

Epidemiology

The first extensive review of PLA was done in 1938 by Ochsner and DeBakey who reported an incidence of 8/100,000 hospital admissions. The most common cause of PLA in their review was portal pyemia secondary to acute appendicitis, occurring mostly in young adults. They also described open surgical drainage of PLA resulting in decrease in the mortality compared to previous studies. Recent data suggest a change in the epidemiology of PLA. Acute appendicitis is no longer the commonest cause of PLA; cryptogenic & biliary causes constitute majority of cases now, occurring mostly in 5^{th} – 6^{th} decade of life. Also, there has been an increase in the incidence of PLA with some studies reporting as high as 22/100,000 hospital admissions. The incidence of PLA is lower in western literature compared to eastern literature. Despite increase in incidence, the mortality has decreased from 50% to less than 10% at present. The preferred treatment of PLA has also shifted from open surgical drainage to minimally invasive percutaneous methods first described by McFadzean et al in 1953. PLA is slightly more common in males with male to female ratio being 1.5:1. Unlike ALA, there are no ethnic or geographic differences in occurrence of PLA.

Etiology & classification

Table 1: Etiology & classification of PLA

1.	**Biliary** *Benign*: Cholelithiasis Choledocholithiasis Hepatolithiasis/ Recurrent pyogenic cholangitis Benign biliary strictures Acute Cholangitis Biliary Ascariasis Prior biliary tract surgery (esp. biliary-enteric anastamosis) Biliary tract intervention (ERCP, PTC, Stenting etc.) Caroli's disease *Malignant*: Periampullary tumours Cholangiocarcinoma Carcinoma GB
2.	**Portal** Diverticulitis Hollow viscus perforation Abdominal & pelvic abscess Anorectal abscess Inflammatory bowel disease Pancreatitis/pancreatic abscess Appendicitis Gastric/Colonic cancer Post-operative collections Omphalitis in newborn child PID
3.	**Hepatic arterial** Bacterial endocarditis IV drug Abuse Head & neck infection Pneumonia & lung abscess Osteomyelitis Pyonephrosis Vascular sepsis
4.	**Traumatic** Blunt hepatic trauma Penetrating hepatic trauma Chemoembolization / radioembolization (TACE/TARE) Thermal ablation (Radiofrequency ablation) Chemical ablation (Percutaneous ethanol injection)
5.	**Adjacent pathology** Acute suppurative cholecystitis/Empyema GB Hollow viscus perforation adjacent to liver (Gastric, duodenal, colonic perforation) Perinephric abscess Subphrenic abscess
6.	**Cryptogenic**

Depending upon the source/ route of infection, the causes of PLA can be classified into six categories:

1. **Biliary** (30-45%): Biliary causes constitute the most common identifiable cause of PLA at present times. The increase in incidence of biliary causes of PLA has been attributed to increased biliary intervention for benign & malignant biliary disorders leading to increased chances of cholangitis. While benign conditions causing PLA are more common in eastern countries, malignant biliary obstruction is more common in the west. The primary cause is biliary obstruction with superimposed infection leading to ascending suppurative cholangitis.

2. **Portal** (10-20%): Portal pyemia or pyelophlebitis can occur secondary to any intra-abdominal infective pathology. This used to be the most common cause of PLA in the past. However, with better antibiotics & treatment of such conditions, the incidence of PLA secondary to portal pyemia has decreased. Portal vein patency must be evaluated by Doppler or CECT in patients with PLA.

3. **Hepatic arterial** (5-10%): Any infective focus elsewhere in the body can lead to systemic arterial dissemination of bacteria & involvement of liver via hepatic artery.

4. **Traumatic** (<5%): Blunt or penetrating liver trauma leads to hematoma & necrosis with secondary infection causing PLA. Although rare, iatrogenic trauma in the form ablative procedures for hepatic neoplasms can also give rise to PLA, especially in the presence of previous biliary-enteric anastomosis.

5. **Adjacent pathology** (<5%): PLA can rarely occur due to spread of infection from inflammatory/infective pathology in adjacent organs.

6. **Cryptogenic** (20-40%): Cryptogenic PLA refers to a condition when an underlying cause cannot be identified. Along with biliary causes, cryptogenic PLA constitute most cases of PLA overall.

Predisposing factors

PLA occurs more commonly in certain patients with associated diseases or comorbid conditions. The following predisposing factors have been identified:

- Diabetes mellitus (10 times increased risk)
- Cirrhosis
- Jaundice
- Chronic renal failure
- History of Malignancy
- Leukaemia & lymphoma
- Immunosuppressive disorders such as AIDS
- Cancer Chemotherapy
- Prolonged steroid use
- Chronic alcoholism
- Chronic pancreatitis
- Inflammatory bowel disease
- Peptic ulcer disease
- Immune disorders in children (Complement deficiencies, chronic granulomatous disorder)
- Other childhood disorders such as Sickle cell anemia, congenital hepatic fibrosis, PCLD, Necrotising enterocolitis

Pathology & Microbiology of PLA

The primary source of PLA is suggestive of the distribution as well as microbiology of PLA. PLA with biliary or hepatic arterial source are more like to be multiple & small with bilateral involvement whereas those with portal or cryptogenic source tend to be solitary & large affecting the right lobe predominantly (due to preferential laminar flow to right lobe from portal vein). PLA from biliary or portal venous source are usually polymicrobial, mostly associated with gram negative bacteria & anaerobes, while those with hepatic arterial source are monomicrobial, predominantly caused by *Staphylococcus* or *Streptococcus species.*

Overall, right lobe is the most common site of PLA, being affected in 75% of cases, followed by left lobe (20%) & caudate lobe (5%). Almost 50% of PLA tend to be solitary, rest half being multiple.

Positive cultures may be obtained from aspirated pus culture as well as blood culture. However, abscess culture positivity (80-90%) is more than that of blood cultures (50-60%). Around 10-20% of abscess cultures tend to be sterile.

Polymicrobial cultures are obtained in 30-50% patients, the rest being monomicrobial. The most common aerobic organisms cultured from PLA include *Escherichia coli* (35-45%), *Streptococcus species* (20%) *& Klebsiella*

Pneumonia (18%), while the most common anaerobe is *Bacteroides fragilis* (15%). Overall anaerobic organisms are cultures in 40-50% of cases. Isolation of these organisms require special anaerobic culture techniques.

PLA secondary to *Klebsiella Pneumonia* are especially common in Asian countries (Taiwan, Korea, etc.), where it is the most common organism associated with cryptogenic PLA. These abscesses occur more commonly in diabetics & alcoholics & are associated with increased risk of septic emboli, the most serious complication of which is vision threatening endophthalmitis.

Table 2: Organisms causing PLA

	Common	**Rare**
Gram negative aerobes	*Escherichia coli* *Klebsiella* *Proteus* *Pseudomonas* *Enterobacter*	*Citrobacter* *Serratia* *Morganella* *Acinetobacter*
Gram positive aerobes	*Streptococcus* *Enterococcus* *Staphylococcus*	
Gram negative anaerobes	*Bacteroides fragilis* *Fusobacterium*	
Gram positive anaerobes	*Peptostreptococcus* *Clostridium* *Actinomyces*	

Clinical features & complications

PLA usually presents in acute or subacute manner, however, cryptogenic PLA may have chronic presentation with non-specific symptoms occurring for weeks. The classic triad of PLA consists of fever, jaundice & right upper quadrant pain, however this triad is rarely noted. Fever is the most common symptom of PLA, being present in 70-95% of patients. Fever is usually associated with chills & rigors. Right upper abdominal pain is the next commonest symptom, noted in 50-70% patients. Jaundice is present in 20-30% patients & is usually secondary to underlying biliary disease. Other non-specific symptoms include nausea, vomiting, weight loss, anorexia & malaise. Involvement of diaphragm & right chest can give rise to symptoms such as cough, pleuritic chest pain & breathlessness in 25% of patients. On examination, right upper quadrant tenderness & hepatomegaly are the most common signs.

PLA can also present with complications. The most common complication associated with PLA is generalised sepsis which may give rise to multi organ dysfunction. Contiguous inflammation can give rise to right sided pleural effusion & basal consolidation. PLA can also present with rupture; abscess rupture is usually contained by omentum or adjacent organs & rarely presents with free intraperitoneal rupture giving rise to generalised peritonitis. Rupture into right pleural cavity may give rise to empyema thoracis. PLA due to *Klebsiella Pneumonia* is specifically associated with high incidence of systemic septic embolization giving rise to metastatic distant organ involvement such as endophthalmitis, meningitis, lung abscess etc.

Differential diagnosis

The most important differential diagnosis of PLA is amebic liver abscess (ALA). It is important to differentiate PLA from ALA since the management is different in each case. PLA is usually treated with antibiotic combined with percutaneous abscess drainage whereas ALA is usually treated with Metronidazole & aspiration being reserved for specific indications.

Table 3: Differential diagnosis of Liver Abscesses

Feature		**PLA**	**ALA**
Epidemiology	**Cause**	Mostly bacterial infection from biliary, portal, hematogenous, traumatic or adjacent sources	Invasive amebiasis caused by *Entamoeba histolytica*
	Number	Equal Solitary & multiple (50% each)	Usually solitary (80%)
	Location	May be central or peripheral	Usually peripherally located (sub-capsular)
	Age	>50 years	20-40 years
	Male : Female	1.5:1	10:1
	Ethnicity	No	Hispanic men

	Endemic areas	No	Central & S America, South-East Asia & Africa
Risk factors	**Diabetes**	Commonly associated	Rarely associated
	Hepato-biliary Malignancy & biliary obstruction	Increased risk	No definite association
	Pregnancy	No risk	Increased risk
	Poverty & poor hygiene	No risk	Increased risk
History	**Travel to endemic area**	Absent	Present
	Fever with chills	Common	Fever is common, chills & rigors less common
	Abdominal pain	Less common	More common
	Diarrhoea	Less common	More common
	Recent history of colitis	Less common	More common
	Pruritus	More common	Less common
Examination	**Jaundice**	Common	Uncommon
	Septic Shock	Common	Uncommon
	Abdominal tenderness/Point tenderness	Less common	More common
	Hepatomegaly	Less common	More common
Investigations	**Hyperbilirubinemia**	Common	Uncommon
	Amebic serology	Negative	Positive (titres >1:256 IU)
	Diagnostic Aspiration	Reveals foul smelling purulent content	Reveals odourless Anchovy Sauce pus
	Pus microscopy	Numerous WBC's & bacteria	Degenerated hepatocytes, No leukocytes, rarely trophozoites seen
	Blood cultures	Positive	Negative
	Pus culture	Positive	Negative
	CT	Classic Target Sign (hypodense lesion with rim enhancement)	Hypodense lesion with peripheral zone of edema but lack of rim enhancement
	Nuclear scan	Warm or hot lesion	Cold lesion
	Radiological resolution of abscess cavity	Occurs earlier (2-4 months)	Occurs late (7-9 months)
Treatment	**Treatment of choice**	Antibiotics plus Drainage	Antibiotics
	Antibiotic	Ampicillin + Aminoglycoside + Metronidazole or 3rd gen. Cephalosporin + Metronidazole	Metronidazole (Drug of choice)
	Aspiration/Drainage	Indicated in all cases	Indicated in few cases
Prognosis	**Mortality**	<10%	<5%

Investigations

1. **Laboratory investigations:** Abnormal blood investigations are common in PLA & usually reveal non-specific findings suggestive of hepatic involvement & systemic inflammatory response.

   Leukocytosis & elevated ALP are the most common abnormalities. Leukocytosis is present in 80-90% of patients. LFTs are usually abnormal with mild elevations of ALP (70-80%) & transaminases (50-60%) in most patients. Hyperbilirubinemia is seen in 50% patients. Severe abnormalities of liver function are unusual & if present, indicate biliary origin of PLA. Anaemia, hypoalbuminemia & coagulopathy (elevations of the PT and INR) occur in 60-75% patients & suggest chronicity of the disease. Older patients tend to have higher BUN & creatinine levels. Markers of inflammation such as ESR & CRP may also be elevated. Hypoalbuminemia, increased serum creatinine and prolonged prothrombin time are associated with poor prognosis & increased mortality.

2. **Cultures:** Both blood culture & aspirated pus culture should be sent in all patients with PLA. Abscess culture positivity (80-90%) is more than that of blood cultures (50-60%). Around 10-20% of abscess cultures tend to be sterile. Ideally cultures should be sent before starting empiric antibiotic therapy. Antibiotic should later be changed as per culture & sensitivity reports. Samples for both aerobic & anaerobic cultures should be sent as anaerobic organisms may be encountered in 40% of the patients. Mycobacterial and fungal cultures should be sent in immunocompromised patients.

3. **Amebic serology:** For patients in whom ALA is suspected, amebic serology should be done to differentiate PLA from ALA. The role of amebic serology in ALA diagnosis is discussed later under ALA.

4. **Chest radiographs:** Although only 25% patients have pulmonary symptoms, almost 50% patients tend to have non-specific findings on chest x-rays secondary to contiguous inflammation. Common findings include right pleural effusion, basal consolidation, & an elevated right hemi-diaphragm. Rarely abscess rupture in the pleural cavity may give rise to empyema with collapse of ipsilateral lung, which may require intercostal drainage along with drainage of PLA. Other rare findings include an air-fluid level in the right sub-diaphragmatic region & portal venous gas secondary to pyelophlebitis.

5. **Ultrasound (USG):** Ultrasound is the initial imaging investigation of choice for suspected PLA. Advantages of USG include its low cost, portability, lack of radiation exposure, high sensitivity for PLA (80-95 %) & its ability to differentiate cystic lesions from solid lesions. Moreover, it can also identify underlying biliary pathology such as dilated CBD, hepatolithiasis etc., which may require additional treatment. Doppler scan should also be added to abdominal USG for evaluating portal vein patency. Real time USG also helps in guiding percutaneous treatment of PLA. However, ultrasound is limited in its ability to visualize lesions high up in the dome of the liver close to the diaphragm, lesions located under the ribs, & locating small abscesses. Also, it is less useful in obese patients and is user-dependent.

   The most common finding on USG is a hypoechoic lesion with internal echoes; lesions may be single or multiple, involving right lobe (most common), left lobe or bilateral. USG appearance of PLA depends on the stage of evolution; early lesions are hyperechoic, later as the abscess matures with the formation of pus, it becomes hypoechoic with a well-defined wall. USG may also identify contained or free rupture of the abscess with collection of pus in peri-hepatic region which may be seen communicating with the abscess cavity in the liver.

   Kunze et al have described four sono-morphologic stages of PLA based on the appearance on Contrast USG:

   Stage I: Focal inflammation without necrosis (Least common appearance);
   Stage II: Focal clusters of micro-abscesses appearing to coalesce (2nd most common appearance)
   Stage III: Single cavity with or without capsule (Most common appearance).
   Stage IV: Numerous small abscesses scattered all over the liver

   This morphological staging based on contrast USG may help in guiding treatment decisions, however, at present no standard guidelines are available based on this staging.

6. **Contrast enhanced computerised tomography (CECT):** CECT is the best & the most sensitive investigation for diagnosis of PLA & its complications. CT has higher sensitivity than USG (95-100%) & avoids the anatomic limitations of USG. Also, CT is better than USG for detecting very small abscesses & local complications of PLA. CT can identify lesions as small as 0.5 cm in size. It provides better evaluation of portal vein patency & complete evaluation of underlying intra-abdominal pathology without much inter-observer variation. Like USG, CT can also be used to guide percutaneous drainage of PLA.

   The most characteristic CT finding of PLA is the ***"Target Sign"*** which denotes a central hypodense lesion with intense peripheral rim enhancement during portal venous phase. Similar pattern of peripheral enhancement has been noted in necrotic metastasis, however, the transition zone between the hypodense centre and the peripheral rim is usually narrow in cases of PLA, this can help differentiate PLA from necrotic metastasis. Like USG, the attenuation value of the abscess varies with its evolution; as the abscess matures the attenuation decreases giving rise to the classic hypodense appearance. Another characteristic sign of PLA on CECT that may be noted in some cases is the ***"Double Target Sign"*** indicating hepatic enhancement outside to the enhancing wall, secondary to increased capillary permeability/peri-lesional inflammatory edema. The inner ring corresponds to wall of the abscess cavity showing early intense contrast enhancement which persists on delayed images & the outer ring corresponds to zone of hepatic inflammation & is hypodense with transient enhancement on delayed phase.

   Based on size & distribution on CECT, PLAs are classified as:

   a) **Microabscesses:** Lesions less than 2 cm in size.
      They are further classified into two types:
      1. **Military type:** These are small abscesses which are diffusely present within both lobes of the liver. Military pattern is usually noted secondary to staphylococcal infection from hematogenous source.
      2. **Cluster type:** These are small lesions located adjacent to each other & around a central large lesion. These may be seen coalescing with each other. Cluster pattern is usually secondary to enteric organisms from a biliary or intra-abdominal source.

b) **Macroabscesses:** Lesions more than 2 cm in size.

7. **Magnetic resonance imaging (MRI):** MRI is not a routine investigation for PLA evaluation since it offers little advantage over CT & is more time consuming. It may be indicated in some cases as an alternative to CT where CT is contraindicated or when there is diagnostic uncertainty on CT. MRCP may be useful for evaluating biliary pathology suspected on USG such as choledocholithiasis.
   On MRI, PLA appears hypointense in T1 images and hyperintense in T2 images with rim enhancement on contrast administration.

8. **Nuclear imaging:** Nuclear scans using Indium-111, Gallium-67, technetium-99 etc. are rarely used & have been replaced mostly by USG & CT. they may be useful in certain specific instances, e.g. to identify the infected lesion in case of polycystic liver disease. They may also help in differentiating between PLA & ALA; PLA appears as a hot lesion with increased uptake of radionuclide whereas ALA appears cold due to absence of leukocytes within the abscess cavity in ALA. However, a nuclear scan is rarely used & differentiation is mostly based on other features & investigations.

