Neoplasia

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Lec.3

Objectives

1-To describe the **effects of tumors on the host**.

2-Compare between the **grading and staging** of cancers.

3-List the methods of the **cancer diagnosis**

Effects of tumors on the host:

Although malignant Cancers are more threatening to the host than benign tumors.

However, any tumor , even a benign one , may cause morbidity and mortality.

Both benign & malignant can affect the host by the followings:

1. Location of tumors (benign & malignant) & their effects on adjacent tissue:

Some tumors arise in **critical locations**

e.g. pituitary adenoma.

Although the tumor is benign, its enlargement and expansion can destroy the remaining normal pituitary and thus lead to panhypopituitarism.

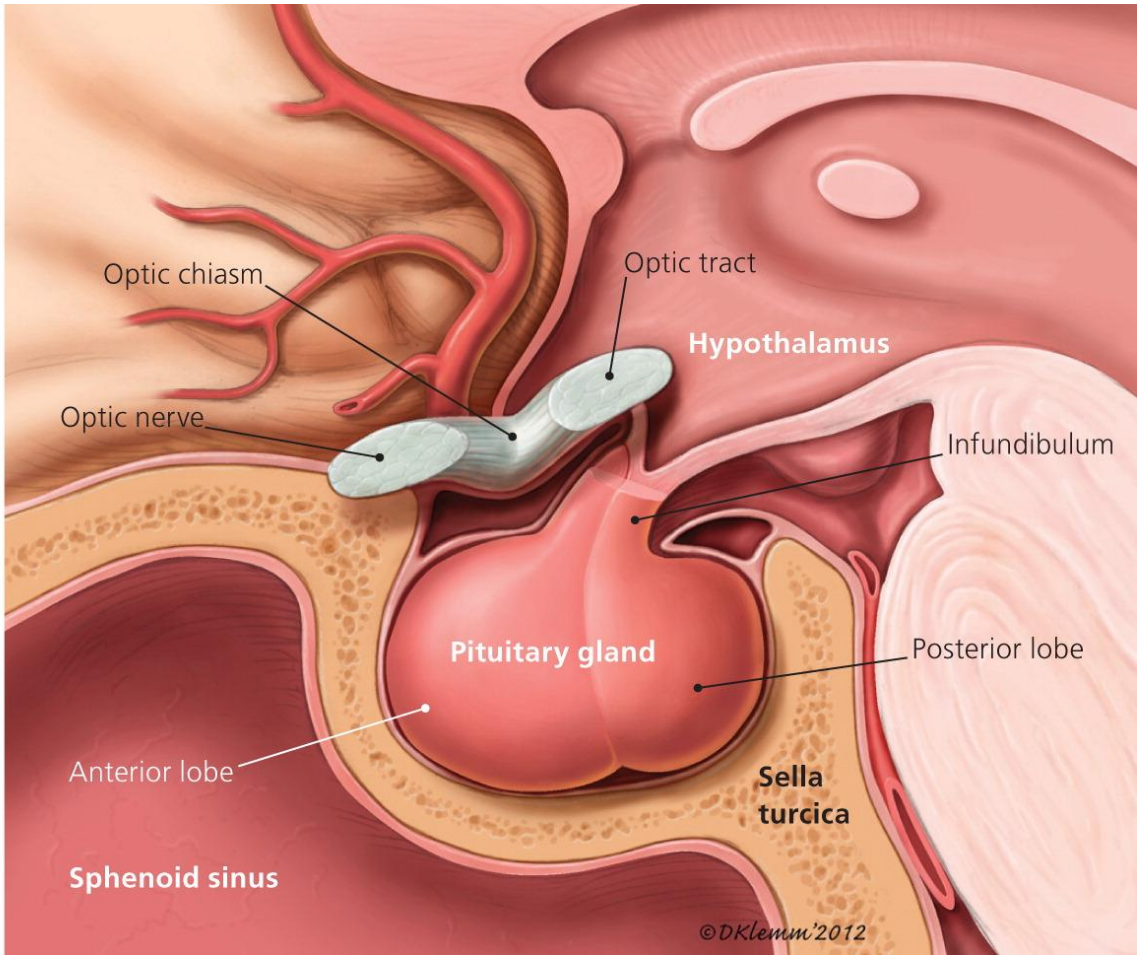
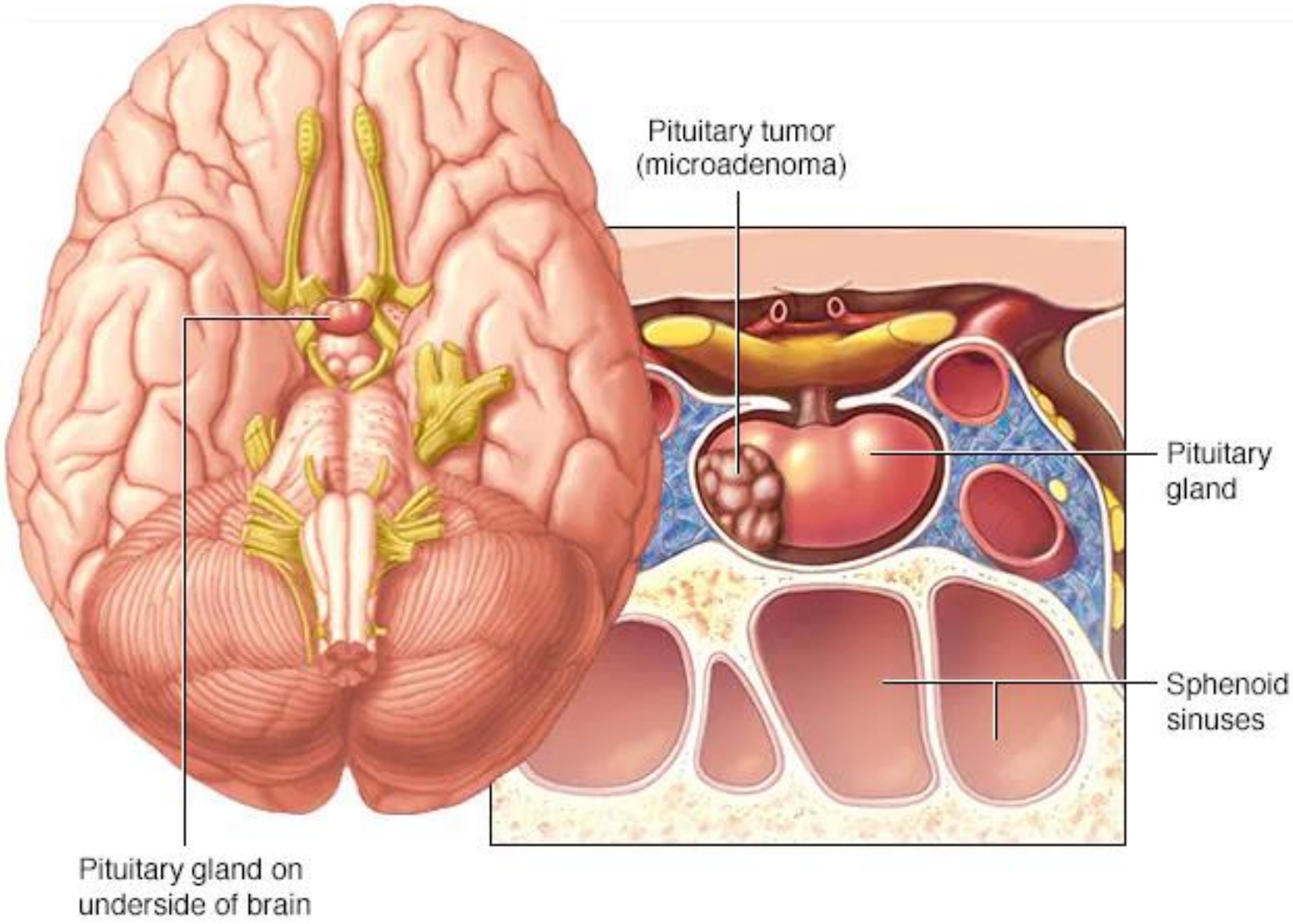
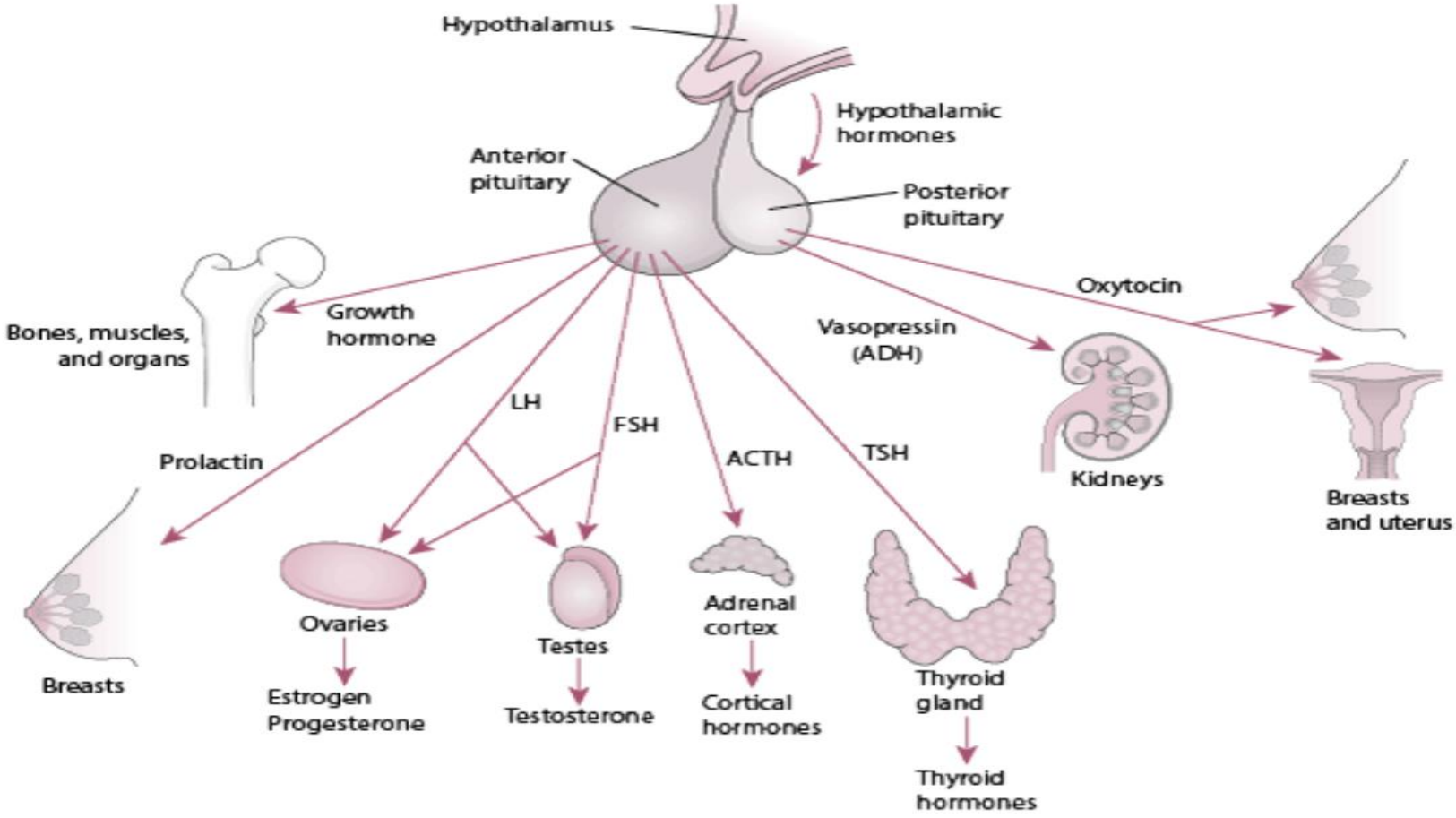


