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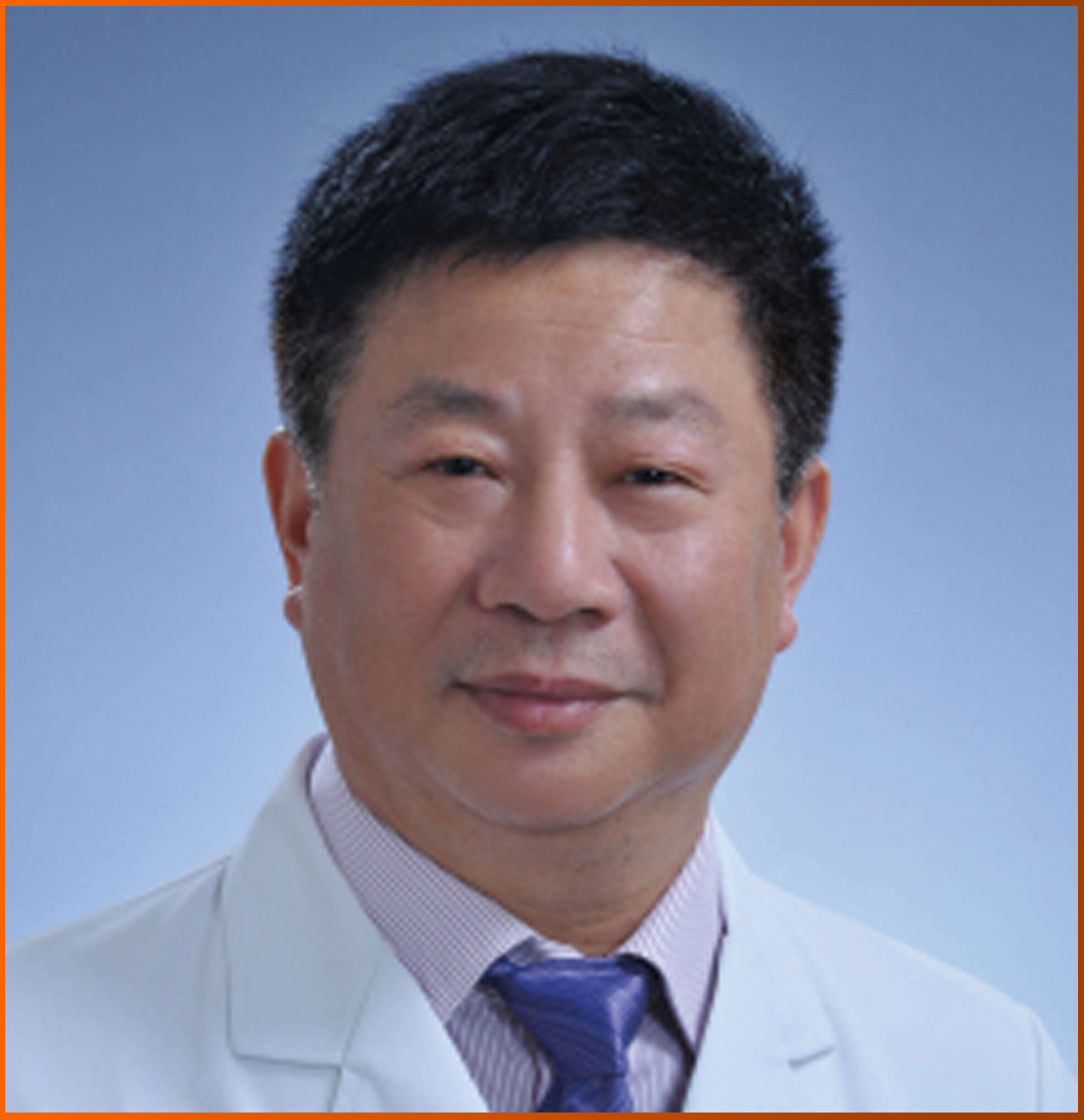

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REVIEW

Role of endoscopy in management of gastrointestinal complications of portal hypertension

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Abstract

The management of patients with gastrointestinal complications of portal hypertension is often complex and challenging. The endoscopy plays an important role in the management of these patients. The role of endoscopy is both diagnostic and interventional and in the last years the techniques have undergone a rapid expansion with the advent of different and novel endoscopic modalities, with consequent improvement of investigation and treatment of these patients. The choice of best therapeutic strategy depends on many factors: baseline disease, patient's clinical performance and the timing when it is done if in emergency or a prophylactic approaches. In this review we evaluate the endoscopic management of patients with the gastrointestinal complications of portal hypertension.