Treatment

Surgical drainage of PLA, as described by Oschner & Debakey, is no longer the preferred treatment of PLA. It has been replaced by percutaneous drainage with antibiotics as the treatment of choice. The aim of treatment is threefold, i.e. adequate drainage of pus, appropriate antibiotic therapy and treatment of the underlying cause (if detected). The following treatment options are available:

Table 4: Treatment options for PLA

1. Antibiotics alone
2. Antibiotics with Percutaneous Drainage (Treatment of choice) a) Antibiotics with Percutaneous Needle Aspiration (PNA) b) Antibiotics with Percutaneous Catheter Drainage (PCD)
3. Antibiotics with Surgical Drainage a) Open surgical Drainage b) Laparoscopic Drainage
4. Liver Resection
5. Biliary decompression with abscess drainage

1. **Antibiotics:** Broad spectrum parenteral antibiotics, covering gram negative, gram positive & anaerobic organisms, should be started empirically as soon as possible without waiting for culture reports. Once culture & sensitivity reports are available, specific antibiotics may be administered. For cryptogenic abscesses, combinations such as ampicillin, aminoglycoside & metronidazole; ampicillin, fluoroquinolone & metronidazole or a third-generation cephalosporin with metronidazole may be considered. Secondary abscesses such as those associated with acute cholangitis are preferably treated with single drug therapy consisting of Imipenem, vancomycin or piperacillin-tazobactam.

   The duration of antibiotic therapy is controversial, but it should continue for at least 2 to 4 weeks. Some studies indicate that parenteral antibiotics should be given for 2 weeks followed by oral antibiotics for another 2 weeks completing a course of 4 weeks. Whereas others recommend that parenteral antibiotics should be continued till clinical improvement (as indicated by resolution of symptoms, decreased leukocyte count etc.) followed by oral antibiotics to complete a course of 2 weeks. However, the exact duration of therapy depends on other factors such as adequacy of drainage, abscess rupture, associated focus of infection, ongoing sepsis etc.

   Treatment of PLA with antibiotics alone without percutaneous drainage is not recommended since it is associated with high failure rate, longer duration of antibiotic therapy, higher risk of complications such as abscess rupture & higher overall mortality. It may be indicated in patients with multiple small abscesses (such as cholangitic abscesses) & fungal abscesses (which are usually miliary in nature). However, even in patients with multiple small abscesses, a percutaneous needle aspiration from the largest abscess should be performed for pus culture so as to guide antibiotic therapy. Rarely antibiotics alone may be used in patients with significant comorbidities & who refuse any percutaneous or surgical drainage.

2. **Percutaneous drainage methods:** Percutaneous drainage is required in most cases of PLA along with antibiotics so as to decrease the duration of antibiotic therapy & increase the success rate, without significant morbidity & mortality. Because of its high success rates (60-90%) & low morbidity & mortality, percutaneous drainage of PLA with antibiotic therapy has now become the treatment of choice for PLA. Even for multiple abscesses this is the preferred approach of management with multiple aspirations or placement of multiple drains. The most important advantage of percutaneous methods compare to surgical drainage is avoidance of general anaesthesia as it can be performed easily under local anaesthesia with mild sedation. Relative

contraindications for percutaneous drainage include presence of gross ascites, close proximity to major vascular structure, uncorrected coagulopathy & inaccessible lesions.

There are two methods of percutaneous drainage of PLA:

a) **Percutaneous Needle Aspiration (PNA)** i.e. aspiration of PLA without placement of a draining catheter.
b) **Percutaneous Catheter Drainage (PCD)** i.e. aspiration followed by placement of a draining catheter.

Both these methods are performed under USG or CT guidance. The approach can either be subcostal or intercostal, depending upon the location of the abscess. Patients who require intercostal approach may also require placement of an intercostal chest drain if pleura has been breached.

A comparison of PCD with PNA is controversial with some studies reporting similar success rates while others reporting a higher success rate with PCD. However, the problem with PNA is that most patients require multiple aspirations for adequate drainage. It is recommended that PCD should be the preferred treatment in most cases except in those patients with small (<5 cm), unilocular abscesses without viscous content, where PNA may be preferred. However, for PNA to be successful, biliary communication should be ruled out. In presence of biliary communication, PCD is indicated.

Although percutaneous methods are successful in most patients, treatment failure may occur in 10% patients. Factors predictive of high failure rate include multiple abscesses, large multi-loculated abscesses containing thick pus, abscesses associated with biliary obstruction (especially malignant biliary obstruction) & fungal abscesses.

3. **Surgical Drainage:** Surgical drainage is required in limited number of patients & is associated with higher morbidity & mortality. Surgical drainage of PLA is indicated in the following group of patients:

a) Patients who fail to respond to percutaneous drainage as indicated by either worsening sepsis or inadequate output from the catheter.
b) Patients in whom percutaneous drainage is not possible such as those with percutaneously inaccessible lesions, lesions close to major vascular structures & those with gross ascites.
c) Patients who require surgical treatment of concomitant abdominal pathology such as acute appendicitis or gangrenous cholecystitis.
d) Patients who develop complications secondary to percutaneous drainage such as bleeding or intraperitoneal pus spillage.
e) Patients with free intraperitoneal rupture of abscess leading to pyoperitoneum & signs of generalised peritonitis.

Surgical drainage can be done via laparotomy (subcostal or midline transperitoneal approach) or laparoscopy. Laparoscopic drainage has some benefits over open drainage such as decreased wound complications, less bleeding, early post-operative recovery & shorter hospitalisation. However, data comparing open versus laparoscopic drainage is still inadequate. Laparoscopy may be considered in selected patients if not otherwise contraindicated.

Some basic principles should be followed during surgical drainage. Intra-operative USG is mandatory for localisation of PLA, especially deep lesions which may not be otherwise apparent & multiple lesions for adequate & complete drainage of all significant abscesses. Superficial lesions are aspirated & then the abscess cavity is opened to break the loculi. Deeper lesions may require a hepatotomy after localisation followed by drainage of pus. Biopsies should be obtained from the abscess wall to rule out malignancy. Closed suction drain should be inserted in all cases. Peritoneal lavage is done in cases with ruptured abscess & pyoperitoneum. Lastly a thorough search should be made to rule out any co-existing intra-abdominal cause of PLA that may require surgical treatment at the same time.

Recently, a new surgical technique has been described for patients with failure of percutaneous drainage. This technique, known as ***Video Assisted Hepatic abscess Debridement (VAHD)***, is similar to Video Assisted Retroperitoneal Debridement (VARD) being used for debridement of infected pancreatic necrosis. This involves placement of a percutaneous guided drain in the abscess cavity followed by visualisation of the abscess cavity through a 10 mm videoscope & debridement of the abscess contents using the percutaneous catheter as a guide to the cavity. The advantage of this technique is that it is less invasive compared to laparoscopic or open surgical drainage, although this too requires general anaesthesia. However, the safety & efficacy of this method needs to be studied through randomised trial & at present it cannot be recommended over surgical drainage.

4. **Liver resection:** Liver resection is rarely required for PLA. It may be indicated in the following cases:
    a) Severe destruction of hepatic parenchyma secondary to very large or multiple abscesses involving one lobe predominantly.
    b) Associated hepatothiasis & intrahepatic biliary strictures causing segmental biliary obstruction & atrophy of affected segment.
    c) Infected hepatic neoplasm or doubtful mass lesion causing diagnostic uncertainty.

5. **Biliary decompression:** Biliary decompression through ERCP & sphincterotomy/ stenting/ stone extraction is required if biliary cause is suspected based on imaging investigations. PTC or even surgical biliary decompression may be required if ERCP is not successful. Some patients may continue to have persistent biliary drainage through the percutaneous catheter due to biliary communication of the abscess & distal biliary obstruction. In such cases, ERCP & sphincterotomy with stenting is required so as to decrease the transpapillary pressure gradient.

Prognosis

The overall mortality from PLA has improved significantly over the past years, with recent reports indicating mortality rates less than 10%. Recurrence rates for cryptogenic PLA are low (2%), however PLA due to biliary cause (especially malignant biliary obstruction) have higher recurrence rates (23%).
The following factors have been found to be associated with poorer prognosis & a higher mortality from PLA:

- Malignancy & its associated abnormalities such as elevated bilirubin & markedly elevated lever enzymes
- Signs of sepsis such as marked leucocytosis, high APACHE II scores (≥15), septic shock, MODS
- Liver cirrhosis
- Signs of chronic disease such as hypoalbuminemia, coagulopathy & raised serum creatinine & BUN
- PLA due to gas forming organisms, anaerobic organisms, polymicrobial infections & multi drug resistant organisms
- Multiple abscesses & complicated abscesses such as rupture.

Age alone is not associated with poor outcome, provided there are no other comorbidities. Similarly, mortality rates in diabetics are not increased despite increased risk of developing PLA. Also, PLA secondary to *Klebsiella pneumonia* may be associated with higher incidence of septic metastasis, especially endophthalmitis, with increased morbidity, however, overall mortality is low. Patients with cirrhosis, abscess ≥6 cm in diameter, gas-forming abscesses and PLA with other septic metastases should be monitored closely as they have high chances of developing spontaneous rupture.

AMEBIC LIVER ABSCESS

Epidemiology
Amebic liver abscess is the most common extra-intestinal form of amebiasis caused by protozoan *Entamoeba histolytica*. It occurs more commonly in developing countries & is endemic in tropical & sub-tropical countries including India, Africa, Central and South America & Southeast Asia. It occurs much more commonly in males compared to females (Male to Female ratio 10:1). Especially menstruating females are found to have a low incidence of ALA. The prevalence of infection is more than 5% to 10% in endemic areas & less than 4% per year in developed countries. The exact occurrence is difficult to establish since most previous studies do not differentiate between pathogenic & non-pathogenic forms of *Entamoeba,* which are asymptomatic & do not need any treatment. It is believed that 10% of the world population is infected with *Entamoeba* (both pathogenic & non-pathogenic). However, most people remain asymptomatic. Around 5-10% of patients with amebiasis develop ALA.

Predisposing factors
The following predisposing factors have been identified that tend to increase of developing amebiasis & ALA:

- History of travel to endemic area (travellers and immigrants)
- Poverty & poor hygiene in developing countries
- Chronic Alcohol intake: Alcohol suppresses Kupffer cell function which have a role in clearing amoeba. Also, invasive amebiasis is dependent on free iron. Increased iron in country made liquor thus, increases the chances of ALA.
- Advanced age
- Immunosuppressed states such as HIV, steroid use, malnutrition
- Pregnant females (pregnancy mitigates the protective effect of menstruating females)
- Male homosexuals
- Institutionalized populations
- Diet rich in iron and carbohydrates
- HLA-DR3 gene expression
- Breast feeding has protective effect in the newborn due to presence of immunoglobulins & low iron content.

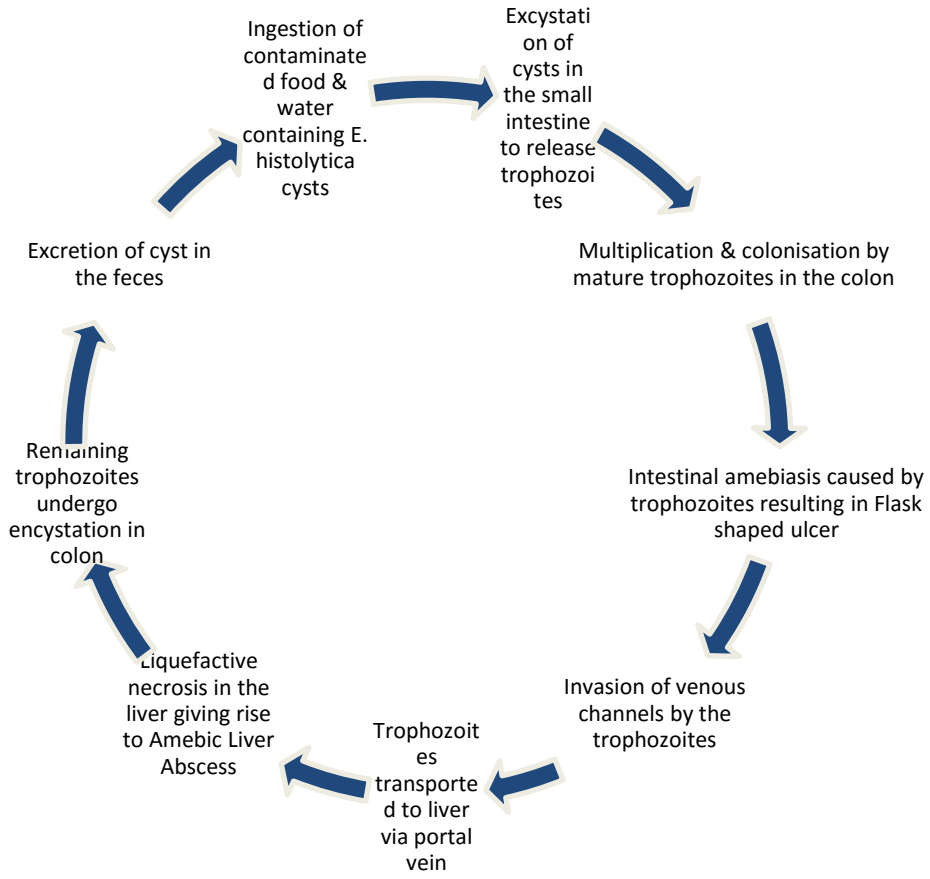
Etio-pathogenesis & Microbiology

Amebiasis is caused by protozoan parasite *Entamoeba histolytica.* Other non-pathogenic species include *Entamoeba dispar* & *Entamoeba moshkovskii.* The non-pathogenic species are morphologically identical to E. histolytica & cannot be differentiated on the basis of stool microscopy. They remain asymptomatic & do not need any treatment.

E. histolytica exists in two morphological forms: trophozoite & quadrinucleate cyst. Mode of infection is via ingestion of the cyst form through feco-oral route. Cysts are excreted in the feces by a carrier & are ingested by the host with contaminated food & water. The cysts resist degradation in acidic pH in the stomach & reach the small intestine where excystation occurs at alkaline pH. The released trophozoites multiply & colonise the large intestine. In the colon, these trophozoites cause intestinal amebiasis causing classical "Flask Shaped ulcers" with an undermined edge. The trophozoites invade the venous system & are carried to the liver via portal vein. Remaining trophozoites in the colon undergo encystation & are excreted as cyst form in the feces to complete the life cycle.

Liver is the most common site of extra-intestinal amebiasis. Within the liver, these trophozoites cause enzymatic hydrolysis causing hepatic liquefactive necrosis resulting in a cavity filled with degenerated hepatocytes, blood & proteinaceous debris. The appearance of this liquefied content is similar to that of anchovy sauce & has been classically referred to as Anchovy sauce pus. This pus is usually sterile & odourless, except if superimposed bacterial infection has occurred. The dividing trophozoites are present at the periphery of the lesion.
The wall of the abscess is ill defined due to lack of host fibrotic response. As a result, this liquefactive necrosis continues till the periphery of the liver till it reaches the Glisson's capsule which resists degradation. Thus, most amebic liver abscesses are large & peripherally located abutting closely the liver capsule. ALA are mostly solitary & usually located in the right lobe of liver (Right postero-superior surface is most commonly involved). Left lobe abscesses are less common but more prone to rupture to less volume of left lobe & large size of the abscess.

Life cycle of *Entamoeba histolytica*



Clinical features & Complications

Most patients with ALA (80%) present with symptoms lasting from 10 days to 4 weeks. The most common symptoms are abdominal pain (more than 90% patients) & fever (85-90%). Patients who present acutely within 2 weeks have more severe pain & fever while those presenting in subacute manner from 2 to 4 weeks have less pain

& fever but more non-specific symptoms such as weight loss & anorexia. Other common but non-specific symptoms include nausea, vomiting, malaise. Most patients with ALA do not have concurrent amebic colitis at the time of presentation, although a history of colitis in the recent past may be commonly obtained. Active diarrhea & synchronous active colitis is present in less than one third patients with ALA. Unlike PLA, jaundice is not a common feature of ALA, being present in 5-20% patients. Moreover, the cause of jaundice is usually compression of biliary tree by a large abscess or biliary communication & does not indicate primary biliary pathology as in PLA. Pulmonary symptoms such as cough, pleuritic chest pain, right shoulder pain etc. are present in one fourth of the patients. The most common signs in ALA include tender soft hepatomegaly & classic intercostal or point tenderness.

ALA can also present with complications. The most common complication is abscess rupture occurring in 3-17% patients. The size of abscess (5-10 cm) & left lobe location are the most common risk factors predictive of rupture. Intra-peritoneal rupture is most common & is usually walled off by adjacent organs & omentum. Rarely, it may have free intraperitoneal rupture with signs of peritonitis or it may rupture into adjacent hollow viscus. The abscess may rupture into the right pleural cavity, lung parenchyma or bronchus presenting with right sided empyema, lung abscess & broncho-hepatic fistula (cough with expectoration of anchovy sauce pus). Thoracic rupture occurs in 10% patients. Rarely left lobe abscess may rupture into the pericardium (<3-4%) giving rise to pericardial effusion/ tamponade or acute pericarditis. Metastatic amebic brain abscess is uncommon but can occur & give rise to neurological manifestations. Besides rupture, other complications of ALA include superimposed bacterial infection with sepsis, biliary compression (jaundice), hepatic vein thrombosis (Budd Chiari Syndrome), inferior vena cava thrombosis & hepatic failure.

Investigations

1. **Laboratory investigations:** The most common laboratory abnormalities in ALA include leucocytosis (75-80%) & mild LFT derangements. The most common abnormality in LFT is elevated PT-INR. Hypoalbuminemia is common. Liver enzymes are also mildly elevated but hyperbilirubinemia occurs rarely. The ratio of AST & ALP varies depending on the chronicity of disease. In acute phase, ALP is normal & AST is elevated, while in chronic phase, ALP is elevated & AST becomes normal.

2. **Chest X-Ray:** Chest x-ray findings may be seen in most patients (50-65%) since the most common site is postero-superior surface of liver & lies close to the diaphragm. Common findings include an elevated right hemi-diaphragm, right pleural effusion, right sided basal atelectasis & consolidation.

3. **Ultrasound (USG):** USG is the preferred initial imaging investigation in patients suspected to have ALA. Its accuracy is more than 90% for diagnosis of ALA. Classical findings include a large solitary hypoechoic lesion with poor rim echoes, involving the right lobe of liver (80% patients have single abscess in right lobe. 10% in left lobe, 6% in caudate lobe & rest multiple). The lesion is usually peripheral in location abutting the liver capsule & has a characteristic *"Distal Sonic Enhancement"* i.e. structures distal to the abscess have a white out appearance. However, these classical findings are noted in 40-70% patients only. Radiological resolution of the abscess cavity takes a long time in ALA, usually 7-9 months, however, complete resolution occurs in most patient (90%). Some patients may be left with an insignificant residual cavity with features of a simple cyst.