ILLUSTRATION BY DAVID KLEMM

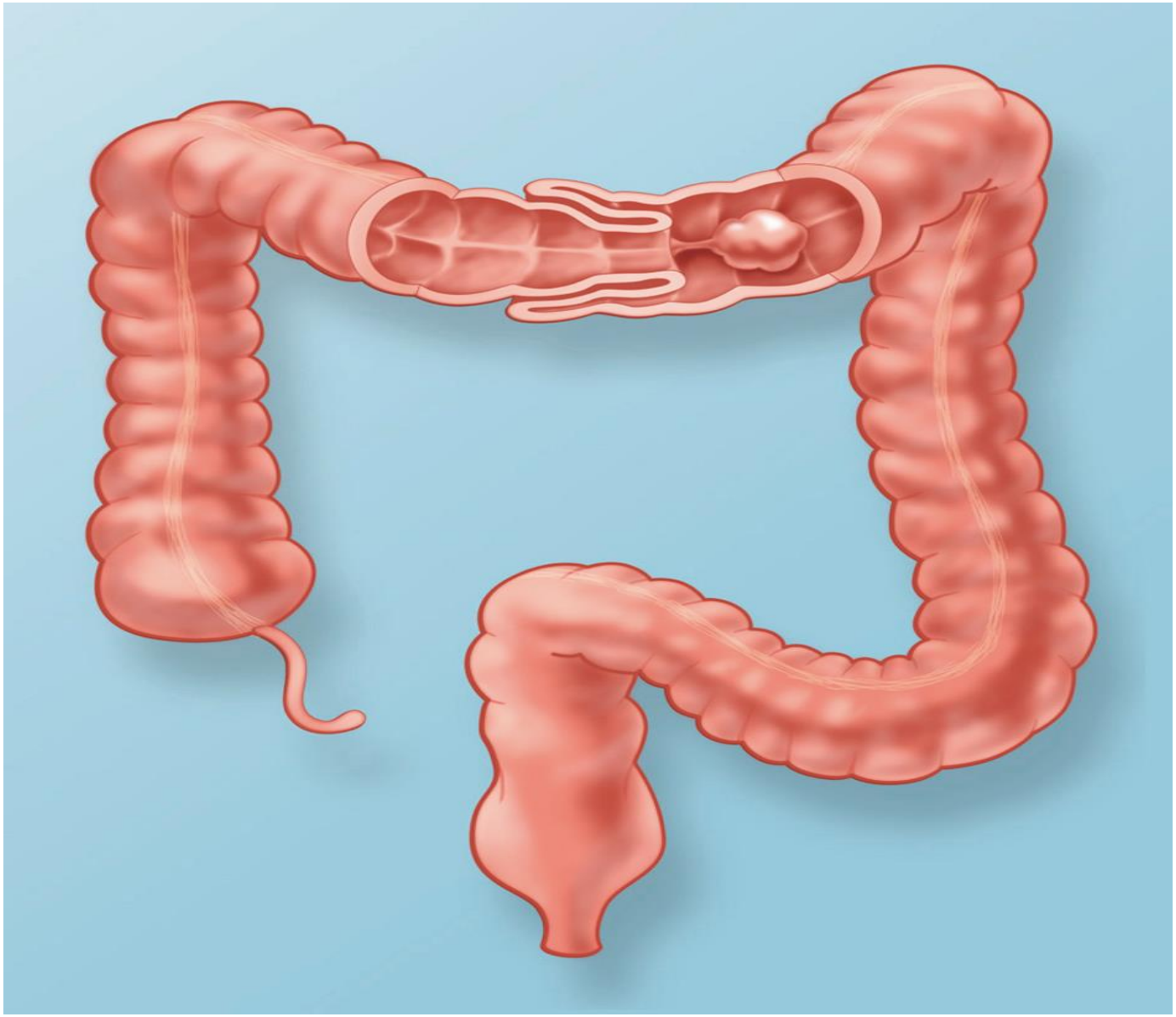


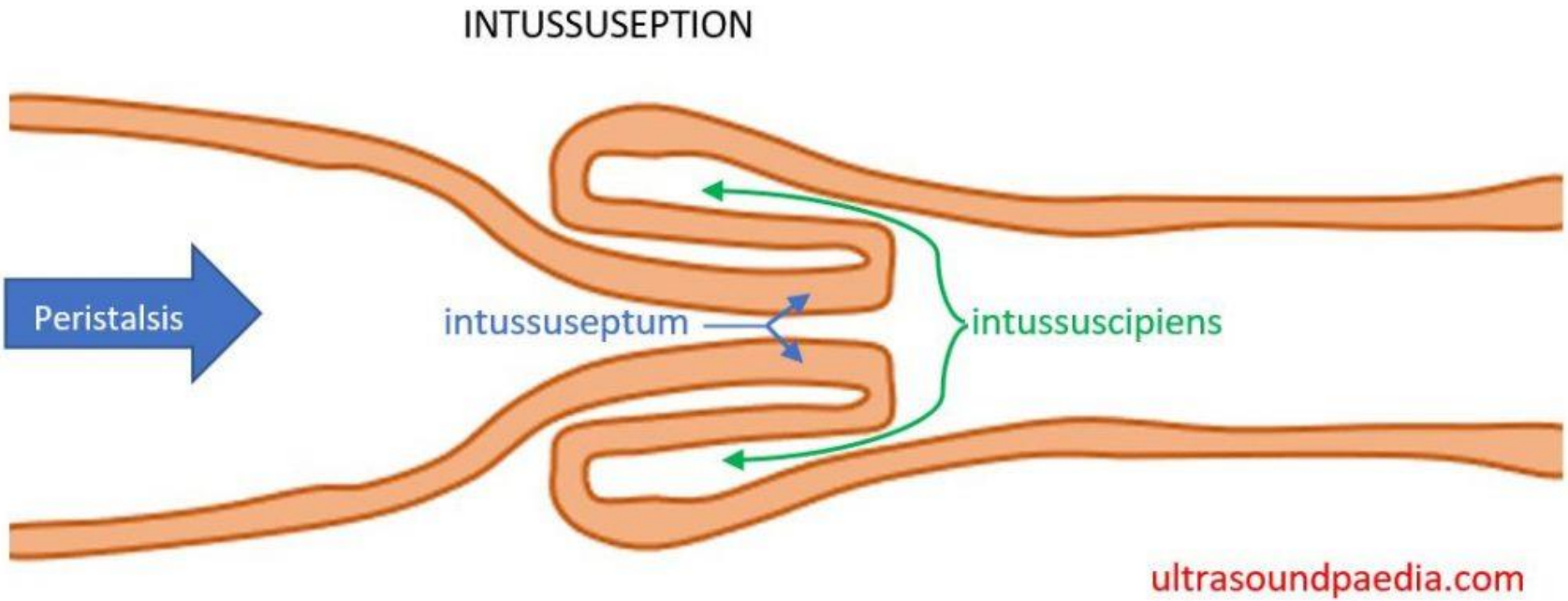

Hypothalamus
Hypothalamic hormones
Anterior pituitary
Posterior pituitary
Bones, muscles, and organs
Growth hormone
Prolactin
LH
FSH
ACTH
TSH
Vasopressin (ADH)
Oxytocin
Kidneys
Breasts and uterus
Breasts
Ovaries
Estrogen
Progesterone
Testes
Testosterone
Adrenal cortex
Cortical hormones
Thyroid gland
Thyroid hormones

Neoplasms in the **GIT** (both benign and malignant) and in any other **tubular organs**(like **urethra ureter and bile duct**), may lead to **obstructions** as they enlarge.