Key words: Portal hypertension; Gastrointestinal complications; Bleeding; Esophageal varices; Gastric varices

Core tip: Endoscopy plays a primary role in the staging, diagnosis and treatment of gastrointestinal complications of portal hypertension. In this review, we summarize data from randomized clinical trials or prospective studies together with meta-analytical data, when applicable, to present the most updated recommendations on endoscopic management of the gastrointestinal complications of portal hypertension.

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INTRODUCTION

Portal hypertension is defined as a pathologic increase in portal vein to inferior vena cava pressure gradient greater than 5 mmHg. According to anatomic location,

the diseases causing portal hypertension are classified as pre-hepatic if involve portal, splenic or mesenteric veins, intra-hepatic if cause acute or chronic liver diseases, and post-hepatic if interfere with the venous outflow of the liver. The most prevalent cause of portal hypertension is liver cirrhosis with greater resistance to portal flow. Hepatic venous pressure gradient (HVPG) is an indirect measurement of portal hypertension which is obtained by placing a catheter in the hepatic vein or by occluding a large branch of hepatic vein by inflating a balloon. Portal hypertension likely causes the development of varices and hemodynamic and mucosal changes in the entire gastrointestinal (GI) tract. Varices are present in the 50% of cirrhotic patients[1-4]. Bleeding occurs in approximately 5%-15% of patients, depends on the size of varices. Other predictors of bleeding may be the presence of red wale mark and decompensated cirrhosis[5]. The variceal bleeding mortality is around 20% at 6 wk despite improvement in therapy over the last decade thanks to the development of endoscopical and pharmacological therapies and antibiotic prophylaxis[6-8].

In the patients with portal hypertension the gut mucosa undergoes microcirculatory changes, such as submucosal angiogenesis and vascular ectasia, that impair its integrity and promote its susceptibility to damage. Stomach changes can cause bleeding [portal hypertensive gastropathy (PHG)], usually the involvement of small bowel is asymptomatic (portal hypertensive enteropathy), but sometimes can cause occult blood loss, finally colon involvement (portal hypertensive colopathy) is often associated with bleeding and the symptoms are similar to inflammatory bowel disease[9].

The aim of this paper is to review the interventional and diagnostic role of endoscopy in patients with GI complications of portal hypertension.

ESOPHAGEAL VARICES

Primary prophylaxis

The goal of primary prophylaxis is to prevent first bleeding episode and consequently improve survival through decreasing bleeding-related death. All cirrhotic patients should be screened for varices through endoscopy to detect the patients that need a prophylactic treatment[10,11]. The Child-Pugh (C-P) score suggests that risk factors of bleeding are the presence of red wale marks, the size of varices and the liver disease severity[5].

Typically, one of two approaches is used for primary prophylaxis: pharmacologic prophylaxis using a non-selective beta-adrenergic blockers (NSBBs) or with endoscopic band ligation (EBL).

EBL consists in the placement of rubber rings on variceal columns which are sucked into a plastic hollow cylinder attached to the tip of the endoscope. Endoscopic ligation causes occlusion of the varix and then thrombosis with ischemic necrosis of the mucosa. Multiple-shot devices have largely replaced the original single-shot ligators, since the procedure is much simpler and faster with multi shot devices. Endoscopic variceal ligation is associated with complications such as hemorrhage, chest pain, dysphagia, and odynophagia and ulceration of the mucosa. There are only few studies that have evaluated the risk of bleeding from ligation-induced ulcers. Schepke *et al*[12] found that the incidence of bleeding from ligation ulcers after EBL was 6.7%. Another retrospective data analysis of EBL described hemorrhage from ligation ulcers as 5.7%, irrespective of the indication[13]. Endoscopic variceal ligation sessions are usually repeated at 1-2 wk intervals until complete obliteration[11]. A randomized, controlled trial of bimonthly *vs* biweekly EBL (primary and secondary prophylaxis) found that EBL bimonthly had a higher total eradication rate, lower recurrence rate, and lower rate of additional treatment than biweekly EBL and that the patients treated bi-monthly showed better ulceration healing in the second and third treatments than the patients treated bi-weekly[14]. This approach may decrease the risk of bleeding or perforation.