4. **Contrast enhanced computerised tomography (CECT) & Magnetic Resonance Imaging (MRI):** CECT is the imaging investigation of choice for ALA. It is more sensitive than USG for diagnosis of ALA & for detecting associated complications. CECT may help in differentiating ALA from PLA but this may not always be possible. The characteristic finding in ALA is a solitary large peripherally located lesion with non-enhancing rim & a peripheral zone of edema. Rim enhancement may sometimes be noted in ALA & makes differentiation with PLA difficult.

   MRI does not have any added advantage over CT & USG. It may be used in cases with diagnostic uncertainty. ALA appears hypointense on T1 & hyperintense on T2 images with perilesional edema on T2 images.

5. **Nuclear scans:** Gallium or Technetium based nuclear scans are rarely used nowadays. They may help in differentiation between ALA & PLA as ALA appears as cold lesion on nuclear scan due to absence of viable leukocytes within the abscess cavity, whereas PLA usually appears hot or warm.

6. **Serological tests:** Amebic serology is one of the most useful diagnostic tests for invasive amebiasis, especially in non-endemic regions. In non-endemic regions a positive amebic serology is diagnostic of acute invasive amebic infection since serology is highly sensitive (>94%) & specific (95%). However, serology may not be much useful in endemic regions as a positive test may indicate a prior infection.

   Various serological tests have been devised such as indirect haemagglutination assay (IHA), latex agglutination, immunoelectrophoresis, complement fixation, agar gel diffusion, indirect immunofluorescence assay, enzyme linked immunosorbent assay (ELISA) etc. These tests are based on detection of serum antibodies (such as anti-lectin antibodies) which are present in more than 85% patients with invasive amebiasis

& 99% in ALA. Out of these tests, IHA & ELISA have been most useful. IHA has a sensitivity of >90%. ELISA is even more sensitive & specific than IHA having a sensitivity of 99% & specificity of >90%. Thus, ELISA has mostly replaced IHA for diagnosis of amebiasis. ELISA is positive in 95% patients with extra-intestinal disease, 70% patients with active intestinal disease & 10% asymptomatic cyst passers. A limitation of these tests is that in 10 % patients a false-negative results can be obtained in early stages during the first 7 -10 days. This is because antibody titres are detectable from 7-10 days after onset of illness & peak levels are reached during 2nd to 3rd months. Serological tests usually return to normal within 6-12 months, however in some patients these may persist for many years. Another limitation is that they may not be able to differentiate acute infection from past infection, especially in endemic areas. Moreover, in endemic areas even asymptomatic patients have high incidence of positive tests, making it difficult to differentiate ALA from PLA in such areas.

ELISA based on antigen detection has been found to be more useful than antibody detection. It is based on detection of *E. histolytica* lectin antigen in the sera & ALA pus from affected patients. It has high sensitivity (>95%) for diagnosis of ALA. Moreover, serum antigen levels appear to clear rapidly following metronidazole treatment (82% reversal rate after 1 week of treatment), thus making it more useful than antibody detection in endemic areas.

More recently, PCR for detection of *E. histolytica* in aspirated pus has been found to be the most sensitive & specific method for diagnosis of ALA. It has the highest sensitivity & specificity & like antigen detection, results become negative after adequate treatment. Moreover, it can differentiate between pathogenic & non-pathogenic species of *E. histolytica*. A limitation of both antigen based ELISA & PCR is that both these tests may become falsely negative if treatment with metronidazole has already been started.

Thus, serological tests are most useful when both antibody & antigen detection are performed along with PCR based methods. However, in developing countries which are endemic for the disease, the cost & availability of antigen detection & PCR, may be the limiting factors.

7. **Diagnostic Aspiration:** In some patients when there is diagnostic uncertainty with serology being negative & pyogenic abscess needs to be ruled out, a diagnostic aspiration of the ALA may be indicated. Aspiration of ALA reveals characteristic odourless Anchovy Sauce pus which on microscopic examination reveals no bacteria or leukocytes. Only degenerated hepatocytes are seen in a proteinaceous background. Trophozoites are usually not seen in pus aspirated from the centre of the cavity, however, they may be detected if pus is aspirated from the periphery of the lesion since trophozoites proliferate at the edge of ALA. PLA pus will have a foul smelling odour with purulent character & on microscopy reveals numerous bacteria & leukocytes. Gram stain & Culture are usually negative in cases of ALA, while in PLA pus culture may be positive.

8. **Stool examination (Stool microscopy & Stool antigen detection):** Stool examination is not very useful for patients with ALA since most patients with ALA do not have co-existing amebic colitis. The sensitivity of stool microscopy & stool antigen detection in patients with ALA is less than 40%. Thus, routine stool examination is not useful. It may be selectively done in patients presenting with symptoms suggestive of acute amebic colitis. For amebic colitis stool antigen detection has better sensitivity than stool microscopy.

Table: Sensitivity of microbiological tests for ALA

Test	Sensitivity
Stool microscopy	<10-40%
Abscess fluid microscopy	<20-25%
Stool antigen detection	<40%
Abscess antigen detection	~100%
Serum antigen detection	>95%
Serum antibody detection	Acute – 70-80% Convalescent - >90%
Real-time PCR	>95%

Treatment

Treatment of ALA is mainly based on anti-amebic antibiotic therapy with tissue amebicides followed by luminal amebicides for cyst eradication. Drainage of ALA & surgical intervention is reserved for specific circumstances. The following treatment options are available:

Table: Treatment options for ALA

1. Anti-amebic therapy
   a) Tissue amebicides
      - Nitroimidazoles: Metronidazole, Tinidazole, Secnidazole, Ornidazole
      - Emetine & Dehydroemetine

• Chloroquine b) Luminal amebicides • Paromomycin • Diloxanide Furoate • Iodoquinol
2. Percutaneous drainage a) Percutaneous Needle Aspiration (PNA) b) Percutaneous Catheter Drainage (PCD)
3. Surgical drainage a) Open surgical drainage b) Laparoscopic drainage

1. **Anti-amebic therapy:** Anti-amebic therapy alone is considered to be the treatment of choice for uncomplicated ALA. Simultaneous drainage does not seem to be improve the resolution of ALA. It is recommended that ALA be treated with a tissue amebicide followed by treatment with a luminal amebicide for cyst eradication so as to prevent recurrence & to decrease further spread of disease.

   Metronidazole is the drug of choice for treatment of ALA. It is administered IV initially & later switched to oral therapy after initial clinical improvement. The IV dose is 500 mg every 6 hourly & the oral dose is 750 mg three times a day for adults. The paediatric dose is 35-50 mg per kg in three divided doses. The total duration of therapy is 10-14 days. This is successful in most patients (90%) with a cure rate of more than 95% after 10 days & clinical improvement being noted within 3-4 days.

   Other nitroimidazoles such as tinidazole, ornidazole, secnidazole, satranidazole may be used if metronidazole is not tolerated. These agents have longer half lives compared to metronidazole & can be given for shorter durations, usually 5 days. Also, they are better tolerated.

   Around 5-15% patients may not respond to metronidazole. These patients may be treated with alternative tissue amebicides such as Chloroquine & Emetine/Dehydroemetine. Chloroquine can be given orally, however emetine requires intramuscular injections

   Almost half of the patients treated with nitroimidazoles have persistent cysts in the colon. Thus, a luminal amebicide should be given to eradicate the cysts. Luminal agents include paromomycin, diloxanide furoate and iodoquinol.

Table 3: Drug therapy for ALA

Drug	Dose & Route	Side effects	Precaution
Tissue Amebicides			
Nitroimidazoles (Metronidazole, tinidazole, secnidazole, ornidazole etc)	Metronidazole: 500 mg IV 6 hourly or 750 mg TDS PO X 10 days Tinidazole: 2 gm PO X 5 days	Common: GI symptoms – Most common, Nausea, vomiting, Dysgeusia, darkening of urine, headache, vertigo, insomnia, paraesthesia, Disulfiram like reaction Rare: CNS toxicity – Most serious toxicity (Seizure, ataxia etc.), peripheral neuropathy, neutropenia, allergic reaction, pancreatitis, hepatitis	-Drug of choice for ALA -Category B drug -Contraindicated in 1st trimester of pregnancy & lactation -Avoid alcohol during therapy as it can cause disulfiram like reaction
Emetine & Dehydroemetine	1 mg/kg/day (Maximum 60 mg for emetine & 90 mg for dehydroemetine) IM or deep subcutaneous X 10 days	Common: Pain at injection site, headache, dizziness, GI symptoms, myalgia Rare: Cardiotoxicity – T wave inversion & QT prolongation (Most serious complication)	-Category X drug -Contraindicated in pregnancy, cardiac, renal & neuromuscular disease -Cardiac evaluation before treatment -dose reduction in children & elderly -Avoid re-administration for 6 weeks as levels persist for 40-60 days
Chloroquine	600 mg base per day in divided doses X 2 days followed by 300 mg base per day	Common: Nausea, vomiting, headache, dizziness, bitter taste, blurring, dysphoria, pruritus, dermatitis,	-Contraindicated in retinopathy -Safe in pregnancy & in children -Ocular examination before treatment -May worsen psoriasis

	for 2-3 weeks (10 mg base/kg/day then 5 mg base /kg/day)	Rare: Retinopathy (Most serious complication), blood dyscrasia, convulsion, cardiopulmonary arrest	
Luminal Amebicides			
Paromomycin	500 mg TDS PO X 10 days (30 mg/kg/day)	Common: GI intolerance - nausea, abdominal pain, diarrhea Rare: Nephrotoxicity, ototoxicity (not usual with oral use)	-Preferred drug for luminal treatment -Oral paromomycin is safe in pregnancy & lactation
Diloxanide Furoate	500 mg TDS PO X 10 days (20 mg/kg/day)	Common: Flatulence, nausea, vomiting, diarrhea Rare: Pruritus, urticaria	-Contraindicated in pregnancy, lactation & children <2 years
Iodoquinol	650 mg TDS PO X 20 days	Common: Headache, nausea, vomiting, diarrhea, abdominal pain, rash (iodine dermatitis), pruritus, thyrotoxicosis Rare: Optic neuritis, peripheral neuropathy, seizures, encephalopathy, nephrotoxicity	-Category C drug -Contains iodine, caution advised in hyperthyroid patients -Ocular examination should be done before starting treatment -Contraindicated in liver dysfunction, renal disease & iodine hypersensitivity

2. **Percutaneous drainage:** USG or CT guided percutaneous drainage is indicated in some patients with ALA. For large abscesses (>5-10 cms), percutaneous catheter drainage (PCD) appears to be better, while for smaller abscesses percutaneous needle aspiration (PNA) may be sufficient. The indications of aspiration of ALA as follows:

    a) Diagnostic uncertainty with negative serology & suspected PLA (Failure to differentiate PLA from ALA)
    b) No improvement seen within 3-5 days of starting therapy
    c) ALA with high risk of rupture such as left lobe abscess & size more than 5 cm.
    d) Anti-amebic therapy in not tolerated or is contraindicated, e.g. in pregnancy
    e) Secondarily infected ALA
    f) ALA associated with complication such as peritoneal, pleural or pericardial rupture, or when rupture is imminent.

3. **Surgical Drainage:** Open or laparoscopic drainage of ALA is rarely required. The basic principles of surgical drainage are similar to PLA. It may be indicated in the following situations:

    a) Free intraperitoneal rupture with signs of peritonitis
    b) Failure of percutaneous drainage when indicated
    c) Secondary infection & worsening sepsis despite drainage & antimicrobial therapy.
    d) Fistulisation of ALA into adjacent viscus when control of viscus is necessary to prevent bleeding or further sepsis.

4. **Treatment of complications of ALA:** Complications arising from ALA may require some other measures for adequate control. When ALA presents with rupture, drainage of the abscess should be considered along with anti-amebic therapy. Rupture into the pleural cavity require early intercostal drainage. Some cases may even require decortication, if intercostal drainage in not successful. Broncho-hepatic fistula is usually self-limited with postural drainage, bronchodilators & adequate drainage of the liver abscess. Cardiac tamponade requires pericardiocentesis, emetine should be avoided due to its potential cardiotoxicity.

Prognosis

Overall mortality of ALA is less than 5%. Factors associated with poor prognosis & a higher mortality rate include:

- Ruptured ALA
- Pericardial rupture
- Secondary bacterial infection
- Immunocompromised patients
- Hyperbilirubinemia >3.5 mg/dl
- Hypoalbuminemia <2.0 g/dl
- Anaemia
- Diabetes
- Multiple abscess cavities
- Large size abscess >500 ml

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Organ Transplantation

Sandeep Guleria

Introduction

Human organ transplantation ranks as one of the most outstanding achievements in medical history. The procedure involves the expertise of various branches of medicine and is often the only hope for survival for patients. Advances in immunosuppressant technology are translating into not only longer graft survival, but also transplant of organs like bones, uterus and even intestines. The donor pool has similarly expanded, encompassing living donors and increasingly non-heart beating donors.

Historical Aspects

The refinement in vascular anastomosis pioneered by Alexis Carrel, father of transplantation, led to attempts at solid organ transplantation in the early nineteenth century. Voronoy is credited with the first renal allograft (1933-1949). However, all they failed, as the concept of immunology was largely unknown. Gibson and Medawar carried out experiments on skin transplantation in response to search for treatment of badly burned pilots in Second World War. They concluded that an auto graft survives indefinitely, while an allograft is not only destroyed, but induces memory and accelerated destruction in further transplants.

Murray et al did the first successful renal transplant between identical twins in 1954. Starzl first attempted liver transplantation in man in 1963. The first successful clinical heart transplant was performed in 1967 by Dr. Christian Barnard at University of Cape Town. Hardy performed the first human lung transplant 1963 in a patient with carcinoma left lung. Kelly at the University of Minnesota initiated pancreatic transplantation in 1966.

However, the success rate was very limited until effective immunosuppresion was developed. Among the first drugs to be used was Azathioprine, developed by Ellion and Hitchings, used for renal transplants by Murray. Steroids were added to the immunosuppressive regimen later. Cyclosporine, discovered by Borel in 1976 was the most

significant advance in immunosuppression. Calne is credited for introducing its widespread usage, initially in renal and later to all transplants.

The Live Donor

Renal Transplantation is the best treatment for patients with end stage renal disease. The shortage of cadaver kidneys for transplantation has resulted in patients waiting for a longer period to receive the benefits of transplantation. The presence in most normal individuals of two kidneys – each with a physiological reserve capable of providing four to five times the minimum required function has led to the acceptance of renal transplantation using living related or unrelated volunteers as organ sources.

Through the history of its evolution medical practice was paternalistic in the Hippocratic tradition. “Primum non nocere” (First do no harm) was a defining principle in the practice of medicine and live donor transplant was considered unethical as it involved putting a perfectly healthy individual at the risk of surgical complications without any advantages to his/her health . However soon the life saving potential of this procedure received widespread public support and with advancements in immunology the graft survival rates improved and transplantation received acceptance among the medical fraternity. The impact of public opinion and growth for consumerism in American culture led to a decline in the primacy of Hippocratic paternalism · The end result was that as long as the donor’s participation was voluntary, fully informed and un-associated with financial or psychological coercions, transplantation was considered acceptable.

Living kidney donation appears to be safe with low morbidity and mortality. It offers several potential benefits, including better results for the recipient enhanced self esteem for the donor and reduced financial burden to the society. The success of live kidney donor transplantation has been so overwhelming that from 2000 to 2004 in the United States, the number of live donor kidneys surpassed that of cadaver donors . However in most parts of the world cadaver organ donation is still limited and live kidney donors are the most common source of organs for organ transplantation.

Conservative estimates put the annual incidence of ESRD in India at 80-100 per million populations (PMP). This would mean approximately 80,000 to 1, 00,000 new patients every year not including the patients living in rural areas who never seek specialist advice because of ignorance and poverty. The final acceptance rate of patients for renal replacement therapy turns out to be less than 5 PMP per year.

The high costs associated with long term dialysis makes renal transplantation the only viable alternative for long term survival of ESRD patients in the developing nation. Organized cadaver donor programs do not exist and transplants are almost exclusively done using living donors.

Despite reduced morbidity and mortality of the donation process it is important to discern patients who are not candidates for organ donation because of the risk on immediate and future health . However singular abnormalities such as well controlled hypertension and obesity are no longer considered absolute contraindications to organ donation. Living donors present unique ethical, legal and social implications that must be addressed to protect the health and rights of the donor.

Why Living Donors

There are many reasons that can be cited for the continued use of live donors. Among them has been the more favourable results that can be achieved with a well matched kidney. With the introduction of monoclonal and polyclonal antibody immunosuppression as well as the use of calcineurin inhibitors and other new immunosuppressive drugs live kidney donors still have a 10-12% better survival rate at one year and a significant higher probability of function thereafter.

Another justification for using living donors is that the timing of the operation can be planned and the operation can be performed when the recipient is in optimal medical condition.

Despite these compelling reasons for using living donors the procedure could not be justified if unacceptable morbidity or mortality were to be incurred by the donor. The concept of removal of an organ for transplantation is unique among major surgical operations that it exposes the healthy donor to the risks of surgery solely for the benefit of another individual.

With the advent of minimally invasive techniques including the mini donor nephrectomy to living kidney donation, the potential adverse impact of the operation has become less significant. The major advantages to the donor are decreased morbidity of the surgery and quicker return to normal daily activities including earlier return to work.

Informed Consent

An extremely important part of living kidney donation involves informed consent. Emphasis on the adequacy of the consent process is important as unlike standard procedures, living kidney donation is not specifically designed to

help the donor or advance the donor's health. The person who gives consent to donate an organ must be competent (possessing decision making capacity) , willing to donate, free from coercion medically and psychosocially suitable ,fully informed of the risks and benefits of donation and fully informed about alternative treatments available to the recipient.

Risks to the Donor

Living donor nephrectomy is a major surgical operation. Responsibility for the donor lies ultimately with the surgeon performing the donor operation but optimal care demands cooperation with the anaesthetists, the operating room nurses as well as post operative care by the surgical team can be divided into the early risks associated with the donor operation (i.e. peri-operative mortality and morbidity) and the late or long-term risks of life with a single kidney. In the absence of national donor registries or large prospective studies with effective follow-up, the long-term risks of donor nephrectomy remain incompletely defined. There is, however, a wealth of retrospective evidence, which suggests that kidney donation is associated with a low level of medical risk in a healthy donor.