The following are examples of tumors can cause **outlet obstruction** of their respective organs as they enlarge:

1. Carcinoma of esophagus
2. Carcinoma of gastric pyloric antrum
3. Carcinoma of small & large intestines
4. Carcinoma of the head of pancreas, common bile duct, or duodenum leading to obstructive jaundice.
5. Sometimes, peristaltic movement telescopes the neoplasm and its affected segment into the distal adjacent segment, producing intussusception of intestine

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2. Effects on functional activity of the host:

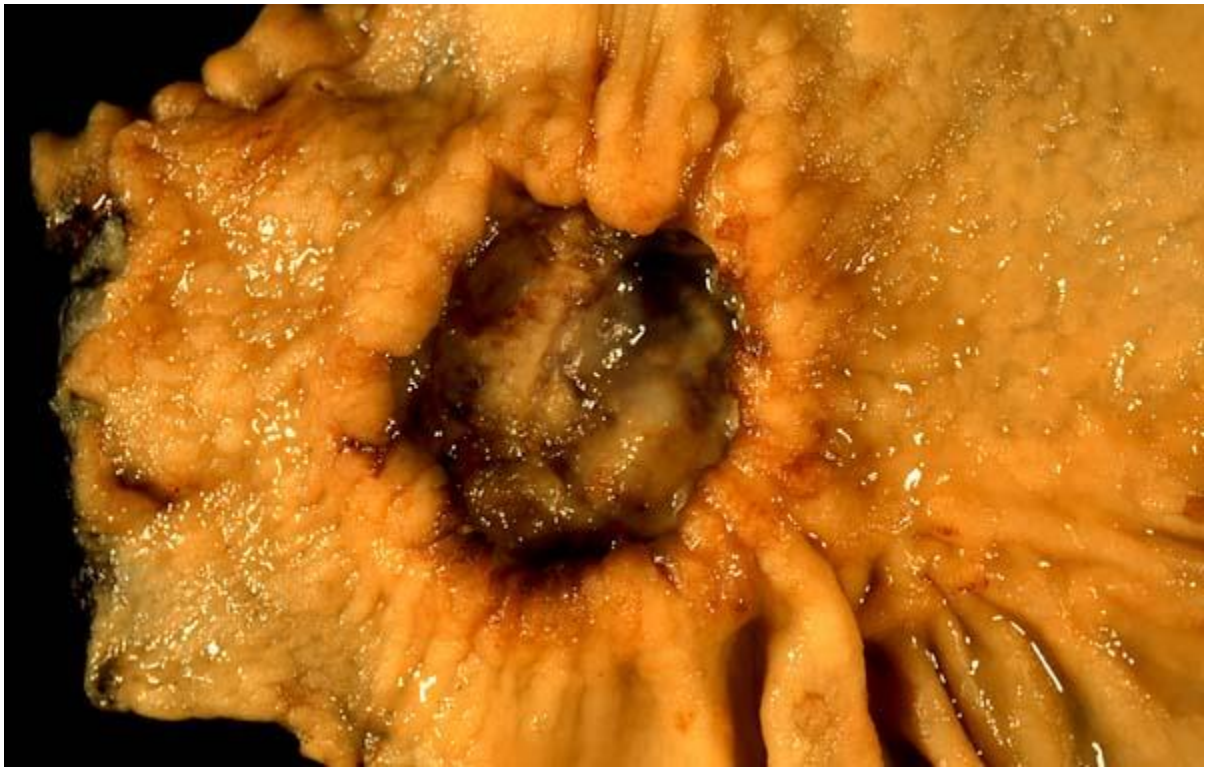
Neoplasms (both benign & well differentiated malignant tumors) arising in endocrine glands may produce manifestations by synthesizing hormones.

(poorly differentiated or undifferentiated may lose their functional activity i.e. hormone synthesis).

e.g**. adenoma & well differentiated carcinoma of adrenal gland** cause increase level of **steroid hormone** that has effects on the host.

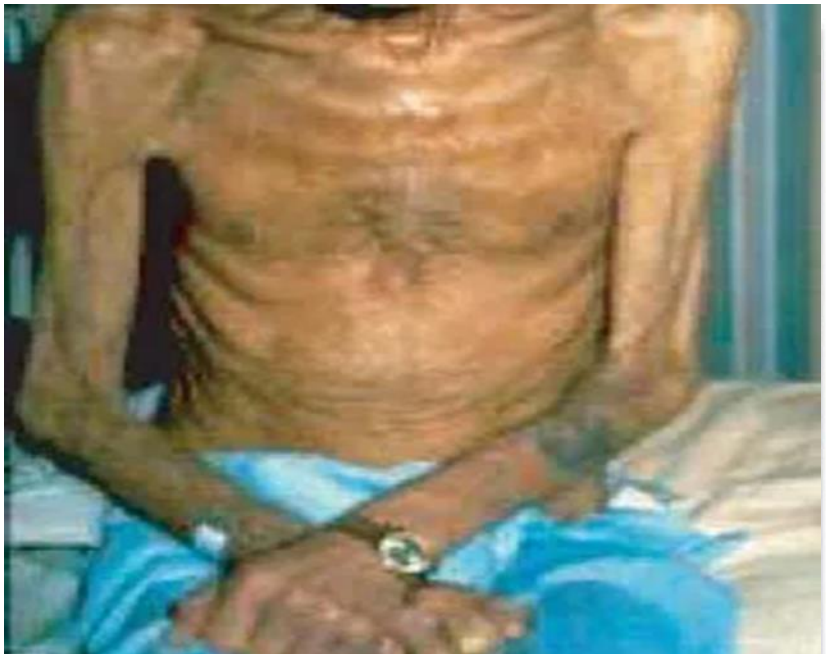
A benign **beta-cell adenoma** of the **pancreatic islets** less than 1 cm in diameter may produce sufficient insulin to cause **fatal hypoglycemia**

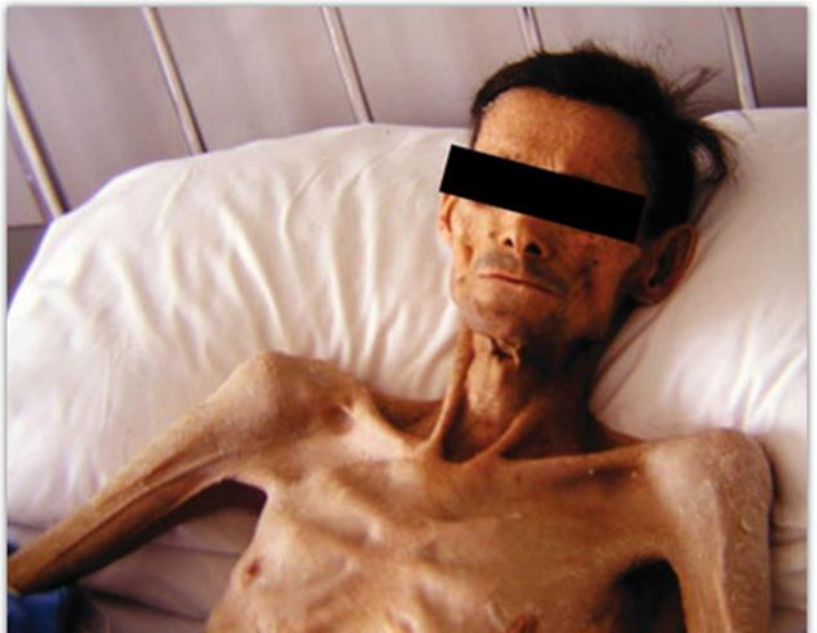
3. Producing bleeding & secondary infection, when the lesion is ulcerated through adjacent tissues (one of important cause of death in malignant tumors)
4. Many malignant tumor produce **cancer Cachexia & Paraneoplastic syndrome.**



Cancer Cachexia

Def.: It is a syndrome of progressive loss of weight accompanied by weakness, anorexia, anemia and loss of muscle mass (with or without loss of fat) that occur in about **50% of cancer patients** , most commonly in individuals with advanced **GIT, pancreatic, and lung cancers.**





It is a highly debilitating condition

It is responsible for about **30% of cancer deaths,** mortality is generally the consequence of atrophy of the diaphragm and other respiratory muscles.

There is correlation between the size & extent of spread of cancer & severity of cachexia,

e.g. small size malignant tumor dose not produce Cachexia

Pathogenesis of cancer cachexia:

It is a hypercatabolic state that cannot be explained by diminished food intake alone.

The most accepted theory : It is of multifactorial pathogenesis

Possible causes:

the action of soluble factors (cytokines)such as tumor necrosis factor (TNF) produced by the tumor cells as well as by the host inflammatory cells in response to the tumor that will lead to the following :

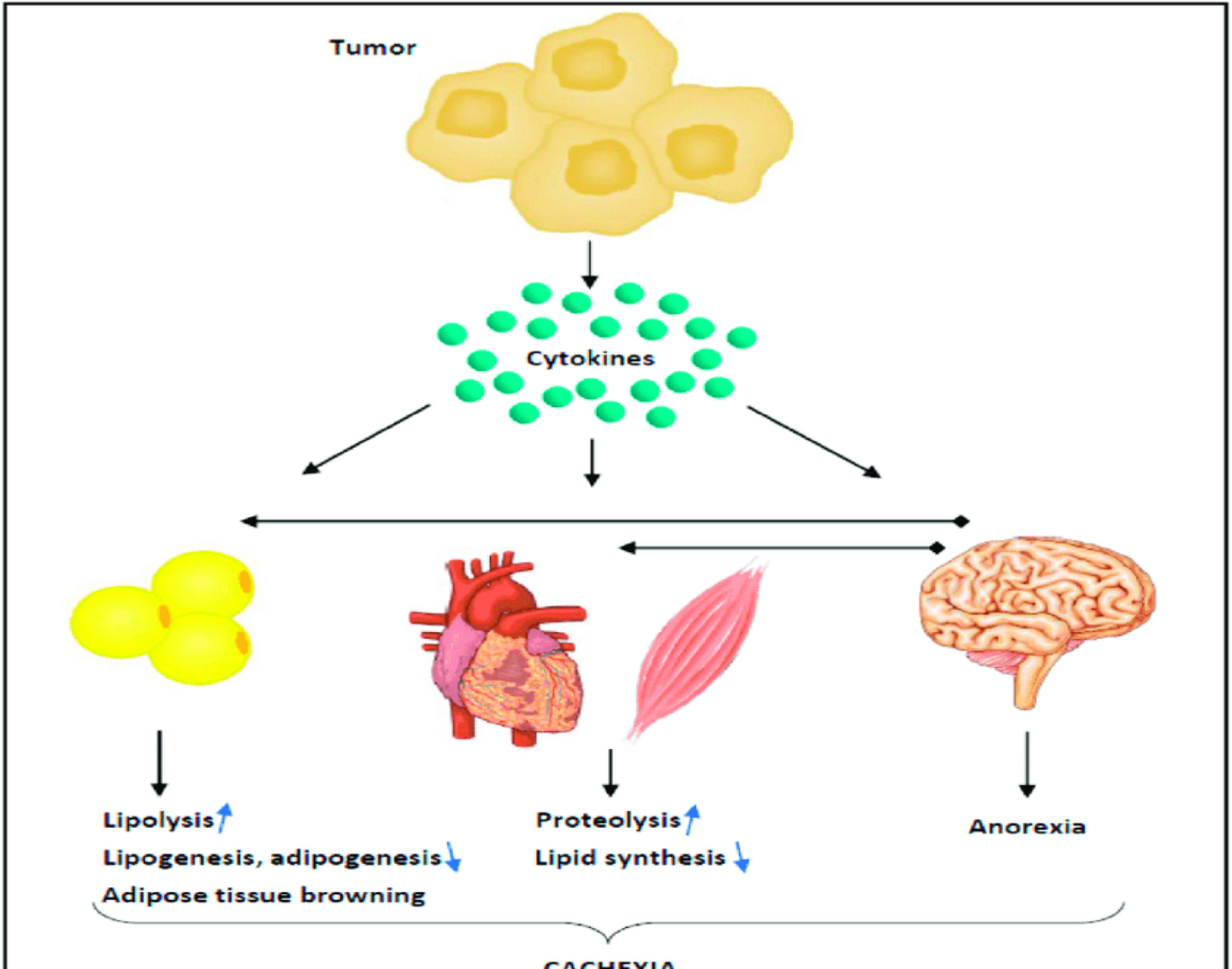
1. **Anorexia:** It is common problem in patient with cancer; even in those don't have cancer of GIT. So the cause of Anorexia is due to central cause like inhibition of taste & appetite center.