NSBBs can be used in patients that present cirrhosis, small varices and risk of bleeding according to C-P score[10,11]. It's known that patients with small varices with red signs on its wall or with C-P score class C, have the same risk of bleeding of patients with large varices[5]. In patients with medium/large varices either NSBBs or EBL are an appropriate choice for primary prophylaxis of bleeding[10,11]. A systematic review of 11 randomized controlled trials (RCTs) about prevention of variceal hemorrhage,has compared NSBBs with placebo or non active treatment, and has shown a 9% absolute risk reduction of first variceal bleeding at two years[15]. A significant reduction in mortality was also seen with NSBBs use[16]. The use of NSBBs is limited by their side-effect profile, which includes hypotension, fatigue, lethargy, depression, and dyspnea in patients with associated pulmonary disease. Around 15%-20% of patients suffer from intolerable side effects that require discontinuation of the drug[17].

A meta-analysis of 5 trials comparing prophylactic EBL with controls found that EBL decreases the risk of variceal hemorrhage and the mortality related to hemorrhage[18]. The treatment choice is based on patient preference, local resources and side effects[10]. A Cochrane meta-analysis that included 19 RCTs, has compared prophylactic EBL with NSBBs and has shown a slight beneficial effect for EBL, without different bleeding-related mortality in the two arms[19].

Evolving data suggest novel uses for endoscopic ultrasonography (EUS) in patients with esophageal varices, in fact a RCT has shown that in the treatment of esophageal varices EUS-guided injection sclerotherapy is most safe and efficacious respect to endoscopic injection therapy[20].

In patients treated with NSBBs endoscopic follow-up isn't necessary, conversely in patients treated with EBL, is necessary repeat endoscopy every one or two

weeks until obliteration, 1-3 mo after obliteration and finally every year to check for variceal recurrence[11]. In patients with small varices and who not receive NSBBs, is necessary repeat endoscopy in two years. In the case of hepatic decompensation, endoscopy should be repeated every year and in cirrhotic patients without the presence of varices on the initial endoscopy it should be repeated every three years[10,11].

Acute variceal bleeding

Ruptured esophageal varices cause 70% of all upper GI bleeding episodes in patients with portal hypertension. Therefore, a variceal origin should be suspected in any cirrhotic patient that presents a GI bleeding[7]. In patients with hematemesis or hemodynamic instability, an endoscopic evaluation should be done in the first 12 h after admission[10,11].

The use of new drugs, which are able to decrease portal pressure, the novel and specialized endoscopic endoscopic therapy, the use of antibiotics and the interventional radiologic procedures improved the survival in the last 25 years[6]. Mortality during the bleeding episode remains high and ranges from 24% in unselected cirrhotic variceal bleeders to about 16% among those receiving the current standard of care (band ligation + vasoactive drugs + antibiotics)[21-23]. For the treatment of acute bleeding related to variceal the current recommendation is to combine antibiotic prophylaxis, hemodynamic stabilization, the use of drugs and the treatment through endoscopy[11]. It's important maintaining hemodynamic stability and a hemoglobin of 8 g/dL[11]. The restitution of lost blood causes an increasing in portal pressure to levels higher respect to baseline[24]. A recently RCT showed that a restrictive transfusion strategy in patients with portal hypertensive bleeding reduced further bleeding, need for rescue therapy and length of stay in the hospital. In the restrictive-strategy group the hemoglobin threshold for transfusion was 7 g/dL per deciliter with a target range of 7 to 9 g/dL per deciliter[25]. Antibiotic prophylaxis is a standard practice, in fact it is known that is able to decrease the rate of bacteria infections and the incidence of rebleeding, and increase the survival[26,27]. The combination of endoscopic and pharmacological therapy is the most common approach for treatment of acute variceal bleeding[10,11]. For example a meta-analysis of 8 RCTs has shown that vasoactive drugs enhance the efficacy of endoscopic therapy respect to endoscopic therapy alone, without evidence of side effects or mortality[28].

EBL is the best endoscopic therapy for active bleeding because respect to endoscopic sclerotherapy (ES), allows a greater control of bleeding, the possible adverse events are lower and improves the survival[10,29,30]. When EBL is not technically feasible, endoscopic sclerotherapy is recommended[10]. Endoscopic ultrasound allows a more effective distribution of sclerosant, the injection of sclerosant agents can be realized into esophageal varices, and causes a decrease of the recurrence rate[31].