Types of Grafts

- Allograft: Transplantation from one individual to another
- Isograft: Transplantation between identical twins
- Xenograft: A transplant performed between different species
- Orthotopic: A transplant placed in its normal anatomical site
- Heterotopic: A transplant placed in a site different to that where the organ is normally located

Immunological Response

HLA system

Antigens on the transplant tissues are recognized by the non-identical recipient as foreign. This process of self and non-self recognition initiates rejection. The specificity of the antigens involved in graft rejection is under genetic control. A single chromosomal complex of closely linked genes makes up the code for the major histocompatibility antigens. The major Histocompatibility complex (MHC) in humans is termed the HLA system (Human Leukocyte Antigen), as it was initially detected in leukocytes. This gene is found in the short arm of chromosome 6. It has at least seven loci, A, B, C, D, DR, DQ and DP; each highly polymorphic.

HLA-A, B and C are grouped together as Class I antigens. They are present in virtually all nucleated cells in the body, including Lymphocytes and platelets. They are composed of a heavy (Alfa) chain and light (Beta-2 microglobulin, a non-MHC coded peptide) chain. They act as targets of cytotoxic (CD8) T cells.

Class II antigens include HLA-D (DR, DP and DQ) antigens. They are expressed only on B Lymphocytes, monocytes, activated T lymphocytes and some endothelial cells. They are composed of and alpha and one beta chain. They stimulate the proliferative response of Mixed Lymphocyte culture (MLC) and are vital for antigen presentation in vivo. They are preferentially recognized by Helper (CD4) T lymphocytes.

Allograft rejection is a complex event that results from the cytodestructive effects of activated helper T cell, cytotoxic T cells, B-lymphocytes, antibodies and activated macrophages. The initiating event seems to be activation of CD4 cells by class II antigens in the graft. This releases various cytokines, most importantly Interleukin 2 (IL-2). Class I antigens stimulate CD8 T cells to develop IL-2 receptors. In addition, activated macrophages secrete Interleukin 1 (IL-1), which in turn stimulates secretion of IL-2. IL-2 interacts with various IL-2 receptors expressed on T Lymphocytes to stimulate their clonal proliferation. In essence, the activation of helper T cells by alloantigens and IL-1 stimulates the release of a variety of lymphokines from CD4 cells and this in turn activates macrophages, CD8 cells and antibody secreting B-lymphocytes. Also, the continued viability of activated T cell clones is IL-2 dependant. Thus, IL-2 is at the centre of all rejection phenomenon and most of the immunosuppressant drugs aim to attack this phenomenon.

Histolocompatibility Testing and Cross-Match

a) ABO blood group compatibility is considered essential in most of the solid organ transplants, liver being an exception. However with the availability of Rituximab a CD 20 blocker and plasma exchange excellent results are now being achieved in ABO incompatible renal transplantation. The use of the Glycosorb filter which binds the A and B antigen has also led to considerable success.
b) HLA Histocompatibility testing is done primarily to search for HLA identical siblings. It is not of much value in choosing between parents, offspring, or HLA non-identical siblings as donors. Even in perfect matching of MHC antigens in an HLA identical sibling match, immunosuppression will be required due to incompatibility at minor Histocompatiblity loci. HLA matching is usually not done in cadaver renal transplants. Nevertheless, a six antigen match (at the DR, B and A, in the order of importance, also known as full house match) cadaver kidney donors has a better long-term survival than lesser-matched grades. Currently almost all HLA typing is done by a lymphocyte cytotoxicity procedure. The clinical application of histocompatibility holds great relevance for the transplantation of most solid organs. The presence of HLA antigens on a cell surface can be detected both functionally and serologically. Both tests are frequently performed before transplantation because the functional method is most specific for class-II antigens while the serologic method detects those

in Class I. The serologic method uses antigen-specific antisera that bind to cells expressing that specific antigen. The functional method measures the reactivity of the lymphocytes of a potential recipient to the donor. The responding lymphocytes will proliferate in response to transplantation antigens they recognize as foreign. Only HLA (MHC) antigens can be detected with the functional method. The antigens most effective at generating this response are those of the Class II MHC. However, since Class I antigens also play an important role in transplantation, antisera specific for each of the Class I loci (A, B or C) are also used for serologic typing of a potential donor and recipient.

c) A complement mediated cytotoxic crossmatch with pretransplant recipient sera against non-activated T lymphocytes expressing class I antigens, and not class II, from the potential donor is essential. Presence of IgG antibodies against class I MHC antigens represents a positive test and an absolute contraindication for transplant. This test screens for preformed antibodies in the recipient against donor antigens thus, avoiding Hyperacute reaction.

The Rejection Phenomenon

Rejection is invariable in transplants between non identical twins without immunosuppression. A Perfect HLA match in non identical twins is very rare owing to the extreme polymorphism in the HLA system.

The various types of Rejection are:

1. **Hyperacute Rejection (HAR)**
   It is due to presensitisation of the recipient to an antigen expressed by the donor. The recipient has circulating antibodies prior to transplant owing to prior exposure through pregnancy, previous transplants or blood transfusion to donor alloantigens. A complement-mediated lysis is initiated resulting in immediate graft thrombosis. The graft swells up and becomes blue and hard on the operating table itself. The only measure against it is prevention. The tests used preoperatively are the ABO compatibility and lymphocytotoxicity cross match. They effectively prevent HAR in 99.5% of transplants.

2. **Accelerated Rejection (Vascular Rejection)**
   This is a delayed variant of HAR. The mechanism seems to be presence of alloantibodies at levels undetectable buy the crossmatch assay, in spite of presensitisation. Sometimes, massive antibody production by T cell dependant B cell activation may cause de novo accelerated rejection. Thus, the graft initially functions well, but deteriorates by day three. Pulse therapy and plasmapheresis may reverse the condition in certain cases.

3. **Acute Rejection (AR)**
   This is a T cell dependant process and the only variant that can be effectively treated. It commonly occurs within the first six months of transplant. Acute rejection is invariable in transplants between non identical twins without immunosuppresion. The incidence of acute rejection declines with decreasing MHC disparity, though even a full house match mandates immunosuppresion. Activation of CD4 T cells leads to IL-2 secretion ultimately resulting in massive infiltration of the graft of mainly CD8 cells and its destruction. A cell-mediated counterpart of HAR is also known; presensitisation at T cell level causing accelerated form of acute rejection mediated by memory T cells. Prompt recognition and treatment leads to graft function retrieval in 90 to 95% of patients. Biopsy should be performed in unexplained graft dysfunction (Impaired LFT, raised liver enzymes, increased urinary amylase). Biopsy would reveal lymphocytic infiltration (eosinophilic also in liver). In renal transplant, the onset of oliguria, weight gain, hypertension and impaired renal function signals AR. The classic signs of fever, graft enlargement and tenderness are seen infrequently in patients treated with cyclosporine.

   The differential diagnoses could be cyclosporine toxicity (Levels are high), Acute tubular necrosis, extrinsic compression on the graft or ureteric obstruction.

   Diagnostic modalities include renal diuretic scan with pertechnetate Tc 99, Ultrasound (prominence of renal pyramids and loss of renal sinus fat, hematoma) and MRI (loss of CMD).

4. **Chronic Rejection (Chronic Allograft Nephropathy)**
   This is a poorly understood process leading to insidious, slow and irreversible graft loss. It usually occurs over a period of months to years. It is not treatable by any method yet. Histologically it is characterized by replacement of graft parenchyma with fibrous tissue with a relatively sparse lymphocyte infiltrate. Non-immunological factors may also play a part. AR may sometimes cause rapid deterioration in a known case of CR and if treated, may lead to partial return of graft function. The only treatment is retransplantation.

Immunosuppressant Drugs

Immunosuppresion is a vital part of transplantation. However, it is a double-edged sword, carrying with it the risks of infection and malignancy, apart from the side effects of the drugs itself. The immunosuppression in the initial postoperative period is intense as the chances of rejection are maximum during this period, known as induction

immunosuppression. They are also used as Rescue agents, used to reverse an established rejection episode. The dosage of immunosuppressants gradually tapers off, known as maintenance immunosuppression.

The various drugs available for immunosuppression are:

1. **Steroids**
   The most commonly used steroid is Prednisolone. It alone is ineffective and usually is added to Azathioprine and Cyclosporine in the most commonly used regimen for immunosuppression. The glucocorticoid effect causes a generalized immunosuppression by blunting T-cell proliferation. High dose Methylprednisolone (500-750mg/day IV bolus X 3-5 days) is used as a rescue agent for reversing acute rejection. Steroids are responsible for cushingoid features like acne, obesity, diabetes and peptic ulceration. They may cause growth retardation in pediatric transplants. The trend now is towards minimal steroid usage and even steroid free immunosuppression.
2. **Azathioprine**
   The first immunosuppressive used, it is an antimetabolite. It is a prodrug, which is metabolized to 6-Mercaptopurine and then its derivatives. These then deprive the cell of adenosine, a vital ingredient in DNA synthesis. It is relatively nonspecific acting on all rapidly dividing cells. Its chief use is for maintenance immunosuppression and has no value as induction or rescue agent. It is rarely used in liver transplants. The dosage is usually 1-2 mg/kgBW. The dose limiting side effects are bone marrow depression and hepatotoxicity. Hence, the dose is withheld or reduced if TLC is less than 3000 cells/cc or liver dysfunction is present.
3. **Mycophenolate Mofetil (MMF)**
   It is also an antimetabolite. It is a reversible inhibitor of IMP dehydrogenase, interfering in Nucleic acid synthesis. It is relatively specific against lymphocytes as they lack the salvage pathway (HGPRT catalyzed GMP production). Both T and B cell proliferation in response to antigen stimulation is blocked. The drug has potential for both induction and maintenance therapy. The side effects, including bone marrow depression are minimal. It is gradually replacing Azathioprine, especially in patients with high risk of rejection. It is regularly used in liver transplants in place of azathioprine due its low hepatotoxicity.
4. **Tacrolimus (FK506)**
   It is a macrolide calcinuerin inhibitor. It blocks IL-2 translation by binding to FK Binding Protein, the effect and toxicity being additive to cyclosporine. Tacrolimus is 100 times more potent than cyclosporine. However, unlike the latter, it can be used as a rescue agent. The side effect profile is similar to cyclosporine, with more pronounced neurological and diabetogenic effect Tacrolimus is the drug of choice for liver transplantation and renal transplantation
5. **Cyclosporin**
   Discovered by Borel in 1976, it came into clinical practice in 1983. It is at present the mainstay of maintenance therapy in almost all type of transplants. It is a calcinueurin inhibitor, binding cyclophilin and inhibiting the transcription of IL-2 gene and thus T cell activation. It is remarkably specific against immunocompetent lymphocytes. However, it cannot be used as rescue agent presence of IL-2 in the graft bypasses the drug effect. At present, a micro emulsion formulation that has better bioavailability and pharmacodynamics is used. Since most of the metabolism is through the cytochrome P 450 enzyme system, Hepatic dysfunction mandates reduced dosage. The absorbed drug is almost totally metabolized and excreted in bile. Also, drugs influencing the cytochrome enzyme system alter the metabolism of cyclosporine (increased by rifampin, Phenobarbital, Phenytoin, decreased by ketoconazole, erythromycin and calcium channel blockers). The usual dosage is 7.5 to 25mg/kg. The main toxicity is Nephrotoxicity due to vasoconstrictor effect on proximal renal arterioles. Hyperkalemia, Hemolytic Uremic syndrome, Hypertrichosis, Gingival Hyperplasia, Neurotoxicity are the other side effects seen. This mandates strict monitoring of cyclosporine levels to avoid toxicity. Usually the level of cyclosporine 2 hours after intake is measured (C2levels).
6. **Sirolimus (Rapamycin/Rapamune)**
   It is the latest immunosuppressant agent for solid organ transplants, prescribed for induction therapy, refractory rejection, steroid withdrawal, and combination therapy. It is an immunophilin binding drug, blocking signal transduction by the IL-2 receptor, hence the response of T-cells to IL-2. It is structurally similar to but antagonizes the action of Tacrolimus and is synergistic with cyclosporine. It is at present in use for renal and heart transplants. The main toxicity of sirolimus is hypertriglyceridemia and pulmonary toxicity.
7. **Monoclonal antibody (muromonab-CD3/OKT3)**
   They are produced using the Hybridoma technology, developed by Kohler and Milstein in 1970. The immunoglobulin is targeted against the CD3 molecule, part of T Cell Receptor found Thymocytes and mature T cells. It is used for treatment of acute rejection episodes, usually steroid refractory cases. The side effects include a systemic cytokine release syndrome, which can cause hypotension, pulmonary edema, fatal cardiac myodepression and aseptic meningitis. Pretreatment with high dose methylprednisolone, antihistamines and antipyretics reduces the side effects. The usual adult dose is 5mg/kg/day for 10-14 days. Use of OKT3 is also associated with increased risk of cytomegalovirus, Epstein Barr and in children, varicella viral infection.
8. **Anti Lymphocyte Globulin/Anti Thymocyte Globulin (ALG/ATG)**
   This is a polyclonal serum developed by collecting antibodies produced by various animals against human lymphocytes. Most commonly, Horse or rabbit are used. ATGAM is the purified IgG fraction most commonly used. The antibody coats the T cells and promotes its clearance. The drug is most commonly used as part of multidrug induction immunosuppression. Severe thrombocytopenia is occasionally seen. The patient is usually

pretreated with antipyretics, antihistamines and antipyretics. Viral infections, both primary and reactivation are seen more frequently in patients treated with this drug.

9. **Anti IL-2 Receptor Antibody (Basiliximab/ Daclizumab)**
   The chimaeric monoclonal antibody basiliximab specifically binds the alpha subunit of the interleukin-2 (IL-2) receptor on activated T lymphocytes. Renal transplant patients usually receive basiliximab 20 mg 2 hours before and then 4 days after transplantation surgery. These antibodies have been shown to reduce the incidence of acute rejection without increasing the incidence of opportunistic infections or malignancy. Side effects are not very significant. Longer follow up however, is required to fully evaluate the efficacy of these agents.

Complications of Immunosuppression

Immunosuppression is not obtained without paying a significant price in terms of side effects. Infection and malignancy are the most frequent complications encountered with the use of non-specific immunosuppressive agent.

a) **Infection**. Transplant recipients who receive immuno-suppression encounter a greatly increased incidence of infection, which remains the most common cause of mortality. Most deaths used to be due to invasive infections. These have been controlled by antibiotics. Nowadays most infections are caused by opportunistic pathogens, including fungi, protozoa and viruses, the latter being specially common among kidney transplant patients. Candida albicans and Aspergillus species are the most common fungi encountered in transplant patients. The latter produces upper lobe pulmonary cavities. The protozoan Pneumocystis carinii is also a frequent cause of pulmonary infection, producing n alveolar infiltrate with severe dyspnoea and cyanosis. However, it is seen less often since the use of prophylactic trimethoprim and sulfamethoxazole in transplant recipients.Among the viruses, cytomegalovirus (CMV) and Epstein-Barr virus (EBV) commonly infect transplant patients. CMV is the most important virus infection seen in immunosuppressed transplant patients. The virus itself produces severe immunosuppression rendering the patient susceptible to bacterial and fungal opportunists.

b) **Malignancy:** Cancer is seen more often in transplant recipients than in the general population. Most cancers that arise in transplanted patients are either epithelia l(carcinomas of the cervix an lip and basal cell carcinomas, constitute about one half of these) or lymphoid(B-cell lymphomas).

c) **Other complications**: are mostly due to the use of steroids : Cushing's syndrome, cataracts, gastrointestinal bleeding, hypertension, pancreatitis, and avascular necrosis of the femoral heads.

Organ retrieval & Organ Preservation

Graft damage must be minimized from the time the organ is removed from the donor to the time it is implanted into the recipient. Graft damage may start while the organ is still within the donor while awaiting consent for donation. This damage may also occur during removal, storage and transport of the graft or during the transplantation operation.

Organ Preservation

The kidneys are usually perfused with a special solution. This could be Phosphate based Sucrose, Hyperosmolar Citrate, or the University of Wisconcin Solution. The essential components of preservation include:

1. **Hypothermia**: Cooling of the organ to 4-10 degrees C. markedly reduces the metabolic rate and prolongs the storage time of 1 to 2 hours to about 12 hours.
2. **Prevention of Cell Edema:** This is done by using a hyperosmolar flushing solution with an impermeable solute to achieve a 'No flow' phenomenon. This solute could be Mannitol, Sucrose, Glucose or Raffinose.
3. **Energy Source and lysosomal stabilizers:** This is usually achieved by steroids and the use of Magnesium
4. **Free Oxygen Radical Scavenger**: like Gluthaione and Allopurinol inhibt organ damage.
5. **Continuous cold perfusion**: combines all these benefits : hypothermia, continuous buffering, continuous provision of oxygen and nutrients, and continuous washout of accumulating toxic metabolites.This is usually done in marginal donors and asystolic donors.

TRANSPLANTATION OF INDIVIDUAL ORGANS

Kidney

Indications for Renal Transplant

A. Glomerulonephritis	**D. Systemic Diseases**
Idiopathic and post Cresentic	Diabetes
Membranous	Cystinosis
Mesangiocapillary	Amyloid
Focal Glomerulosclerosis	**E. Obstructive Uropathy**
Anti - GBM	**F. Irreversible Acute Renal Failure**

IgA Nephropathy	
B.Toxic	**G**. Multi - System Disease
C.Trauma	SLE
	Vasculitis

Contraindications to renal transplant

STRONG CONTRA-INDICATIONS	**RELATIVE CONTRAINDICATIONS**
Unresolved Malignancy	Obesity or malnutrition
Ongoing Metabolic disease	Urinary tract infection
Active Sepsis	Severe peripheral vascular disease
Active tuberculosis	Poorly controlled diabetes
Severe Vasculitis	Prior Malignancy
End Stage Vascular disease	History of non compliance
Active AIDS	Inadequate social support
Active Drug Abuse	Life expectancy less than five years
Active Lupus	Emotional Instability
Recent MI	Decreased mental capacity
Insufficient Financial Resource	

Bilateral nephrectomy: is now rarely performed. The only indications for this in the current day and age is intractable upper urinary tract infection, Severe hypertension refractory to medical treatment, Complex renal cyst with suspicion of malignancy or large polycystic kidneys precluding placement of graft are other rare indications for a bilateral nephrectomy.