2. **Increase Basal Metabolic Rate (BMR):**

In patient with cancer there is **increase BMR** & Calorie expenditure, the exact mechanism of this change is not fully understood

3. **Protein mobilizing factor** has been detected in the serum of patient with cancer (skeletal muscle weakness).

4. **Lipolytic Factor** is thought to be the cause of Cachexia


Tumor
Cytokines
Lipolysis
Lipogenesis, adipogenesis
Adipose tissue browning
Proteolysis
Lipid synthesis
Anorexia
CACHEXIA

Cancer cachexia in Comparison to starvation

In patients with **cancer**, basal metabolic rate(**BMR**) is paradoxically i**ncreased** despite reduced food intake.

This is in contrast to starvation, where there is an adaptational lowering of metabolic rate. Furthermore, in cancer cachexia, there is equal loss of fat and muscle,

whereas in starvation the muscle mass is relatively preserved at the expense of fat stores.

Paraneoplastic syndromes:

Symptom complex other than Cachexia that occur in patient with cancer & that cannot be easily explained by local or distant spread of the tumor or by elaboration of hormones indigenous to tissue of origin of tumor.

- They appear in 10 – 15% of patient with cancer .
- **it is important to recognize them for many reasons, include:**

1. They may represent early manifestation of occult cancer.
2. In the affected patient, may represent significant problems & may be lethal.
3. they may mimic metastatic cancer and this affect on the managment.

Clinical Syndromes	Major Forms of Underlying Cancer	Causal Mechanisms
Endocrinopathies		
Cushing syndrome	Small cell cancer of the lung	ACTH or ACTH-like substance
Syndrome of inappropriate ADH secretion	Small cell carcinoma of lung	ADH
Hypercalcemia	Squamous cell carcinoma of lung	PTHrP, TGF-α, vitamin D
Carcinoid syndrome	Bronchial carcinoid	Serotonin, bradykinin
Polycythemia	Renal carcinoma	Erythropoietin
Nerve and Muscle Syndromes		
Disorders of the central and peripheral nervous systems	Small cell carcinoma of lung	Immunologic (?), toxic (?)
Myasthenia gravis	Thymoma	Immunologic (?)
Osseous, Articular, and Soft Tissue Changes		
Hypertrophic osteoarthropathy and clubbing of the fingers	Carcinoma of lung	Unknown
Vascular and Hematologic Changes		
Venous thrombosis (Trousseau phenomenon)	Pancreatic carcinoma	Hypercoagulability
Nonbacterial thrombotic endocarditis	Advanced cancers	Hypercoagulability

Hypertrophic Osteoarthropathy

- HPOA has only been reported in 1–10% of cases of Lung carcinomas
- Among these, HPOA is most commonly found with Non–small cell lung carcinoma

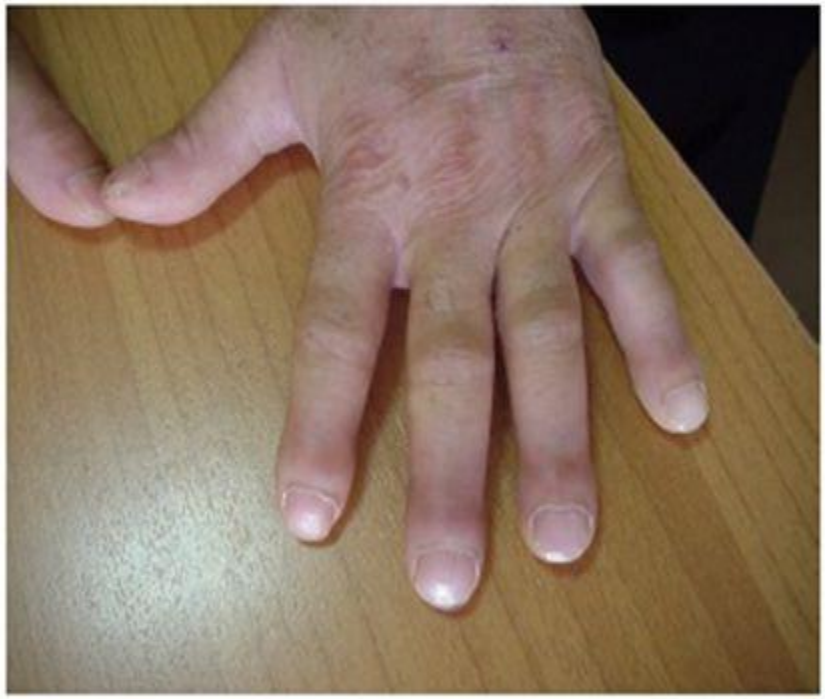
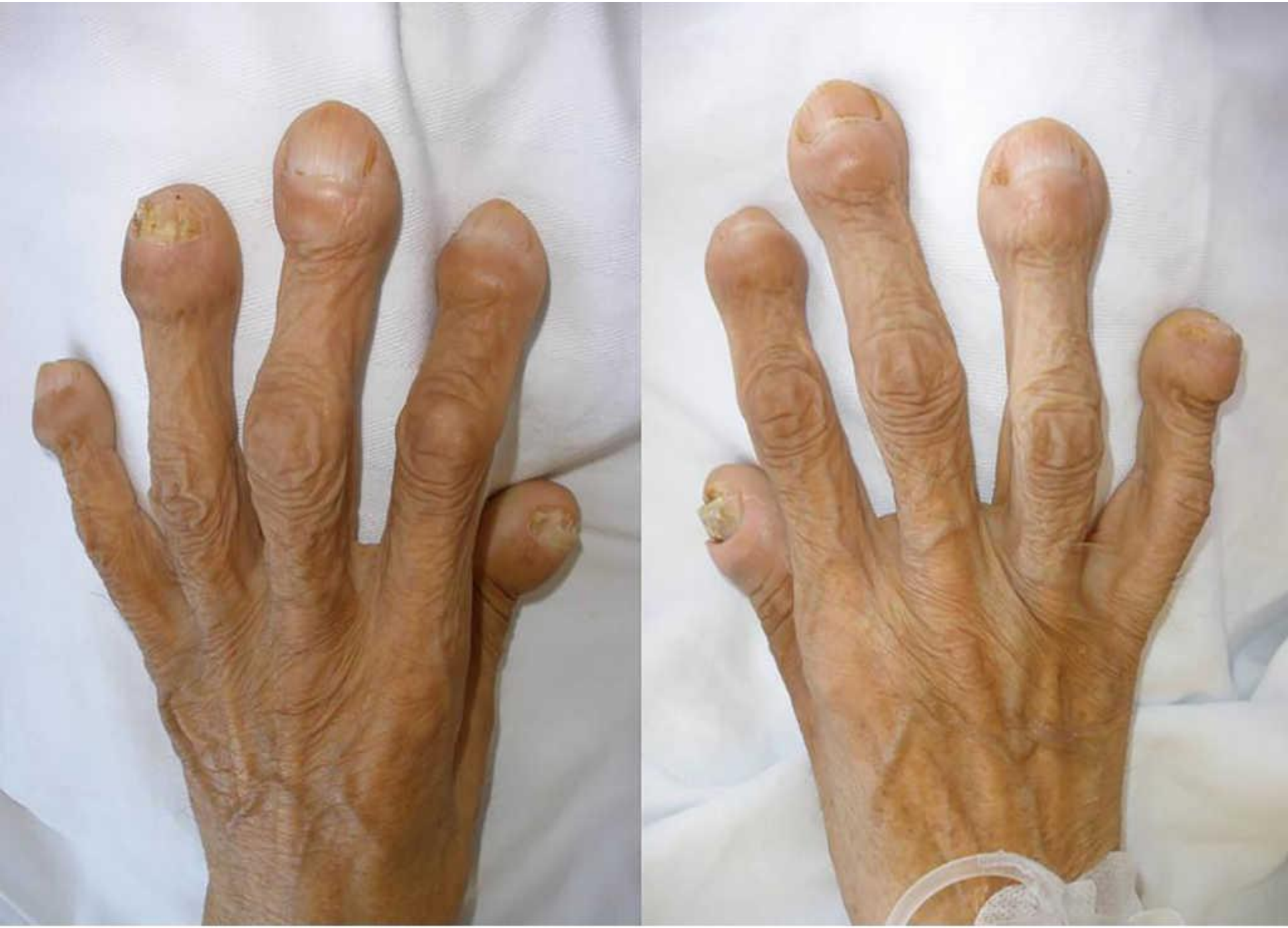


Figure 1
Finger clubbing.