The Donor

Donors can be live related, unrelated or cadaveric.

a. In a **live related program** the donor is sacred to the program and must be free of any condition that could increase the risk of any complication or diminish the function of the remaining kidney. Screening for diabetes and end organ damage by hypertension must be done. With the current paucity of donors more and more borderline donors are being now accepted in programs that have considerable experience in renal transplantation. These include donors that have hypertension, Ectopic kidneys or kidneys with multiple renal arteries that are amenable to vascular reconstruction. In India, the commonest donor is the mother followed by the sister and then the brother.

   Long term studies on the donor have shown that the incidence of the donor developing a major complication is less than .05%. 15% will have a minor complication. The incidence of hypertension in donors over a period of time is probably higher than the normal population but the incidence of renal failure is far lower than the normal population. The donor should be in excellent health being between 18 to 70 years and should be blood group compatible with the recipient. He should have a good H.L.A. match and should be motivated to donate the organ on his own and without any coercion. An angiogram should be done to assess the renal vascular supply. There are reports in literature now of spiral CT angiogram giving as good a delineation of vascular anatomy and this is likely to replace a conventional angiogram in the future.

b. Cadaver donors should not have any disease that could affect the kidney or the potential recipient. These include Hepatitis, HIV active infection or malignancy.

   Criteria for Cadaveric Renal Donor Selection

Age < 65 years
No Evidence of any renal disease
Pre- Terminal urine output exceeding 0.5cc/kg/hr
Normal Serum Creatinine and BUN
No Evidence of HIV, HbSAg , or Hepatitis C

Kidney Removal

In living related donation the kidney that is usually removed is the left kidney. This is because of the long length of the renal vein that is available. This can now be done through a flank approach or transperitoneally. There are number of centers retrieving these kidneys laparoscopically..

Cadaveric harvesting is done through a long midline incision and is usually part of a multi organ harvest.

The Renal transplant Operation

The surgery for renal transplantation is fairly standardized now. The live donor should be well hydrated and a flank incision should be used. Meticulous dissection is required and the kidney with the artery vein and a lot of periureteric fat with the ureter is harvested. This is done so that the blood supply of the ureter is not compromised. After harvesting the kidney is perfused with a renal preservation solution and stored in ice before transplanting. The renal transplant operation is carried out through a right or a left curvilinear extra-peritoneal incision. The external

iliac artery and vein are mobilized and the renal artery and vein anastomosed end to side to the external iliac artery and vein. The ureter is anastomozed to the bladder by an extravesical nonrefluxing ureterneocystostomy. This may be done over a double J stent.

Post Operative Care
The patient is usually nursed in an intensive care where attention is given to fluid and electrolyte balance. Most kidneys from live elated donors have a massive initial diuresis and it is important to keep the patient well filled. Care is also taken to ensure that electrolyte balance is maintained. Most patients are eating and drinking by the third or fourth day and can usually be discharged on the tenth day.

Delayed or Non function of the transplanted Kidney:

Causes:

- Acute Tubular Necrosis
- Renal Artery Thrombosis
- Renal Vein Thrombosis
- Hyperacute Rejection
- Ureteric Obstruction

A DTPA scan, A Doppler and an ultrasound can usually help to distinguish between the various causes. A renal graft biopsy is usually the diagnostic modality of choice .

Results
The one-year graft survival rate in India is currently in the range of 92-93%. Infectious complications are common due to the poor development of basic amenities. Most of our successful transplant patients have an excellent quality of life and view their post-transplant period as a rebirth. Most grafts carried out in the Western world are cadaveric, most of those in the underdeveloped countries are from living related donors. Patient survival rates are around 90% at 1 year and 80% at 5 years.

Liver Transplantation
Liver tranplantation has been successfully used in large number of patients suffering from congenital and acquired disorders. It is now an accepted modality for the treatment of Liver failure .The grafted liver may be placed in the normal anatomical position after total hepatectomy of the recipient (orthotopic transplantation). Alternatively, the donor organ is placed in an ectopic site (heterotopic transplantation), usually with retention of the host's liver (auxiliary transplantation) Most clinicians prefer orthotopic transplantation.

Indications for liver transplantation :

Extrahepatic Biliary Atresia (Common in Children)
Hepatitis C (Commonest Cause in Adults)
Alcoholic Liver Disease
Primary Biliary Cirrhosis
Primary Sclerosing Cholangitis
Acute Hepatic Necrosis
Hepatitis B
Auto Imunne Hepatitis
Malignant Disease
Metabolic Disease
Benign Neoplasm
Cryptogenic

In infants, biliary atresia which is in correctable surgically is the most common indication. If the initial Kasai portoenterostomy fails, the baby should me immediately considered for transplantation as multiple attempts at revising biliary drainage compromise the likelihood of success of the transplant.

In late childhood, inborn errors of metabolism, post necrotic cirrhosis, and small unresectable neoplasms are the other common indications. In children, the non-availability of suitable sized donors has led to the development of reduced size liver transplants, the right or the left lobe being used.

In adults, the leading indication has been postnecrotic cirrhosis. Patients with high levels of hepatitis B antigens are at higher risk of developing recurrence, and are often excluded from consideration for transplantation. On the other hand hepatic replacement for other conditions leading to end-stage cirrhosis, such as primary biliary cirrhosis, sclerosing cholangitis, and autoimmune hepatitis is highly successful. Since liver transplant today is a fairly common modality he recent trend is to carry out the operation early, instead of allowing the patient to deteriorate to the point of repeated gastrointestinal bleeding, malnutrition, sepsis and coma.,

Patients with small sized primary carcinomas of the liver with pre-existing cirrhosis, which precludes partial hepatic resection, should be offered hepatectomy and liver transplantation .More than half of these patients have long term disease free survival in the long term. Acute liver failure represents a difficult indication for liver transplantation. If stage III-IV encephalophaty has set in the mortality rate will be forbiddingly high. To be successful, therefore, hepatic replacement should be carried out before stage IV come is established.

Contraindications to Liver Transplantation

Advanced uncorrectable cardiac or pulmonary disease
Irreversible pulmonary Hypertension
Recent Intracranial Haemorrhage
Sepsis
Disseminated Malignancy
Active substance Abuse
Age > 70 years
Inability to comply with post transplant regimen

Donor Selection

Blood group compatibility and size are the two criteria that must first be met. About 11% of liver transplants will have primary non function and will require urgent retransplantation. Donor risk factors for non function include a donor whose age is more than fifty years, high transminases , prolonged stay in the intensive care unit and those who have required vasopressors in the intensive care unit. Steatosis has also been considered as a risk factor for primary non function.

The Cadaver Donor procurement procedure

Several teams are now involved in the harvest of organs from a single donor. The donor operation is usually carried out through a midline incision. Any intra-abdominal pathology is noted that may preclude organ donation. The dissection is usually commenced in the gastrohepatic ligament and any abnormal vascular supply to the liver is noted. A replaced left hepatic artery arising from the left gastric artery usually occurs in 14% of donors. The porta should also be inspected to identify a right hepatic artery that is arising from the Superior Mesenteric Artery. The splenic artery is ligated . Next the portal vein is dissected out and a cannula inserted into the inferior mesenteric vein as well as in the aorta. The superior vena cava is used to drain the preservation fluid which is infused from the aorta and the inferior mesenteric vein. The inferior vena cava is divided proximal to the drainage of the renal veins and the liver wirh the hepatic artery traced right down to its origin from the aorta as well as a sufficient length of the portal vein is dissected out. The liver is thus delivered. Dissection is then done in the bench where the branches of the phrenic vein that is draining into the inferior vena cava as well as small branches of the portal vein are ligated and divided.

The Recipient Operation

This first involves the recipient hepatectomy in which the the liver is mobilized and then dissection is commenced at the hilium and the left and the right hepatic artery are dividedclose to the liver to maximize the length of the artery that is available at the time of transplantation. The portal vein is mobilised to its bifurcation and the common duct is ligated adjacent to the liver. The Infra hepatic vena cava is then mobilized. The recipient vena cava can either be removed as part of the liver by establishing the patient on veno-venous bypass or alternatively the vena cava can be completely mobilized to allow divison of the anterior surface of the inferior vena cava and the liver is dissected off the vena cava.. The inferior vena cava is left in situ which obliterates the need for veno- venous bypass.

Veno- Venous bypass

During clamping of the portal vein and the inferior vena cava during the anhepatic phase the patient is unstable. To minimize mesenteric edema , increase renal perfusion as well stabilize the patient veno-venous bypass is an excellent alternative. This allows provides additional time to attain haemostasis. A cannula is inserted into the femoral vein and the other cannula is in the portal vein. These are then connected via a pump to the internal Jugular vein or the axillary vein.

Cadaver Donor Transplant

The supra-hepatic vena-cave is first anastomosed as an end to end anastomosis. The infra-hepatic vena cava anastomosis is then performed. This anastomosis is done while perfusing the portal vein with human albumin . This is done so as to wash out the UW solution which has a high content of potassium. It also flushes out heparin and air from the liver.The portal anastomosis is then done next and the liver is re-perfused. The hepatic artery is next anastomosed either end to end to the hepatic artery or to the bifurcation of the hepatic artery to the gastroduodenal artery. The bile duct is subsequently anastomosed.end to end to the common bile duct.
Haemostasis is maintained and the abdomen closed in layers.

Living Related Liver Transplantation

This essentially evolved from a scarcity of donor livers and essentially involves the left lobe or the right lobe with the respective branches of the portal vein , artery and bile duct. The left hepatic or the right hepatic vein is also taken from the donor and is anastomosed in the recipient. There are now excellent results that have been reported

from this technique. Donor safety and the report of donor mortality have however seriously questioned the safety of this technique.

Results

At centres with considerable experience of liver transplantation, 5 year survival rates of over 78% are being obtained. Most deaths occur in the first 3 months. Most of the surviving patients are adequately rehabilitated, 80% resuming their previous occupations. Some of the earlier patients have survived for over 20 years and death in patient who survived over 5 yeas has occurred only rarely.

Small Bowel

Improvement in total parental nutrition have significantly improved survival of patient with short - bowel or severe malabsorption syndromes. However, prospects remains poor for patient whose remaining bowel does not hypertrophy enough to allow at least partial external nutrition. The reasons are mainly two recurrent infections at venous sites take their toll; and liver function progressively deteriorates from prolonged high calorie intravenous feeding. The only viable alternative is replacement of the diseased or absent bowel by a functioning allograft.

Indications for Small Bowel Transplantation

Intestinal Atresia
Volvulus
Necrotising Enterocolitis
Mesenteric Infarction
Crohns Disease
Trauma
Desmoid Tumors requiring multiple resections
Motility disorders
Massive gut Resection

Three main problems make small bowel transplantation difficult ; the allograft inevitably becomes colonised by microbes ; huge numbers of immunocompetnet donor lymphocytes are necessarily transplanted and the incidence of thromobotic complications is high.

The small bowel transplant may be carried out as an independent procedure or as part of a multivisceral transplantation in which the liver is also transplanted. This may be required in patients who have been on TPN for a long time.

The entire small bowel is usually harvested with a patch of the aorta from which the superior mesenteric artery is arising. The patch is usually anastomosed to the aorta of the recpient and the superior mesenteric vein to the vena cava. The proximal end is anastomesed to the duodenum and the distal end is either bought out as an ileostomy or anastomosed distally.

The one year survival after small bowel transplantation is about 64% and is usually better with isolated small bowel transplants than with combined liver and small bowel transplants.

The commonest cause of mortality is sepsis or multi-organ failure. Graft versus host disease may occasionally occur after small bowel transplantation.Post transplant Lymphoproliferative disease (PTLD) is also more common after small bowel transplantation.

Pancreas

In spite of the availability of insulin and oral hypoglycaemic agent, diabetics are 17 times more liable to kidney disease, 5 times to gangrene of the extremities, and twice as likely to develop heart disease, for the simple reason that the control of the blood sugar level is both inaccurate and intermittent. If control could be continuous as well as accurate, it would be very great advance. Transplantation of whole pancreas or islets provides precisely that.

However in considering the indication for pancreatic transplantation these advantages must be carefully weighed against the risks of the pancreatic transplant and the immunosupressive protocol that is used. This risk may be justified in patients with renal failure. In most case the transplantation that is performed is the pancreas and the kidney are harvested from the same donor : Simultaneous Kidney Pancreas transplantation (SPK), Occasionally the pancreas transplantation is performed after the kidney transplantation : Pancreas after Kidney transplantation (PAKT). Only rarely is pancreas transplantation performed alone (PTA).

The procedure is usually performed in patients who do not have advanced coronary disease. Cardiac angiography is usually performed as assessment prior to transplantation.

The major problem in pancreatic transplantation is difficulty in establishing drainage of the pancreatic duct. In the most popular technique the whole pancreas and the second part of the duodenum are taken from cadaver. The superior mesenteric artery of the donor is anastomosed to the iliac artery of the patient, while the portal vein is joined to the recipient's inferior vena cava. The duodenum is anastomosed to the urinary bladder, so that the pancreatic juice is drained to the urinary tract.(bladder drainage). One advantage of the technique of the technique lies in the ease with which urinary amylase levels can monitor the survival and function of the graft. Enteric drainage is now commonly performed ,the kidney being a monitor for rejection i.e. both organs should reject simultaneously.

The immediate effect of successful pancreatic transplantation is dramatic. Within 24 hours the allograft provides a self-regulating source of insulin. Results have been encouraging as many as 60% of pancreatic transplants are still functioning at 3 years.

Islet transplant

Transplantation of the pancreatic islets is a far more attractive idea than transplanting the whole pancreas as the complications of the exocrine pancreas are excluded. Islets are obtained by mechanically disrupting the pancreas after injecting collagenase into the pancreatic duct. The islets are then purified and are injected into the recpients liver.Attractive option include protecting isolated islet cells from rejection by encapsulating them in a semipermeable membrane that allows insulin to pass through but prevents antibodies and leucocytes from reaching them. This may obviate the need for immunosupression. There are now numerous reports now in literature of a large number of patients being insulin free but this modality has yet to be accepted as the treatment of choice.

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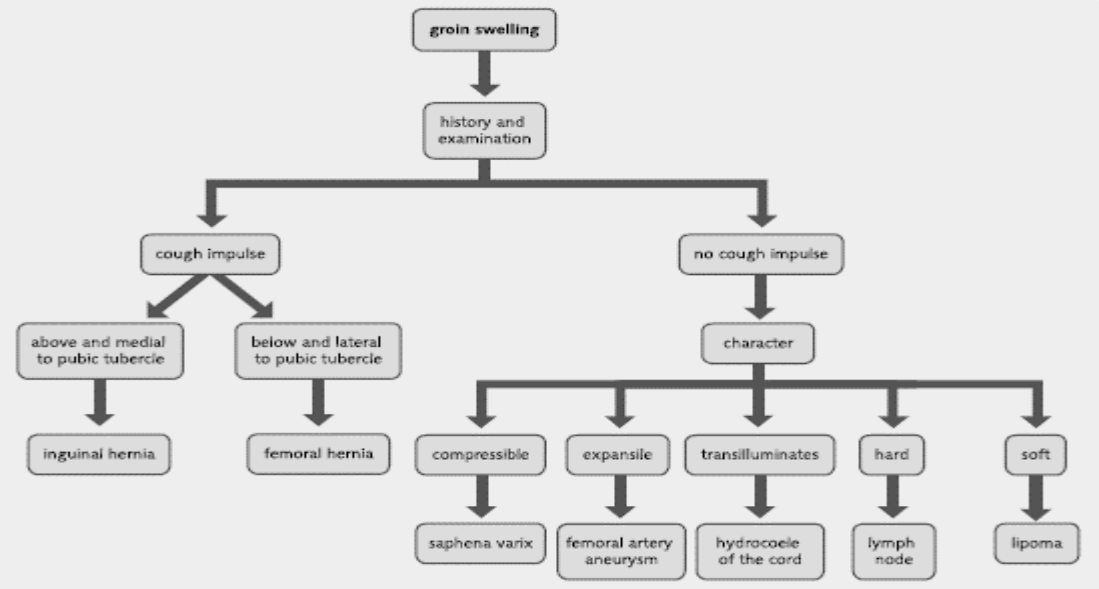
Management of Inguinoscrotal swelling

Lovekesh Kumar, Sanjeev K Tudu

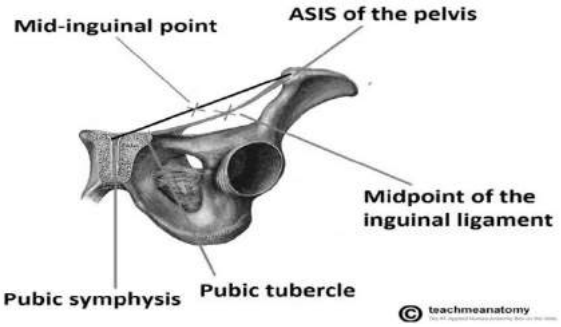
Pure Scrotal swelling -top of swelling can be reached.
Inguinoscrotal swelling-top of swelling cannot be reached.

Causes of Groin swellings	Causes of Scrotal swellings
Inguinal hernia- direct and indirect	Torsion testis
Femoral hernia	Epididymo orchitis
Undescended testis	Torsion of testicular appendages
Inguinal lymphadenitis	Hydrocele
Lipoma of spermatic cord	Epididymal cyst
Encysted hydrocele of cord	Spermatocele
Hydrocele (Congenital, infantile)	Testicular tumour
Hydrocele of hernia sac	Varicocele
Saphena varix	
Femoral artery aneurysm	
Psoas abscess	
Hematoma	



Anatomy of inguinal region: Why ?

"No disease of human body belonging to the province of the surgeon requires in its treatment a better combination of accurate knowledge with surgical skill than hernia in all its varities" - Sir Astley Paston Cooper ;1804

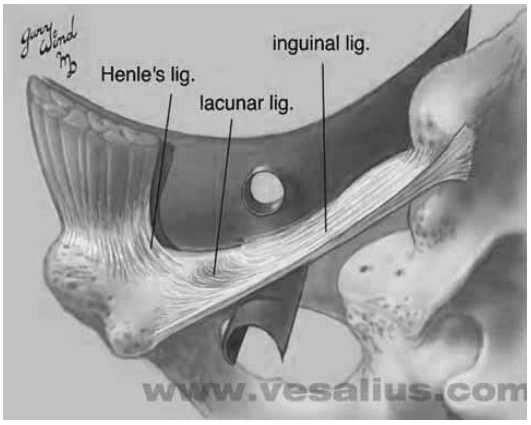


Mid-inguinal point
Halfway between the pubic symphysis and the anterior superior iliac spine. The femoral artery crosses into the lower limb at this anatomical landmark.

Inguinal ligament (Poupart's ligament)
A fibrous band extending from the anterior superior iliac spine to the pubic tubercle. Formed by the lower border of external oblique aponeurosis, which is thickened and folded on itself. Transition from pelvis to lower limb.

Inguinal Canal
Inguinal canal is about 4cm in length extending from deep inguinal ring to the superficial inguinal ring. In neonates, the deep ring lies almost directly posterior to the superficial ring.

- Anteriorly- external oblique aponeurosis and fleshy fibres of the origin of internal oblique in its lateral 1/3rd.
- Posteriorly—Fascia transversalis along the whole length of the canal. In the medial half there are conjoint tendon and reflected part of the inguinal ligament.
- Superiorly—There are arched fibres of internal oblique and transversus abdominis before they fuse to form the conjoint tendon.
- Inferiorly—Inguinal ligament and the lacunar ligament on the medial side (Gimbernat's ligament).



Superficial inguinal ring*:* triangular opening in aponeurosis of external oblique muscle 1.25 above pubic tubercle normally ring does not admit tip of little finger.

Deep inguinal ring*:* It is ½" or 1.25cm above the mid-inguinal point. It is U-shaped defect in transversalis fascia.

Ligament of Henle/Falx inguinalis: Lateral vertical expansion of the rectus sheath that inserts on the pecten of the pubis. In one-third to one-half of patients and is fused with the transversus aponeurosis and fascia

Conjoint tendon*:* By definition, the fusion of lower fibers of the internal oblique aponeurosis with similar fibers from the aponeurosis of the transversus abdominis where they insert on the pubic tubercle and superior ramus of the pubis.The trouble is that the anatomic configuration thus described is extremely rare (3 – 5%). The distinction between falx inguinalis and conjoined tendon is one of anatomic nicety and admittedly of little practical significance

in the operating room provided that the distinction is understood. The term conjoined area can be applied correctly to that region that contains the ligament of Henle.

Cooper's or Pectineal ligament: The periosteum of the superior ramus of the pubis, strongly reinforced by endoabdominal fascia (transversalis fascia), with more reinforcement by the transversus abdominis aponeurosis and the iliopubic tract medially

Iliopubic tract*:* Aponeurotic band formed by transversus abdominis muscle and aponeurosis and the transversalis fascia. Begins near the anterior superior iliac spine extends medially to attach to Cooper's ligament

Preperitoneal space:

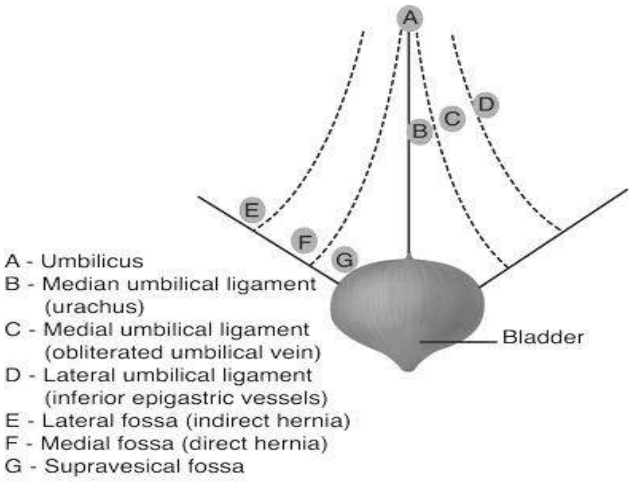
- Space of Retzius- Retropubic space
- Space of Bogros – Lateral extension of space of Retzius. Contains inferior epigastric artery

Hasselbachs triangle: The boundaries of the inguinal triangle are as follows

- Medial: Lower 5 cm of the lateral border of the rectus abdominis muscle.
- Lateral: Inferior epigastric artery.
- Inferior: Medial half of the inguinal ligament.

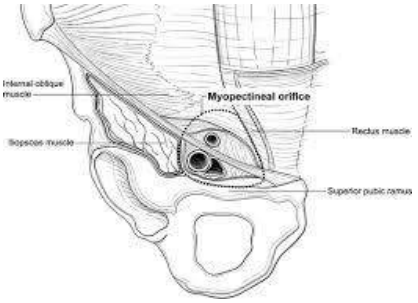
The floor of the triangle is covered by the peritoneum, extraperitoneal tissue, and fascia transversalis.

The lateral umbilical ligament (obliterated umbilical artery) crosses the triangle and divides it into medial and lateral parts. The medial part of the floor of the triangle is strengthened by the conjoint tendon. The lateral part of the floor of the triangle is weak, hence direct inguinal hernia usually occurs through this area.



Myopectineal Orifice of Fruchaud

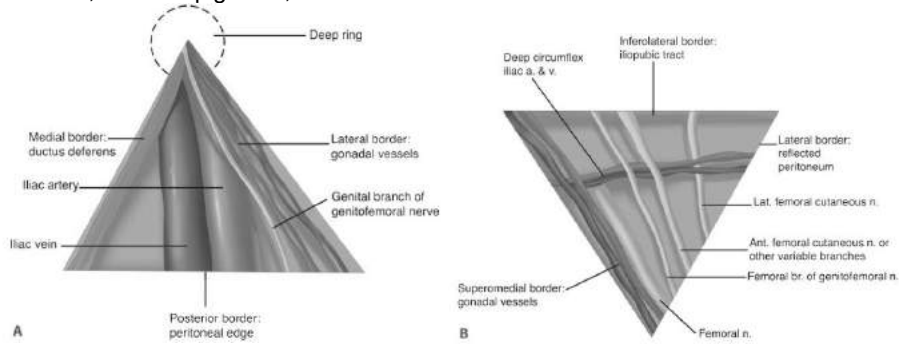
The arch of the internal oblique muscle and transversus abdominis muscle constitute the superior margin, the iliopsoas muscle the lateral margin, inferiorly by the Cooper ligament, the lateral edge of rectus abdominis medially, and the pubic pecten medially. MPO is divided anteriorly by the inguinal ligament, and posteriorly by the iliopubic tract. The iliopubic tract divides the orifice into a superior portion housing the spermatic cord and an inferior portion containing the iliac vessels.



Triangle of Doom: Bordered medially by the vas deferens, laterally by the vessels of the spermatic cord, thereby pointing its apex superiorly. The contents of the space include the external iliac vessels, deep circumflex iliac vein, femoral nerve, and genital branch of the genitofemoral nerve.

Triangle of Pain: The triangle of pain can be conceptualized as the space bordered by the iliopubic tract and gonadal vessels. The structures within this space include nerves such as the lateral femoral cutaneous, femoral branch of the genitofemoral, and femoral nerve.

Circle of Death: It is a vascular continuation formed by the common iliac, internal iliac, obturator, aberrant obturator, inferior epigastric, and external iliac vessels.



GROIN HERNIA

Definition: The word 'hernia' has its origins from the Greek which means 'budding'. Classically hernia is defined as the protrusion of the viscus or a part of it through the wall that contains it.

Inguinal Hernia

Inguinal hernia can be of two types direct and indirect inguinal hernias.

Indirect inguinal hernia passes through the defect in the deep ring, traverses through the inguinal canal to reach the superficial ring down into the scrotum.

Direct inguinal hernia comes through the defect in the anterior abdominal wall at the region of Hasselbach's triangle.

Femoral Hernia:It is the herniation through the femoral canal.

Etiology: Presumed causes of Groin herniation

Coughing	Pregnancy	Congenital connective tissue disorders
COPD	Birth weight <1500 gms	Defective collagen synthesis
Obesity	Family history of hernia	Previous Right lower quadrant incision
Straining	Valsalva maneuvers	Arterial aneurysms
Constipation	Ascites	Cigarette smoking
BPH	Upright position	Physical exertion?

Classification of groin hernias

Various classification systems have been used. The comprehensive table is given below.

Modified Traditional		Nyhus-Stoppa	Modified Gilbert	Schumpelick/Aachen
IA	Indirect small	I	1	L1
IB	Indirect medium	II	2	L2
IC	Indirect large	IIIB	3	L3
IIA	Direct small	IIIA	5	M1
IIB	Direct medium	IIIA	—	M2
IIC	Direct large	—	4	M3
III	Combined	IIIB	6	Mc
IV	Femoral	IIIC	7	F
0	Other	—	—	—
R	Recurrent	IV A, B, C, D	—	—

Characteristics of the Classification systems

Nyhus	Most commonly used system in the United States, not easy to remember
Gilbert	Lack of description of femoral hernias (has been added in the modification) or combined hernias
Bendavid TDS	Type, staging, and dimension described, but very complex
Aachen	Simple, easy to remember, differentiates between anatomic localization, objective measurement of size of hernia orifice defect
European Hernia Society	Newer system, has objective description of hernia orifice

Latest European Hernia Society Classification

EHS Classification*	Primary				Recurrent
Size	0	1: ≤1 finger	2: 1-2 fingers	3: ≥ 3 fingers	X- diffuse defect of transversalis fascia where imbrication is not possible
L: lateral M: medial—direct hernia where repair by imbrication of transversalis fascia is possible F: femoral					

*Combination of hernias is depicted by checking two or more appropriate boxes.
Note: Hernia description is by checking the appropriate box.

Clinical Classification

1. Reducible hernia: When the hernia can be reduced spontaneously on lying down or by 'Taxis'.
   'Taxis' is the maneuver of manually reducing the inguinal hernia in which the hip is flexed and internally rotated, followed by exerting uniform pressure over the fundus of the sac while guiding the contents of the hernial sac back into the abdominal cavity.
2. Irreducible hernia: in which the contents of the sac are not completely reduced into the abdominal cavity.
3. Obstructed hernia: when the content of the hernia sac is bowel, it can get obstructed at the level of the neck of the hernia sac resulting in a closed loop intestinal obstruction.
4. Strangulated hernia: when the blood supply of the contents of the hernial sac is compromised, patient presents with tenderness over the inguinoscrotal swelling, suggestive of strangulation.

5. *Infarcted hernia:* when the strangulation of the sac contents is not relieved immediately, they can become gangrenous.
6. Incarcerated Hernia: It is a hernia which is irreducible and going towards strangulation.

Hernia-Terminologies

- *Bubonocele:* Inguinal hernia which does not reach the level of superficial inguinal ring.
- *Funicular:* Hernial sac after emerging out of external ring stops just above the testis.
- *Incomplete Inguinal Hernia:* Inguinal hernia which does not reach upto the base of the scrotum.
- *Complete Inguinal Hernia:* Inguinal hernia which reaches upto the base of the scrotum.
- *Enterocele:* When the content of the hernia sac is bowel.
- *Omentocele:* When the content of the hernial sac is omentum.
- *Richter's hernia:* When the content of the hernia sac is a part of the circumference of the bowel.
- *Littre's hernia:* When the content of the hernia sac is Meckel's diverticulum.
- *Hernia en glissade/Sliding hernia:* When the portion of the sac is formed by the wall of the content.
- *Reduction en masse:* When the hernia sac along with its contents is reduced into the abdominal cavity.
- *Pantaloon/Dual/Saddle Hernia:* When the hernia has both direct and indirect components.
- *Maydl's hernia:* When the sac contains a W shaped loop of bowel as its content.
- *Amyand's hernia:* When the content of the hernia sac is appendix.

Clinical examination pearls

- Patient is better examined in standing position.
- On inspection: Skin over swelling-Normal in uncomplicated, Reddened in strangulated hernias.
- Visible peristalsis in abdomen, external urethral meatus, opposite groin has to be examined.
- Swelling above the inguinal ligament and medial to pubic tubercle-Inguinal hernia.
- Swelling below the inguinal ligament and lateral to pubic tubercle-Femoral hernia.
- *Head or leg raising test:* to test for abdominal muscle tone & malgaigne's bulging.
- *Malgaigne's bulging:* oval shaped b/l bulge on straining above & parallel to medial half of inguinal ligament
- On palpation: Ziemann's test: Can be used only if the swelling is completely reducible.
- Impulse is felt over ring finger in case of femoral hernia.
- Impulse on coughing and expansile cough impulse: Characteristic of hernia. Cough impulse may be absent in irreducible and strangulated hernias.
- Testis traction test: Pull testis downward; Encysted hydrocele descends slightly & become fixed whereas inguinal hernia can't be fixed.
- In case of a child inguinal hernia is invisible due to presence of thick pad of fat over inguinal region. To make it visible ask him to jolt/jump/make it cry.
- *Gornalls test:* child is held from back by both hands of the clinician on its abdomen, Abdomen is pressed and child is lifted up. It causes increased intra-abdominal pressure making the hernia more prominent.
- Per-rectal examination in selected cases may reveal:
  1. Benign Prostate hypertrophy—micturition difficulty
  2. Malignant obstruction
  3. Chronic fissure—constipation

Clinical differentiation of indirect and direct hernias

Indirect Hernia	**Direct Hernia**
Any age from childhood to adult	Common in elderly
Occurs in a pre-existing sac	Always acquired
Protrusion through the deep ring	Herniation through posterior wall of the inguinal canal
Pyriform /oval in shape; descends obliquely and downwards	Globular/round in shape; descends directly forward bulge
Can become complete by descending down into the scrotum	Rarely descend down into the scrotum
Sac is antero-lateral to the cord	Sac is posterior to the cord
Ring occlusion test no impulse after occluding the deep ring	impulse even after occluding the deep ring
Invagination test shows impulse on the **tip** of the little finger	Invagination test shows impulse on the **pulp** of the little finger
Zieman's test impulse on the index finger	impulse on the middle finger
Commonly unilateral may be bilateral	Commonly bilateral
Obstruction/strangulation are common	Rare but can occur

Investigations

Radiological investigations play a minor role in the diagnosis of inguinal hernia, since the clinical examination is almost conclusive.

USG abdomen: In suspected BPH, USG prostate with PVRU. Herniography: is **not needed** for the diagnosis of hernia.

Management of Groin Hernias

Hernia accidents: Obstruction and strangulation of hernia are called as hernia accidents. Indication for immediate surgery.

Truss: A truss is a mechanical appliance consisting of a belt with a pad that is applied to the groin after spontaneous or manual reduction of a hernia and has been used for centuries. It serves to maintain reduction and possibly prevents enlargement of the hernia. No proper studies on its efficacy so far. Complications: Spermatic cord atrophy, fibrosis in local region resulting in difficult hernia surgery.

Loss of domain: With large groin hernias, replacement of hernia contents into the abdominal cavity during herniorrhaphy could be followed by respiratory embarrassment and/or abdominal compartment syndrome. It can be managed with creating artificial pneumoperitoneum before surgery.
Management of precipitating cause if present:

1. Benign prostate hypertrophy
2. Tuberculosis
3. Stop smoking

Procedures

Pediatric congenital: High ligation of sac/ Herniotomy. No need to open up canal in children because superficial and deep ring are superimposed.

Young adults: Herniorrhaphy- suturing together patient's tissues.

1. Bassini's repair- (Bassini's Triple layer) Suturing of transversalis fascia, internal oblique and transversus abdominis aponeurosis with inguinal ligament from pubic tubercle to internal ring.

2. Modified Bassini's repair: Most commonly used before the advent of Lichtenstein's repair. Using **non absorbable monofilament interrupted** suture material strengthening of posterior wall of inguinal canal by approximation of conjoint tendon to inguinal ligament.

3. Shouldice repair (Canadian Repair)- First, the transversalis fascia is divided from the internal inguinal ring to the pubic tubercle. The posterior wall repair is accomplished by imbricating the lateral and medial leaves of the divided transverse aponeurotic fascial fibers with a continuous suture. The superomedial flap is brought over the inferolateral flap. The first suture line begins at the pubic tubercle and is sewn in a continuous fashion up to the internal ring, suturing the free edge of the inferolateral flap to the underside of the superomedial flap. At the internal inguinal ring, the cranial portion of the cremaster may be included in the suture line. This gives additional strength to the internal inguinal ring. The suture line is then doubled back bringing the leading edge of the superomedial flap to the edge of the inguinal ligament. The lacunar ligament is included in this suture line to obliterate the dead space medial to the femoral vessels. A second suture, beginning at the internal ring, brings the internal oblique and transversus muscles down to the deep surface of the inguinal ligament. At the level of the pubic bone, this suture doubles back, attaching the same structures in a more superficial plane and the suture is tied to itself at the internal ring.
4. Maloney's repair→ Darning of posterior wall with nonabsorbable suture material.

5. Mc Vay's repair-(Cooper's ligament repair)- The conjoined tendon is sutured to Cooper's ligament from the pubic tubercle laterally to femoral vein, and to inguinal ligament laterally from here.

6. Halstead's repair: (which otherwise resembles Bassini) external oblique aponeurosis is used to strengthen the posterior wall. This exteriorizes the spermatic cord, placing it beneath the layers of abdominal wall fascia.

7. Desarda repair→ Strip of external oblique aponeurosis is used to strengthen posterior wall

Tanner's muscle slide
Basically all the herniorrhaphy are tension repairs. To avoid tension in the rhaphy site, the incision made curvilinearly over the anterior rectus sheath. This relaxes the conjoined muscles and thus gets approximated with inguinal ligament without tension.

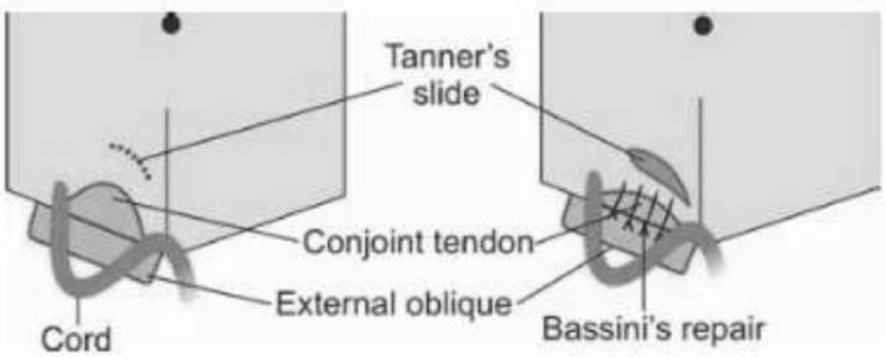


Fig. 18.36: Tanner slide operation—relaxing incision placed over the lower medial rectus sheath to reduce the tension after modified Bassini's repair.