Sridhar KS, Lobo CF, Altman RD. Digital clubbing and lung cancer. *Chest*. Dec 1998;114(6):1535-7.



Other Effects of tumors on the host:

Fever: this is likely to be due to **pyrogen** release (e.g. Hodgkin's lymphoma, renal cell carcinoma, osteosarcoma).

Nephrotic syndrome: (proteinuria, hypoproteinemia and edema): this is seen in various cancers.

Amyloidosis: is sometimes associated with multiple myeloma and renal cell carcinoma.

Grading and Staging of cancer:

Methods to quantify the probable clinical aggressiveness of a given neoplasm and its apparent extent and spread.

The grading of a cancer :

degree of differentiation of the tumor &in some cancers, the **number of mitoses** or **architectural features**.

it indicate the **aggressivenss** or **level of malignancy** based on the cytologic differentiation of tumor cells and the number of mitoses within the tumor.

based on the idea that **behavior and differentiation are related**, (poorly differentiated tumors having more aggressive behavior).

Grading schemes have evolved for each type of malignancy and generally range: from two **(low grade and high grade)** to **four categories**.

The cancer may be classified as grade I, II, III, or IV in order of increasing anaplasia.

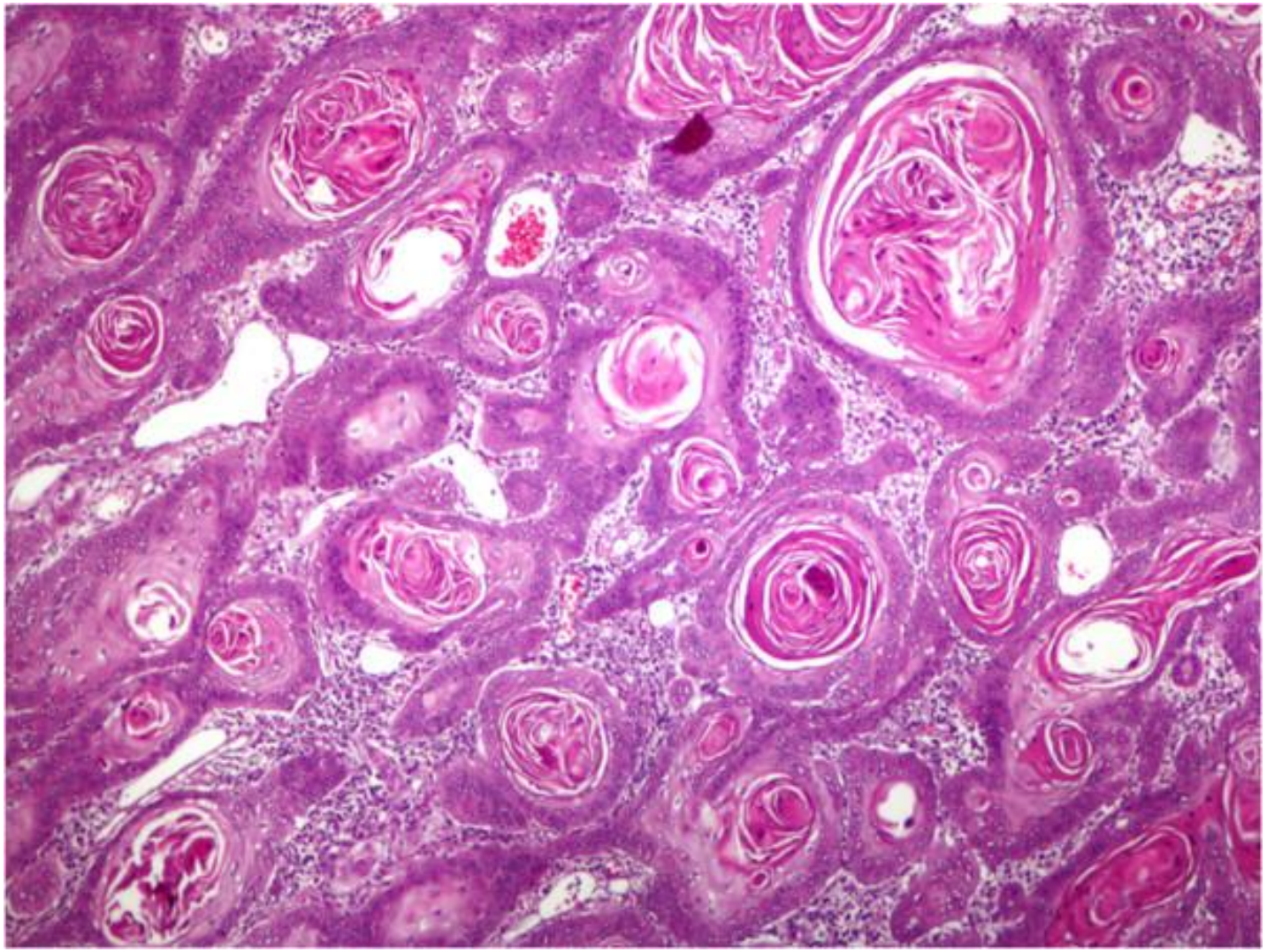
(***Well differentiated, Moderate differentiated, poor differentiated cancer).***

G1: (Well differentiated)

* Include tumors that resemble tissue of origin as having glands in adenocarcinoma.

* Few mitosis .

* Little variation in the size &shape of tumor cells.



G II: (Moderately differentiated)

* Tumor that have less resemblance to the tissue of origin.

* Increase mitosis.

* Increase pleomorphism.

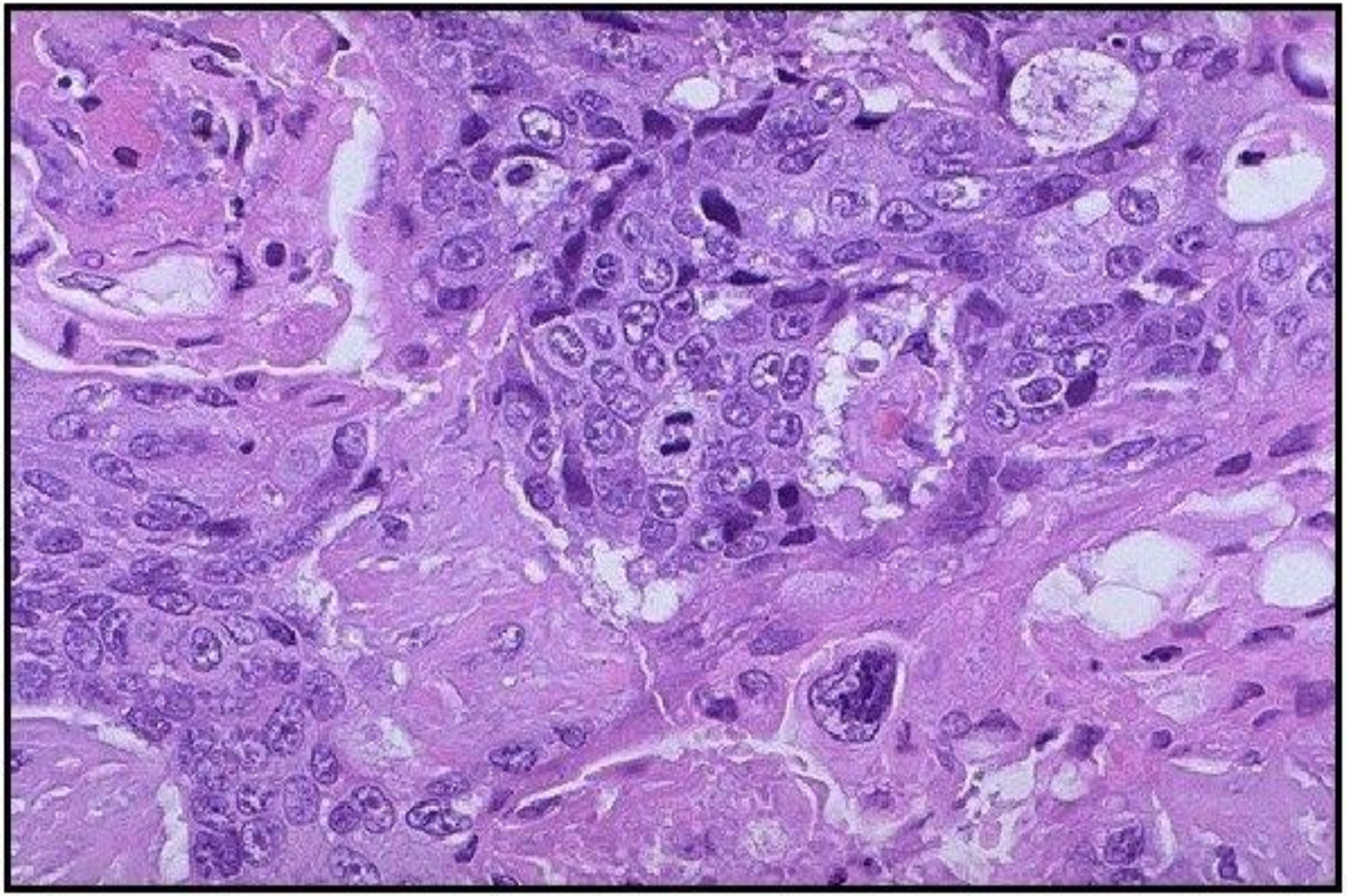
G III : (Poorly differentiated)

* Tumors that does not resemble the tissue of origin.

* Numerous mitosis.

- Very prominent pleomorphism
- **G IV: undifferetiated**

Squamous Cell Carcinoma - HPF



A mitotic figure is seen here in the center, surrounded by cells of a poorly differentiated squamous cell carcinoma, with pleomorphic cells that have minimal pink keratinization in their cytoplasm. In general, mitoses are more likely to be seen in malignant

***Staging* of cancers**

Is the **degree of clinical extent of the malignant tumor spread**.

In solid cancers: is based on the:

size of the primary lesion,

its extent of spread to regional lymph nodes, and the presence or absence of metastases.

This assessment is usually based on clinical and radiographic examination (computed tomography and magnetic resonance imaging) and in some cases surgical exploration (Team work)

Staging is of greater clinical value than grading.