Old people: Hernioplasty→ Litchtenstein's tension free mesh repair

Prolene Hernia System: PHS- Gilbert's open suture less repair

Open pre-peritoneal repair- Stoppa's- It is performed by wrapping the lower part of the parietal peritoneum with prosthetic mesh and placing it at a preperitoneal level over Fruchauds myopectineal orifice. This operation is also known as *giant prosthetic reinforcement of the visceral sac (GPRVS)*.

Laparoscopic repair: TAPP(Total Abdominal Preperitoneal Procedure) & TEP(Total Extraperitoneal repair)
European Hernia Society guidelines for Groin hernia management:

1. INDICATIONS FOR TREATMENT: IN ADULT MALES

Asymptomatic/minimally symptomatic	Watchful waiting
Strangulated hernia	Urgent
Symptomatic	Elective surgery

2. OPERATIVE TECHNIQUE (MALE ADULTS)

Primary unilateral	Mesh repair: Lichtenstein or endoscopic repair (if expertise available)
Primary bilateral	Mesh repair: Lichtenstein or endoscopic
Recurrent inguinal hernia	Mesh repair: modify technique in relation to previous technique.
If previously anterior	Open preperitoneal mesh or endoscopic approach (if expertise is present).
If previously posterior	Anterior mesh (Lichtenstein).

3. DIAGNOSTIC STUDIES

Groin diagnostic investigations should be performed only in patients with obscure pain and/or swelling.
The flow chart recommended in these cases:
Ultrasound (if expertise is available)
If ultrasound negative → MRI (with Valsalva)
If MRI negative → consider hemiography

4. BIOMATERIALS

In inguinal hernia tension-free repair, synthetic nonabsorbable flat meshes (or composite meshes with a nonabsorbable component) should be used.

The use of lightweight/material-reduced/large-pore (>1000-μm) meshes in open inguinal hernia repair can be considered to decrease long-term discomfort, but possibly at the cost of increased recurrence rate (possibly because of inadequate fixation and/or overlap).

5. DAY SURGERY: AN OPERATION IN DAY SURGERY SHOULD BE CONSIDERED IN EVERY PATIENT

6. ANTIBIOTIC PROPHYLAXIS

If low risk (<5%) of wound infection	No antibiotics
Endoscopic hernia repair	No antibiotics
Risk factors for wound infection:	Consider antibiotics
Patient factors: recurrence, advanced age, immunosuppressive conditions	
Surgical factors: expected long operating times, use of drains	

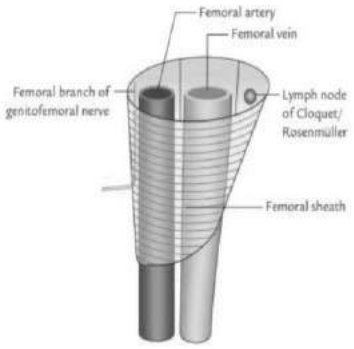
7. ANESTHESIA

Local anesthesia	All open repairs for patients with primary reducible unilateral inguinal hernia
Spinal anesthesia	Avoided
General anesthesia with local infiltration anesthesia	Alternative to local anesthesia

8. AFTERCARE: PROBABLY A LIMITATION ON HEAVY WEIGHT LIFTING FOR 2-3 WEEKS IS ENOUGH. PATIENTS CAN RESUME NORMAL ACTIVITIES

Femoral hernia

Femoral hernia occurs by the herniation through the femoral canal. Femoral hernias compromise about 6% of hernias. This is about 1/10 the incidence of inguinal hernias. About 85 % of direct and indirect hernias are male. However about 85% of femoral hernias occur in females.



Anatomy- Femoral canal
Femoral Canal: It extends from the femoral ring above to the saphenous opening (fossa ovalis) below, being the innermost compartment of the femoral sheath. Length – 2cm, shape: It looks like the inverted truncated cone, the upper end being the femoral ring.

Contents of the femoral canal
1. Fibrofatty tissue
2. Lymph nodes and lymphatics. Lymph node situated at the ring is known as Cloquet's node.

Anatomy- Femoral ring
Femoral Ring: Boundary

- Anterior—Inguinal ligament
- Posterior—Iliopectineal ligament and pubis.
- Medially—Crescentic edge of the lacunar ligament Gimbernat's ligament
- Laterally—Fibrous septum separating the canal from the femoral vein (Silver fascia). The ring is closed above by the septum crurale – a condensed extraperitoneal tissue pierced by the lymphatic vessels

Coverings: Skin, Superficial fascia, Cribriform fascia, Anterior layer of femoral sheath, Fatty content of femoral canal, Femoral septum, peritoneum.

Treatment

Principles:

- Dissection of the sac
- Reduction / inspection of the contents
- Ligation of the sac
- Approximation of the inguinal and pectineal ligaments

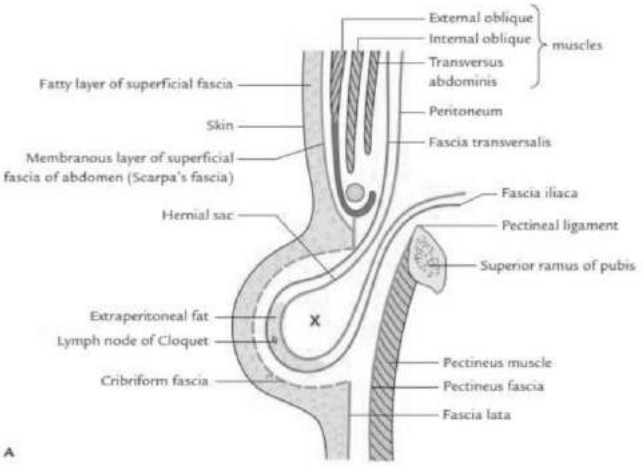
High operation of McEvedy: An incision above the inguinal ligament. Sac is dissected from below, neck from above and repair is done from above. It gives a very good exposure of both neck, fundus of sac and repair is also easier. Preferred for difficult or strangulated femoral hernia.

Lotheissens operation- Through inguinal canal. Used for indeterminate hernia.

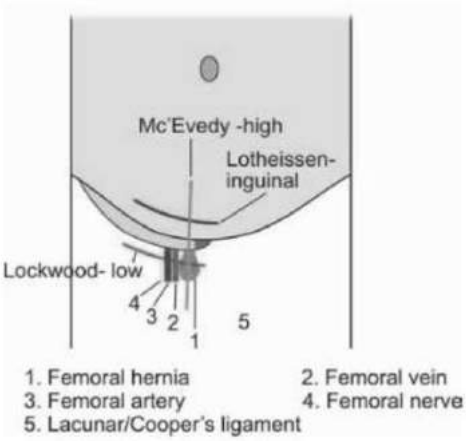
Lockwood operation low approach- Via upper thigh or groin. Used for small and elective hernia.

Laparoscopic- Same approach as for inguinal. Either TEP or TAPP.

Advantage is good exposure and low recurrence rate.



Saphenous Varix



- Prominent Varicosity of Upper Long Saphenous Vein.
- Typical Patient Middle aged and older, F>M
- Usual Risk Factors -Pregnancy, Pelvic Mass
- Clinically -Dragging lump over upper thigh, disappears when lying, Cough impulse +, Thrill down vein when percussing.
- Management-surgical ligation.

FEMORAL ARTERY ANEURYSM.

True aneurysms

- Pulsatile lump in groin
- Associated with other aneurysmal disease
- Mx-Vascular surgical repair if >2-3cm

False aneurysm

- Secondary to puncture
- Dx on duplex
- Mx-Call a vascular surgeon thrombose or repair.

PSOAS ABSCESS

- Abscess within Psoas fascia that tracks to groin and presents as a lump.
- Associated with Retroperitoneal infection/inflammation
- Post Surgical eg. Nephrectomy, Colonic. Pancreatitis, Spinal TB
- Management -Drain and treat underlying cause

UNDESCENDED TESTIS

- Can present as a swelling in the inguinal region.
- Up to 3% in full-term neonates, Up to 30% in premature neonates.
- 70% to 77% UDT can descend normally during the first 3 months.
- UDT 90% have patent processes vaginalis; must be ligated at the time of orchidopexy
- Birth wt is principal determinant of UDT ,independent of gestational age
- UDT may be intraabdominal, intracanalicular, extracanalicular (suprapubic,infrapubic), ectopic.
- 80% cases palpable, 20% cases nonpalpable
- Nonpalpable may be vanishing testis, intraabdominal, atrophic or inguinal.
- Children with retractile testis require annual follow up until puberty.
- 90% of patients have complex epididymal abnormalities.
- Prevalence of carcinoma in situ 1.7%

How can differentiate between Bilateral Cryptorchidism Vs Anorchidism?

1- LH & FSH levels increase= Anorchidism

2- hCG stimulation test: 2000 IU IM daily X 3 {If testosterone level increase= Cryptorchidism if not Anorchidism}

If both test +ve for Anorchidism; no need for surgical exploration

Treatment

- Hormonal treatment-hCG or GnRH ,efficacy less than 20%
- Surgical treatment- gold standard
- Ideal age- 6 months

Standard orchidopexy

- Procedure for high UDT
- Spermatic vessels are limiting factor to obtaining additional length.
- Prentiss maneuver- retroperitoneal mobilization of spermatic vessels
- *Fowler–Stephens orchidopexy* can be done in one or two stages and involves division of the internal spermatic artery to provide additional length, such that the testis is entirely dependent on blood supply from the deferential artery and cremasteric attachments.
- *Testicular autotransplantation* with microvascular anastomosis to the ipsilateral inferior epigastric artery and vein is an option for the intra-abdominal testis
- *Laparoscopy* is the best option for management of nonpalpable testis.

HYDROCELE

A hydrocele is an abnormal collection of serous fluid in a part of the processus vaginalis, usually the tunica.
A hydrocele can be produced in four different ways:-

1. by excessive production of fluid within the sac, e.g. secondary hydrocele;
2. by defective absorption of fluid; this appears to be the explanation for most primary hydroceles although the reason the fluid is not absorbed is obscure;
3. by interference with lymphatic drainage of scrotal structures;
4. by connection with the peritoneal cavity via a patent processus vaginalis (congenital).

Composition of Hydrocele Fluid

- Color—Straw or amber colored.
- Composition—Water, fibrinogen, inorganic salts, albumin and cholesterol crystals
- Hydrocele fluid normally won't clot if it is drained into a container but will clot immediately even if it comes into contact with a drop of blood

Symptoms

- Scrotal swelling
- Pain & discomfort if its secondary
- Frequent &painful micturation if secondary to epididymo-orchitis
- Malaise & weight loss if secondary to tumor with distant metastases
- Testicular sensation will be absent if secondary to tumor
- Don't affect fertility

Examination

- Can 'get above it'. Testes cannot be felt separately
- Transluminates, Fluctuant, Can't be reduced
- Normal skin color & temp, Not tender if primary (may be tender if secondary)
- Size can be reach up to 10-20cm in diameter with a smooth surface.

Classification of hydrocele

1) Congenital
2) Acquired
    (a) Primary
    (b) secondary

Primary Hydrocele

- Develop slowly
- Over 40s
- Defective absorption of fluid
- Ex: Vaginal & infantile hydroceles
- Attain moderate to big size
- Difficult to palpate testis
- Transillumination positive
- Consistency→ tensely cystic
- Tx: Jaboulay's & Lord's operations

Secondary Hydrocele

- Develops rapidly
- Younger age group(20-40)
- Excessive production of fluid
- Ex: Filariasis, tumor, trauma & epididymo-orchitis
- Attain small size
- Testis easily palpable
- Transillumination negative
- Consistency→ Lax cystic
- Tx: Treat underlying causes

Hydrocele of Canal of Nuck

Hydrocele of the canal of Nuck is a condition in females.The cyst lies in relation to the round ligament and is always at least partially within the inguinal canal.

U/S of hydrocele Done to exclude testicular tumor or epididymitits

Complication of Hydrocele

- Infection
- Pyocele

- Hematocele
- Atrophy of testis
- Infertility(rare)
- Hernia of hydrocele sac (rare)
- Rupture & calcifications

EPIDIDYMAL CYST

- Fluid filled swellings connected with epididymis
- If fluid is clear,it is called epididymal cyst
- If fluid is grey opaque,contains few spermatozoa,called spermatocoele
- Symptoms-over age of 40 yrs,painless slowly growing scrotal swelling,often multiple bilateral,doesnot affect fertility

Examination

- Scrotal swelling which you can get above
- Testis palpable separate from the lesion
- Usually smooth and lobulated, fluctuant,nontender, Lies above & slightly behind the testis. The cyst transilluminates if contains clear fluid. The transilluminated appearance of the cyst is classically described as a “Chinese Lantern”
- Rx : None unless large, surgical excision can be done, and that may compromise the fertility of the testis.

SPERMATOCELE

It is a retention cyst due to obstruction of one of the vasa efferentia. The fluid inside is pearly white and contains dead spermatozoa

Clinical picture

- A scrotal swelling which has the following characteristics:
- Painless, rounded or oval in shape and soft or cystic in consistency.
- Small in size and unilateral. +ve transillumination.
- At the upper pole of the testis, separated from it by a groove,
- Described as the third testis.
- Management: Excision is the best treatment if it cause symptoms.

TESTICULAR CARCINOMA

- The commonest malignancy in young men(<35 yrs). Seminoma 30 to 40 yrs Teratoma 20 to 30 yrs. 90% arise from germ cells and are either seminomas or teratomas. 10% are lymphomas, sertoli cell tumours or leyding cell tumours.
- Excellent prognosis if lymph nodes are not involved.
- Yolk Sac Tumor is most common tumor of infants & children.
- Adenomatoid tumors are the most common tumor of paratesticular tumor. 100 % benign.
- No tumor marker for CIS.

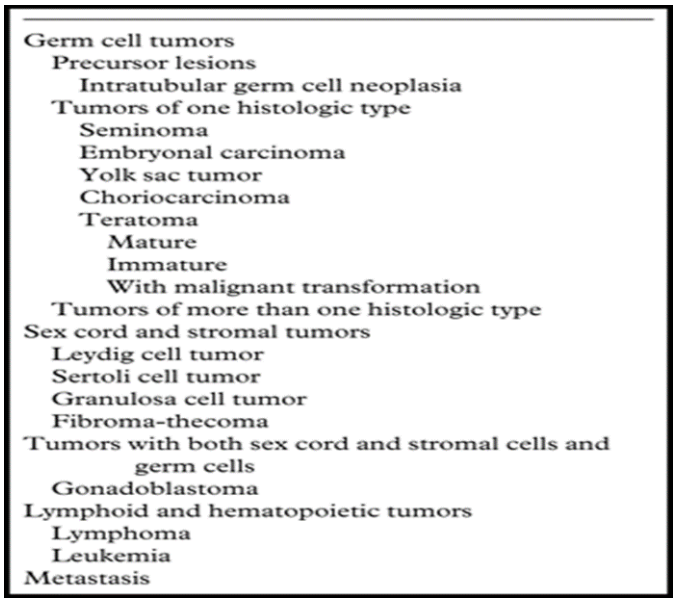
Risk factors for testicular cancer

- History of cryptorchidism
- Klinefelter syndrome
- Testicular cancer in first-grade relatives
- Contralateral tumour
- Testicular intraepithelial neoplasia or infertility
- Testicular atrophy

Symptoms & Signs

- Painless scrotal swelling.
- Chance discovery.
- Testis feels “heavier”.
- Pain in approximately 10% of cases.
- Scrotal swelling which you can get above.
- Loss of testicular sensation.(syphillis,leprosy,carcinoma)
- The lump is craggy & does not transilluminate.
- May be associated with 2ry hydrocele.
- May have palpable liver due to metastases.
- Palpable supraclavicular L.N.
- Respiratory symptoms(cough, hemoptysis).
- Retro peritoneal mass.
- Gynecomastia

Classification of testicular tumours



Patterns of Spread

Metastases can spread by both lymphatic and hematogenous routes. Direct extension through the tunica albuginea with involvement of the scrotal skin is a rare and late finding . Most germ cell tumors spread first via the lymphatics rather than hematogenously. A notable exception is choriocarcinoma, which has a proclivity for early hematogenous spread. Rt sided tumor to interaortocaval & left to paraortic. Spread caudocranial & right to left. Inguinal involvement may occur in scrotal involvement

Testicular Carcinoma- Workup

- USG of Scrotum- Hypoechoic lesions may be noted.
- CT scan/MRI of abdomen and pelvis to assess for metastasis and lymphadenopathy
- Tumor markers
- Tissue diagnosis- high inguinal orchidectomy (diagnostic & therapeutic) – Chevassu maneuver
- Trans-scrotal biopsy – contraindicated

Tumour markers in Testicular carcinoma

- AFP : Normal value < 16 ngm/ml; Half life 5 to 7 days;
  Raised in Pure embryonal Ca, Terato Ca, Yolk sac tumor, Mixed tumor
  REMEMBER: AFP Not raised is Pure Choriocarcinoma or Pure Seminoma

- BetaHCG: Normal value < 5 IU/ml; Half life 24 to 36 hrs;
  Raised in Chorio carcinoma → 100%, Embryonal carcinoma → 60%, Terato carcinoma → 55%, Yolk sac tumor→ 25%, Seminomas → 7%

- LDH: Normal value 105 to 333 IU/ L; Half life 1 day
  Not diagnostic, It is a prognostic marker, correlates tumor burden.
- PLAP –Advanced disease,seminoma
- GGTP -35% seminoma

10 to 15% of patients with NSGCT have normal markers.

Points to remember

- Serum tumour markers : prognostic factors used in diagnosis and staging (LDH).
- The lack of an increase does not exclude testicular cancer
- LDH levels are elevated in 80% of patients with advanced testicular cancer, therefore should always be measured in advanced cancer
- Tumour markers must be reevaluated after orchidectomy to determine half-life kinetics.
- The *persistence* of elevated serum tumour markers *3 wk after orchidectomy may* indicate *the presence of disease*, whereas its *normalisation does not indicate absence* of tumour.
- Tumourmarkers should be assessed until they are normal, as long as they follow their half-life kinetics and no metastases
- During chemotherapy, the markers should decline; persistence has an adverse prognostic value.

Management

The most commonly used chemotherapeutic regimen: EBP (etoposide, bleomycin, cisplatin).The prognosis of seminomas is excellent due to its exquisite sensitivity to radiation!