The major staging system currently in use is the American Joint Committee on Cancer Staging (AJCC).

This system uses a classification called the **TNM system**

T: for primary tumor,

N: for regional lymph node involvement,

M: for metastases.

TNM staging varies for specific forms of cancer, but there are general principles.

The primary lesion is characterized as

T1, T2, T3, and T4 describe the **increasing size** of the primary lesion; Some times the T refers to the **depth of invasion (not the size**) as in

GIT carcinomas.

T0(or Tis) is used to indicate an in situ lesion.

N0 would mean no nodal involvement,

N0, N1, N2, and N3 indicate progressively advancing node involvement

M0 and M1 reflect the absence or presence of distant metastases

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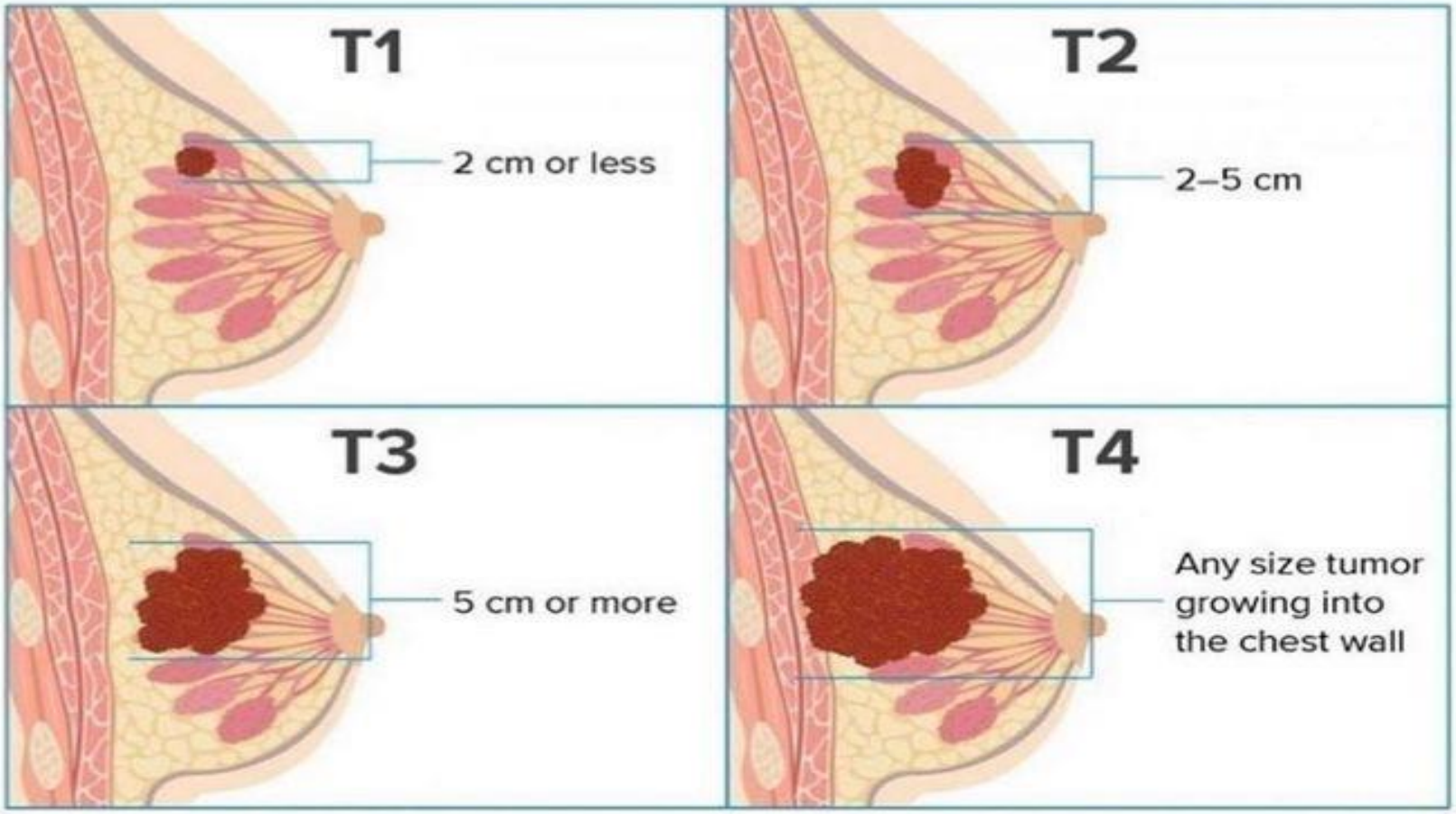
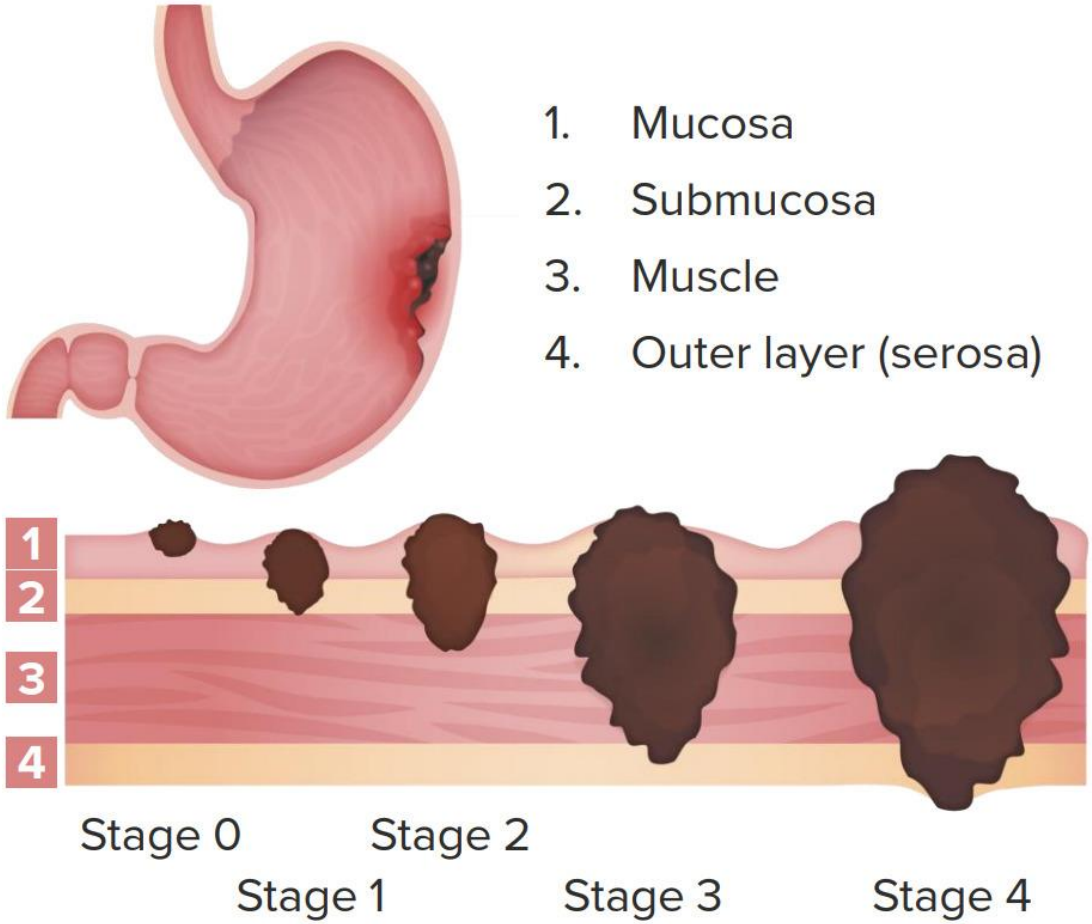
Tumor Size Chart




1. Mucosa
2. Submucosa
3. Muscle
4. Outer layer (serosa)
1
2
3
4
Stage 0
Stage 1
Stage 2
Stage 3
Stage 4

In the AJC method,

the cancers are divided into stages 0 to IV, incorporating the size of primary lesions and the presence of nodal spread and of distant metastases.

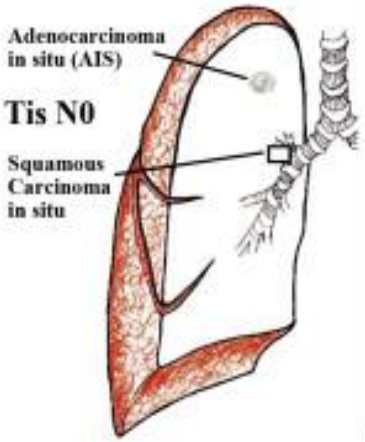
Lung Cancer Stage Classification (8th Edition)

General Note:
All Stage I-III tumors are M0

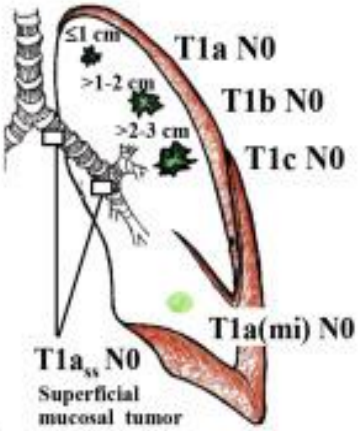
Tx, Nx should be used only if no information at all is available about T or N stage (including no clinical staging information).

Mx is not allowed, because symptoms and physical exam information is always available.

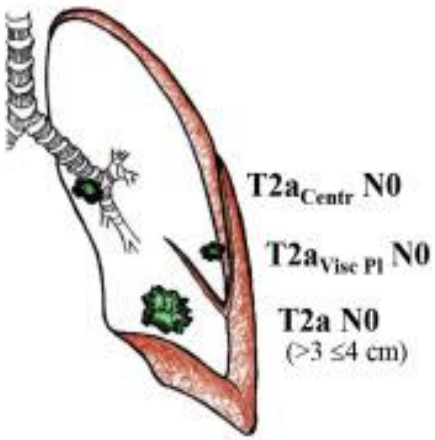
Stage 0



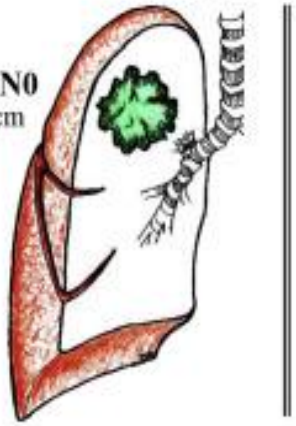
Stage IA

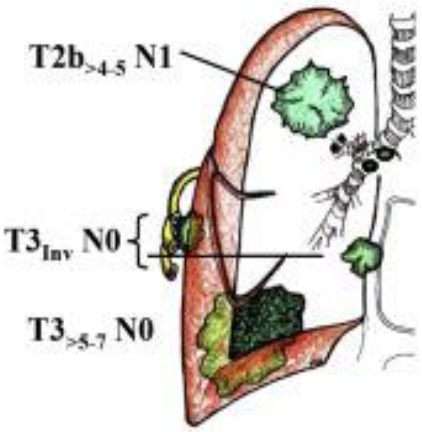


Stage IB

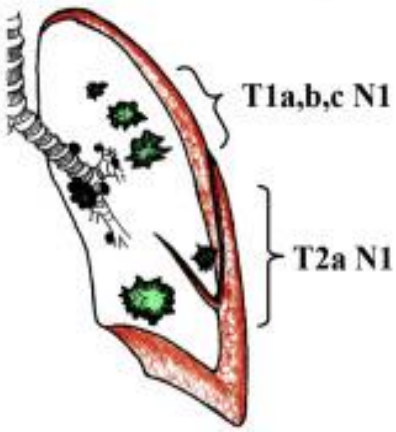


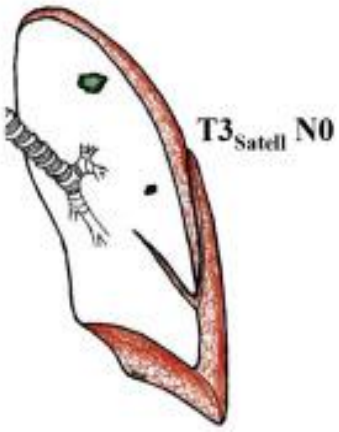
Stage IIA





Stage IIB





Staging of neoplastic diseases is of great importance in:

1-predicting prognosis

2-in the selection of the best form of **therapy** for the patient

3-has proved to be of greater clinical value than grading.

However, the two are generally correlated in that tumors of high grade present at high stage, while tumors of low grade present at low stage

Diagnosis of cancer

The laboratory diagnosis of cancer becomes more complex, more advanced and more specialized, it is broadly divided in to :

1-morphological methods:

Histologic

Cytologic Methods

immunohistochemistry

flow cytometry

2-Biochemical assays: (Tumor Markers)

3-Molecular Diagnosis

PCR .

FISH.

Laboratory Diagnosis of Cancer

1- Morphologic Methods:

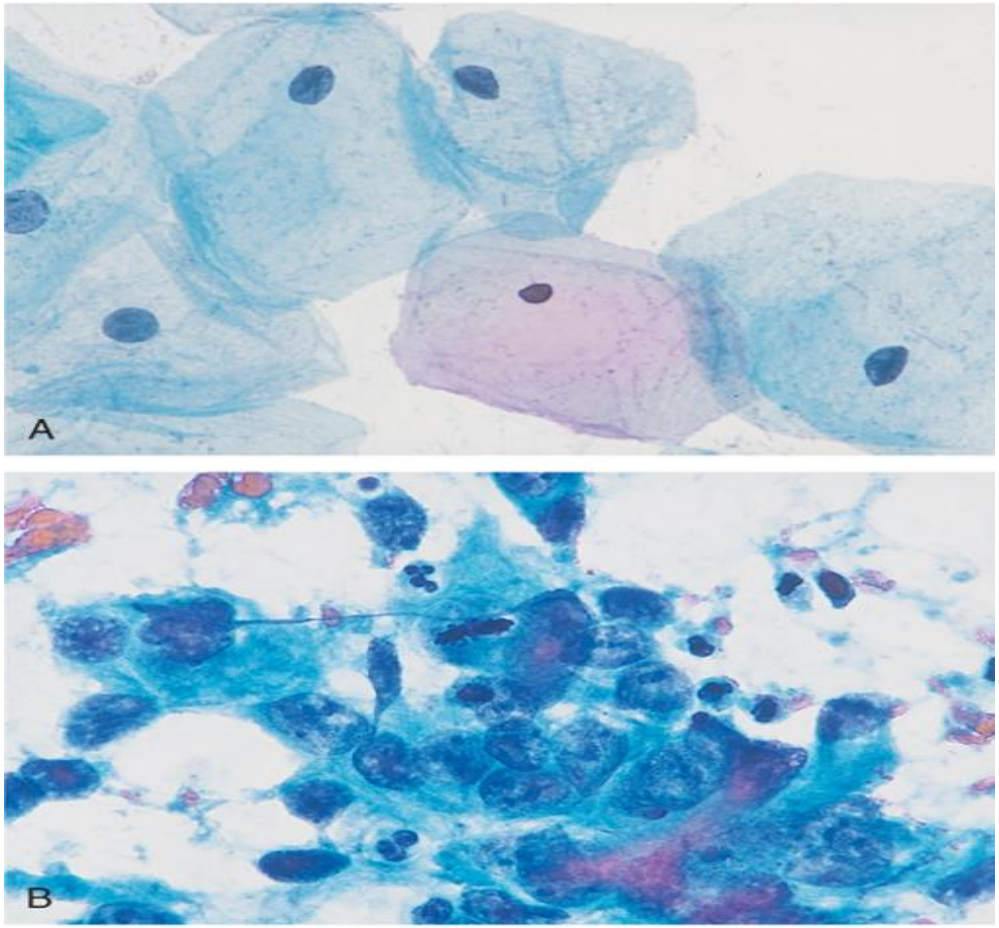
A- Cytological methods

Exfoliative cells (sputum, urine, CSF):

Cytologic (Papanicolaou) smears provide a method for the detection of cancer.

This approach has been used widely for the discovery of **carcinoma of the cervix**, often at an **in situ stage**, but now it is used with many other forms of suspected malignancy, such as endometrial carcinoma, bronchogenic carcinoma, bladder and prostate tumors, and gastric carcinomas

Cytology of cervical smears. (A) Normal cervicovaginal smear shows large, flattened squamous cells and groups of metaplastic cells; interspersed are neutrophils. There are no malignant cells. (B) Abnormal cervicovaginal smear shows numerous malignant cells that have pleomorphic, hyperchromatic nuclei; interspersed are normal polymorphonuclear leukocytes.



Fine needle aspiration

It involves aspiration of cells from a **mass,** followed by cytologic examination of the smear.

This procedure is used most commonly with palpable lesions affecting the **breast, thyroid, lymph nodes, and salivary glands.**

Modern imaging techniques(ultrasound, CT scan and MRI) permit extension of the method to **deeper structures**, such as the **liver, pancreas, and pelvic lymph nodes.**

2- Histopatological diagnosis

It gives the definite diagnosis, it includes:

Paraffin tissue section, stained with H&E &other special stain.

Importance of histopathological diagnosis:

1- determine the **type of the tumor**

2- **grade** of the tumor

3- presence or absence of **lymphovascular invasion**

4- microscopic **size** of the tumor.

5-detect the **margins** if it is free or involved by tumor

6- **lymph node** involved by tumor or not

Other additional methods:

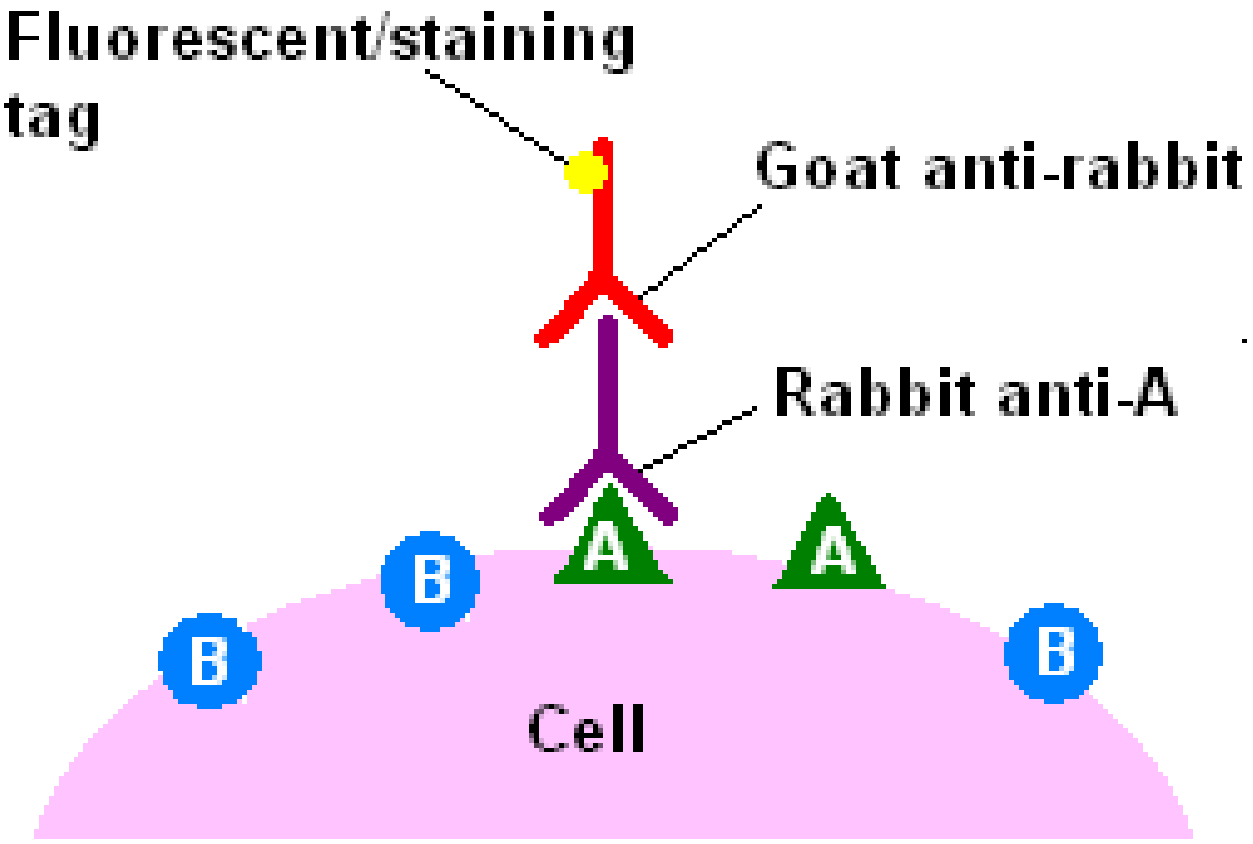
Immunohistochemistry(IHC) :

it is the process of detecting antigens (e.g., **proteins**) in cells of a tissue section by using the principle of antibodies binding specifically to antigens in biological tissues.