Organ-preserving surgery
Synchronous bilateral testicular tumours, metachronous contralateral tumours, or in a tumour in a solitary testis with normal preoperative testosterone levels, provided tumour volume is <30% of testicular volume
Radiotherapy may be delayed in fertile patients who wish to father children. Options must be carefully discussed with the patient.

Seminoma –PLAP,CD 117+, KERATIN,CD 30 –.

- Stage 1 Orchiedectomy+RT(25 Gy to paraaortic) / CT(single agent Carboplatin)/surveillance (T<6cm,HCG N,no vascular invasion)
- Stage 2 (N1 N2) orchiedectomy+RT(abdominopelvic)
- Stage 2 (N 3), Stage 3 -cisplatin based CT +follow

Spermatocytic seminoma -no adjuvant therapy

NSGCT-Radioresistant

- Stage 1modified RPLND +/- 2CYCLES BEP / Primary CT –BEP 3cycles/Surveillance
- Stage 2a/2b B/L RPLND +/- 2CYCLES BEP / Primary CT –BEP 3cycles
- STAGE 2C,STAGE 3
- Good risk Primary CT –BEP 3cycles+follow
- Poor risk –High Dose CT & ABMT

VARICOCELE

Varicocele is an enlarged,tortuous spermatic vein above the testis. Pampiniform plexus of veins (15 – 20) draining the testis and epididymis makes the major bulk of the spermatic cord. As they ascend, the number is reduced to 12 and on reaching the superficial inguinal ring they unite to form 4 veins. At the level of deep ring they are 2 in number and in retroperitoneum, it forms single testicular vein.

WHO concluded that varicoceles are clearly associated with impairment of testicular function & infertility. Most surgically correctable cause of male infertility

- 15 % of the normal male population.
- 40 % of patients with male infertility.
- 70 % of patients with secondary infertility

Etiology

1. Idiopathic/Primary – due to incompetency of valves. 98% occur on the left side
2. Secondary
   - Pelvic or abdominal mass.
   - Lt renal cell carcinoma with tumor thrombus in left renal vein.
   - Retroperitoneal fibrosis or adhesions

Almost always on left side. Why?

- Left testicular vein drains into lt renal vein at a right angle where rt testicular vein drains into ivc at an angle, precluding reflux of venous blood.
- Left testicular vein is longer than right testicular vein
- A loaded sigmoid colon compressing left testicular vein
- Absence of venous valve are more common on left side
- Nut cracker phenomenon –left renal vein may compressed b/w sma &aorta

Clinical examination

- Bag of worms
- Large varicocele may cause persistent, aching discomfort.(chronic orchialgia)
- Typically decrease in size in supine position
- There may be raised scrotal temperature.
- Bow sign- hold varicocele b/w thumb and fingers, patient is asked to bow- reduced in size.
- Sudden onset of varicocele, right sided or a varicocele that does not reduce in size in supine position should be suspected of having a retroperitoneal neoplasm-should undergo USG or CT

Grading

- Grade 1 palpable only during the Valsalva maneuver
- Grade 2 palpable with the patient in the standing position

- Grade 3 visible through the scrotal skin.

USG: Presence of multiple veins with at least one larger than 3 mm in diameter & reversal of blood flow with valsave is indicative of subclinical varicocele whereas diameter of more than 3.5 mm is more predictive of clinical varicocele.

Table 4 – TNM classification for testicular cancer

	pT	Primary tumour*
	pTX	Primary tumour cannot be assessed
	pT0	No evidence of primary tumour (eg, histologic scar in testis)
	pTis	Intratubular germ cell neoplasia (testicular intraepithelial neoplasia)
	pT1	Tumour limited to testis and epididymis without vascular/lymphatic invasion: Tumour may invade tunica albuginea but not tunica vaginalis
	pT2	Tumour limited to testis and epididymis with vascular/lymphatic invasion or tumour extending through tunica albuginea with involvement of tunica vaginalis
	pT3	Tumour invades spermatic cord with or without vascular/lymphatic invasion
	pT4	Tumour invades scrotum with or without vascular/lymphatic invasion
N – Regional lymph nodes clinical		
	NX	Regional lymph nodes cannot be assessed
	N0	No regional lymph node metastasis
	N1	Metastasis with a lymph node mass ≤2 cm in greatest dimension or multiple lymph nodes; none >2 cm in greatest dimension
	N2	Metastasis with a lymph node mass >2 cm but ≤5 cm in greatest dimension or multiple lymph nodes; any one mass >2 cm but ≤5 cm in greatest dimension
	N3	Metastasis with a lymph node mass >5 cm in greatest dimension
pN – Pathologic regional lymph nodes		
	pNX	Regional lymph nodes cannot be assessed
	pN0	No regional lymph node metastasis
	pN1	Metastasis with a lymph node mass ≤2 cm in greatest dimension and ≤5 positive nodes; none >2 cm in greatest dimension
	pN2	Metastasis with a lymph node mass >2 cm but <5 cm in greatest dimension; or >5 nodes positive, none >5 cm; or evidence of extranodal extension of tumour
	pN3	Metastasis with a lymph node mass >5 cm in greatest dimension
M – Distant metastasis		
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
		M1a Nonregional lymph node(s) or lung
		M1b Other sites
pM – Pathologic distant metastasis		
	MX	Distant metastasis cannot be assessed
	M0	No distant metastasis
	M1	Distant metastasis
		M1a Nonregional lymph node(s) or lung
		M1b Other sites
S – Serum tumour markers		
Sx		Serum markers studies not available or not performed
S0		Serum marker study levels within normal limits

	LDH, U/l	hCG, mIU/ml	AFP, ng/ml
S1	<1.5 × N and	<5000 and	<1000
S2	1.5–10 × N or	5000–50,000 or	1000–10,000
S3	>10 × N or	>50,000 or	>10,000

LDH = lactate dehydrogenase; N = upper limit of normal for the LDH assay; hCG = human gonadotrophin; AFP = α-fetoprotein.
* Except for pTis and pT4, where radical orchidectomy is not always necessary for classification purposes, the extent of the primary tumour is classified after radical orchidectomy; see pT. In other circumstances, TX is used if no radical orchidectomy has been performed.

Venography may be used to both document recurrence after repair &embolize the persistent veins.

Toxic effect of varicocele may be manifested as testicular growth failure, semen abnormalities,leyding cell dysfunction & histologic changes. It causes asthenospermia, teratospermia, oligospermia, oligoasthenoteratospermia.

Larger the varicocele, the more likely it is associated with impairment in seman quality. Repair of larger varicocele results in significantly greater improvement in seman quality than does repair of small varicocele. Subclinical varicocele have no impact on infertility and the repair of subclinical varicocele does not improve infertility

Increase in blood flow causes increase in testicular temperature, resulting in impairment of spermatogenesis Bilateral effect of unilateral varicocele Smoking in presence of varicocele has a greater adverse effect.

Indication of treatment

1. Adolescent men with varicocele should be considered candidate for varicocele repair if there is a reduction in volume of testis. Testis size should be approximately equal bilaterally, with the differential normally not greater than2 ml or 20%of volume.
   Testis size can be measured by Prader orchidometer

2. An infertile adult man with a varicocele should be considered a candidate for a varicocele repair if all of the following four conditions are met:
   i) The couple has known infertility
   ii) Female partner has normal fertility or potential treatable cause of infertility
   iii) Varicocele is palpable on examination or confirmed on USG
   iv) Abnormal semen analysis

Surgical approaches

- Retroperitoneal (palomo)-high recurrence (11-15%)
- Inguinal
- Laparoscopic
- Percutaneous embolization –useful in recurrent or persistent varicocele
- microscopic inguinal –significant reduction in postoperative complications eg. Testicular artery injury, hydrocele formation, recurrence

Complications of surgery

1. hydrocele- due to lymphatic obstruction, most common with conventional inguinal
2. recurrence- most common with palomo ,least with microsurgical
3. testicular artery injury

Surgical repair of Varicocele has shown to decrease further damage to testicular function, improve spermatogenesis, improve Leydig cell function, improvement of seminal parameters in 70% of patients after varicocele repair and improvement in motility is most common (70%)

TESTICULAR TORSION

Torsion of the testis (spermatic cord) → strangulation of gonadal blood supply → testicular necrosis and atrophy. The actual torsion is usually of the spermatic cord.

- Window of opportunity to salvage - within 6 hours!
- Acute scrotal swelling in children indicates torsion of the testis until proven otherwise.

Possible mechanism; it is associated with:

1. UDT
2. High investment of tunica vaginalis with a horizontal lie of testis (bell clapper deformity)
3. Epididymis& testis are separated by a mesorchium, & twisting occurs at the mesorchium.
4. Active cremasteric reflex

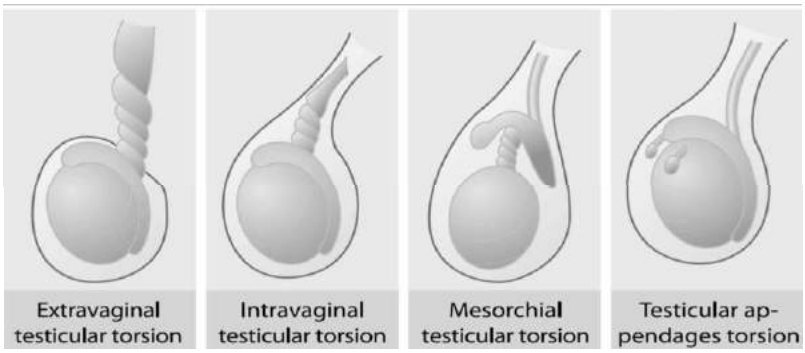
Pathophysiology

- Sexual activity,masturbation,trauma,exercise,cold weather
- Violent contraction of abdominal muscles → contraction of cremaster → favors rotation around vertical axis
- Degrees of twisting determines the salvagability of the testis
- Torsion of 3-4 turns : irreversible changes (necrosis) within 2 hours
- Torsion of 1 turn (360º) : well tolerated for 12 hours (20% viability) necrosis after 24 hours
- Torsion of 90º : well tolerated for 7 days

Types of torsion

1. Extravaginal (5%)
   Testis rotates freely prior to fixation of testis.
   Cord twists outside of the tunica vaginalis.
   Testicle and both layers of tunica vaginalis rotate.
   More common in neonates
2. Intravaginal (16%):
   Tunica attaches higher up on spermatic cord (Bell Clapper deformity).
   Testis freely suspended within tunica vaginalis.
   Cord twists with in the tunica vaginalis.
   Testicle and inner layer of tunica vaginalis rotate.

Most common between 12 to 18 years peak incidence at 13.



Clinical Presentation

- Sudden onset of sever, unilateral testicular pain, with swelling of the testicle.
- Most occurs during sleep. Usually no urinary symptoms or fever
- Swelling and redness of the scrotum. Pain in the groin or abdomen
- Associated nausea and vomiting
- Deming's Sign: Affected testis at higher level because of twisting.
- Prehn's sign: Elevation of the testis exaggerate the pain. Is negative.
- Palpation may show a horizontal rather than normal vertical orientation of the testicle.
- Unilateral loss of the cremasteric reflex on the side of the swelling and pain highly correlates with the presence of torsion, if present, no torsion, if absent 66% rule in torsion.
- Angel's sign- Normal testis lying horizontally.

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DDx of acute painful scrotal swelling

- Torsion of testis or appendages
- Trauma
- Infection/inflammation
- Hernia (incarcerated)

**** Radiologic techniques are helpful but may delay treatment****

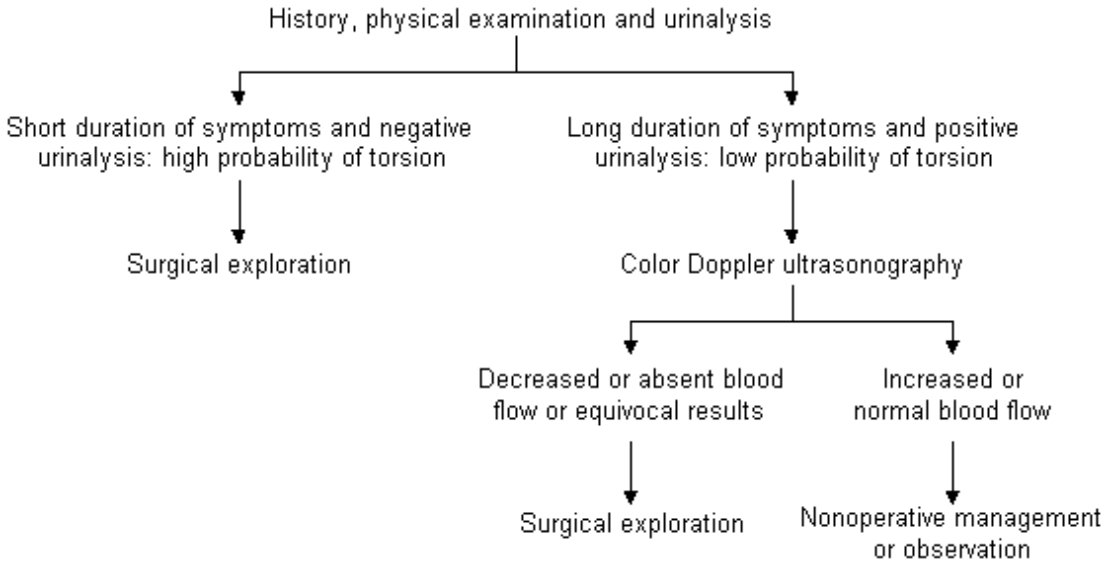
US Doppler scrotum/testis

- Sensitivity 80 - 90% Specificity 100%
- Central testicular blood flow→ Normal Testis
- Complete absence of intratesticular blood flow and normal extratesticular blood flow on color Doppler images is diagnostic, if the flow is normal in the contralateral testis.

Nuclear testicular scan/scintigraphy

- Technetium-99 (^{99m}Tc-pertechnetate) to trace testicular blood flow
- Requires 1-2 hours, 86-100% accuracy

-Technetium-99m scan will show a cold spot which represents decreased perfusion in the affected testis.



Management - surgical emergency

1. Alleviation of symptoms
2. Manual Detorsion
   As in torsion anterior surface of testis turns toward the midline – clockwise on the right and counter clockwise on the left viewed from the foot of the bed , detorsion occurs on the opposite direction.
   - Rotate testicle in medial to lateral direction "open the book"
   - relief of pain
   - return of blood supply to testicle (confirmed with US)
   - patient may not tolerate.
3. Surgical exploration
   In doubtful cases and nonavailability of Doppler USG→ Better to explore rather than unduly delay the treatment. Detorsion on affected side with Bilateral orchidopexy – to prevent future torsion
   In case of testicular necrosis-Orchidectomy + contralateral orchidopexy
4. Placement of testicular prosthesis – after 6 months of orchidectomy via inguinal incision
5. Prognosis
   - < 6 hours, 90% salvage
   - > 6 hours, 20% viability likelihood for orchidectomy
   - > 24 hours, 100% loss and atrophy

Torsion of testicular appendage

Appendix testis- mullerian duct remnant
Appendix epididymis - wolffian remnant

- Testicular discomfort, if present, is typically mild, but point tenderness may be elicited from uppermost pole of the testis near the head of the epididymis
- Torsion of the appendix testis May demonstrate hemiscrotal erythema and swelling
- A blue-dot sign, if the necrotic appendage visible through the scrotal skin, can help make the diagnosis.
- A normal cremasteric reflex is present bilaterally, and the testis is normally positioned within the scrotum..
- When diagnosis is confirmed by clinicaly or radiologicaly tt conservative
- When diagnosis in doubt or failure of cons. Tt then exploration & simple excision of twisted appendage

EPIDIDYMO-ORCHITIS

Inflammation of epididymis & Testis due to infection or trauma. Most common cause of acute scrotum (75-80%)

Acute : < 6 weeks (CDC, STD treatment guidelines)

- Young men – hx of STD exposure (Chlamydia *trachomatis, Ureoplasma urealyticum, Neisseria gonorrhea)*
- Children : UTI, urinary tract structural anomalies *(E. coli*, Streptococci, Staphylococci, Proteus*)*
- Older men : BPH, post vasectomy, post urological operative procedure/instrumentation, indwelling catheter, infectious prostatitis, TB
- Orchitis : Viral cause : Mumps (18% males), usually a/w parotid swelling, Syphilis, leprosy

Clinical Presentation

- Acute progressive onset of scrotal/ groin pain (>24hr)
- Gradual swelling, erythematous, shiny scrotum
- Febrile
- Dysuria,pyuria
- Difficulty in ambulation
- Urethral discharge
- Hx of recent instrumentation
- Cremasteric reflex is usually present
- Prehn sign positive : elevation of the scrotum may provide relief of pain.
- Palpation during early phase of the inflammatory process demonstrates tenderness limited to the epididymis.
- In the later phase, tenderness and inflammation include both epididymis and testis, and the distinction between the 2 structures may be difficult to appreciate.
- TB epididmytis due to retrograde spread, first involve globus minor(tail) then entire epididymis &testis . it involves mainly posterior aspect of scortum.
- Syphilis –involves only testis,loss of testicular sensation

Investigations

- Urethral swab and first void urine: Intracellular gram negative diplococci -gonorrhoeae and only WBC-chlamydia infection.
- Midstream urine for microscopy, culture and sensitivities.

- All patients with sexually transmitted epididymo-orchitis should be screened for other sexually transmitted infections. Sexual contacts should also be evaluated.
- Children should be evaluated with MCU, USG, cystoscopy.

Ultrasound: useful to help distinguish acute epididymitis from testicular torsion if immediately accessible but must not delay intervention or exploration if testicular torsion is suspected

USG Scrotum (sensitivity 82-100%, specificity 100%)
- Thickened Epididymis
- Reactive Hydrocele
- Thick scrotal wall

Doppler USG
- Excessive blood flow to Epididymis
- Normal testicular parenchymal blood flow

Diagnostic Criteria for Epididymitis
- Gradual onset of pain
- Dysuria, discharge, or recent instrumentation
- History of genitourinary abnormality (UTI, neurogenic bladder, hypospadias, etc.)
- Fever > 38ºC
- Tenderness and induration at epididymis
- Abnormal UFEME (>10 leucocytes visual fields/RBC)

- 3 or more findings present - definite Epididymitis
- 2 findings present - probable Epididymitis
- 1 finding present - possible Epididymitis

Management:
Can be treated conservatively with antibiotics and anti-inflammatory drugs

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