IHC takes its name from the roots "immuno," in reference to antibodies used in the procedure, and "histo," meaning tissue (compare to immunocytochemistry)

This involves the detection of cell products or surface markers by monoclonal antibodies.

The binding of antibodies can be detected by fluorescent labels or chemical reactions that result in the generation of a colored product.


Fluorescent/staining tag
Goat anti-rabbit
Rabbit anti-A
A
A
B
B
B
Cell

Immunohistochemistry.

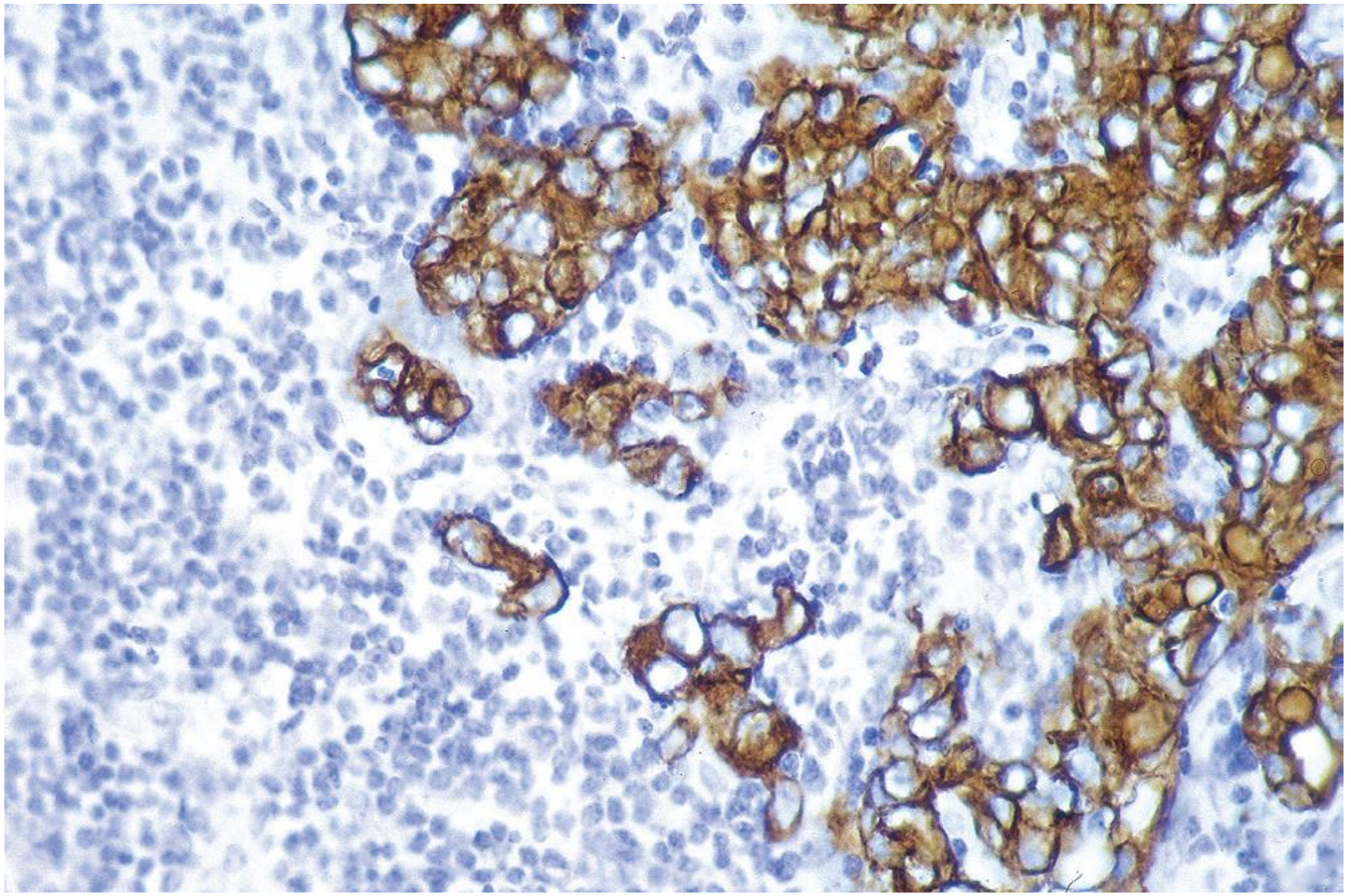
offers a powerful adjunct to routine histopathology.

Uses of immunohistochemistry in the diagnosis or management of malignant neoplasms

1-Categorization of undifferentiated malignant tumors

Detection of cytokeratin by specific monoclonal antibodies points to a diagnosis of undifferentiated carcinoma rather than large-cell lymphoma.

Anticytokeratin immunoperoxidase stain of a tumor of epithelial origin (carcinoma



2-Determination of site of origin of metastatic tumors

Similarly, detection of prostate-specific antigen (PSA) in metastatic deposits by immunohistochemistry allows definitive diagnosis of a primary tumor in the prostate

3- Detection of molecules that have prognostic or therapeutic significance.Immunohistochemical detection of estrogen receptors and HER2/NEU allows prognostication and directs therapeutic intervention in breast cancers.

ER positive breast cancers are susceptible to antiestrogen therapy (tamoxfin).

Breast cancers with strong immunohistochemical staining for HER2 are treated with antibodies that block the activity of the HER2 receptor (Herceptin).

2-Biochemical assays(TumorMarkers):

Biochemical assays for tumor-associated enzymes, hormones, and other tumor markers in the blood cannot be utilized for definitive diagnosis of cancer,

They are used in :

- finding cases
- in determining the effectiveness of therapy
- or the appearance of a recurrence.

e.g: **prostatic specific antigen (PSA)**, used to screen for prostatic adenocarcinoma, may be one of the most used, and most successful, tumor markers in clinical practice.

carcinoembryonic antigen (CEA), which is elaborated by carcinomas of the colon, pancreas, stomach, and breast.

α-fetoprotein, which is produced by hepatocellular carcinomas, yolk sac remnants in the gonads, and occasionally embryonal cell carcinomas.

Table 7.12 Selected Tumor Markers

Tumor Markers	Tumor Types
Hormones	
Human chorionic gonadotropin	Trophoblastic tumors, nonseminomatous testicular tumors
Calcitonin	Medullary carcinoma of thyroid
Catecholamine and metabolites	Pheochromocytoma and related tumors
Ectopic hormones	See Table 7.11
Oncofetal Antigens	
α-Fetoprotein	Liver cell cancer, nonseminomatous germ cell tumors of testis
Carcinoembryonic antigen	Carcinomas of the colon, pancreas, lung, stomach, and heart
Lineage-Specific Proteins	
Immunoglobulins	Multiple myeloma and other gammopathies
Prostate-specific antigen and prostate-specific membrane antigen	Prostate cancer
Mucins and Other Glycoproteins	
CA-125	Ovarian cancer
CA-19-9	Colon cancer, pancreatic cancer
CA-15-3	Breast cancer
Cell-Free DNA Markers	
EGFR mutants in serum	Lung cancer
TP53, *APC*, *RAS* mutants in stool and serum	Colon cancer
TP53, *RAS* mutants in stool and serum	Pancreatic cancer
TP53, *RAS* mutants in sputum and serum	Lung cancer
TP53 mutants in urine	Bladder cancer

3-Molecular Diagnosis

An increasing number of molecular techniques are being used for the diagnosis of tumors and for predicting their behavior.

Uses of molecular methods:

1-Diagnosis of malignancy. polymerase chain reaction (PCR)-based detection of hematopoietic neoplasms, and a few solid tumors.

.

2- *Prognosis and behavior:*

Certain genetic alterations are associated with a poor prognosis, and thus the presence of these alterations determines the patient's subsequent therapy.

FISH and PCR methods can be used to detect amplification of oncogenes such as *HER-2/NEU,* which provide prognostic and therapeutic information for breast cancers.

3-Detection of minimal residual disease

Another use of molecular techniques is detection of minimal residual disease after treatment.

For example, detection of ***BCR-ABL* transcripts** by PCR gives a measure of residual disease, in patients treated for **chronic myeloid leukemia(CML)**

4-Diagnosis of hereditary predisposition to cancer

Germ-line mutation of several tumor suppressor genes, such as ***BRCA1,*** increases a patient's risk of developing certain types of cancer(like breast and ovaries).

Thus, detection of these mutated alleles may allow the patient and physician to devise an aggressive screening protocol, as well as to consider prophylactic surgery. In addition, such detection allows genetic counseling of relatives at risk.

5-Guiding therapy with oncoprotein-directed drugs(targeted therapy).

An increasing number of chemotherapeutic agents target oncoproteins that are present only in a subset of cancers of a particular type. Thus the molecular identification of genetic lesions that produce these oncoproteins is essential for optimal treatment of patients.

examples of genetic lesions that guide therapy and are frequently tested for in molecular diagnostic laboratories include:

1-BCR-ABL fusion gene in chronic myeloid leukemia.

2-EGFR mutations and ALK gene rearrangements in lung Cancer.

3-BRAF mutations in melanoma.


Thank
You