Emergency injection of acrylate glue could be also an effective method for treat the bleeding of esophageal varices[32]. Vaso-active medications decrease portal blood flow which relate closely to variceal pressure and include vasopressine, somatostatin, and their analogs (terlipressin and octreotide, respectively). Vasoactive therapy should be continued for 5 d to prevent the rebleeding[10], the reason behind this treatment is that a higher portal pressure is associated with a prognosis less favorable[33].

Patients with cirrhosis in Child-Pugh class C or those in class B who have persistent bleeding at endoscopy, are at high risk for treatment failure and a poor prognosis and early use of PTFE-covered TIPS (within 72 h) markedly and significantly reduces failures to control bleeding or rebleeding and improves survival[34].

Secondary prophylaxis

Over 70% of patients experience recurrent variceal bleeding within one year of their index bleed[35,36]. To prevent recurrent bleeding all surviving patients should receive prophylactic treatments[11]. Available treatments for preventing variceal rebleeding include pharmacological therapy, endoscopic therapy, transjugular intra-hepatic porto-systemic shunt (TIPS) and surgical shunting. A recently meta-analysis showed that NSBBs and EBL are similarly able to reduce upper GI bleeding, variceal rebleeding and bleeding-related mortality, but the overall mortality rate was only lowered with NSBBs[37]. The beneficial effect of b-blockers goes beyond the reduction in the variceal bleeding risk and is probably related to an improvement of other complications of portal hypertension.

A combination of NSBBs and endoscopic therapy is the currently recommended first line treatment for the prevention of variceal rebleeding[10,11]. Band ligation is the endoscopic therapy of choice and has replaced injection sclerotherapy because it is safer and more effective[38]. EBL should be repeated every 1-2 wk until obliteration, the first surveillance endoscopy is performed 1-3 mo after obliteration and then every 6-12 mo to check for variceal recurrence and NSBBs should be adjusted to the maximal tolerated dose[10,11].

Recently, a meta-analysis of 9 trials has confirmed that the combination of EBL and drug treatment reduces the risk of overall and variceal rebleeding, but not overall mortality, when compared with b-blockers or EBL alone[39]. However, data evaluating this issue are not very strong. Lo and de la Pena, have shown that adding b-blockers to EBL reduces the risk of rebleeding and variceal recurrence but this effect was not confirmed in a third study[40-42]. Another two trials failed to show a clear-cut benefit from adding EBL to combined pharmacological therapy with nadolol plus isosorbide mononitrate[43,44].

In cirrhotic patients that are unable or that refuse EBL, NSBBs is a valid option, in fact causes a reduction in portal pressure and a slight increase of side effects[11,45].

TIPS should be considered in patients who are Child A or B who experience recurrent variceal hemorrhage despite combination pharmacological and endoscopic therapy[10,11]. The use of polytetrafluoroethylene (PTFE)-covered stents significantly decreased the rates of obstruction and re-intervention[46]. Surgical shunt prevents rebleeding but markedly increases the risk of hepatic encephalopathy[47].

Rescue therapy

In about 10% of patients, despite urgent endoscopic, variceal bleeding cannot be controlled and thus they may be candidates for salvage therapy[11]. A TIPS is suggested in patients with uncontrolled hemorrhage from esophageal varices with bleeding recurs[11,48-50]. Balloon tamponade (BT) is a temporary measure in patients with uncontrollable bleeding[10]. The main complications associated with BT include aspiration pneumonia in unventilated patients, esophageal ulcers, esophageal tears and airway obstruction with fatal complications in 6%-20% of cases[50].

Fully covered self-expanding metal stent (FCSEMS) placement have been recently proposed as rescue therapy[51], their use allow the stabilization of the patients until is performed the definitive therapy. Preliminary studies showed an high success rate, with minor complications[51-54]. Recently the hemostatic powder TC-325 was used as rescue therapy with good results[55].

GASTRIC VARICES

Seventeen percent of patients with hepatic cirrhosis are affected by gastric varices (GV)[56]. Gastric varices are classified according their location in: esophago-gastric varices, *i.e.*, esophageal varices extending either from the gastroesophageal junction to the small curvature of the stomach (GOV1), or to the fundus (GOV2); and isolated gastric varices (IGV), located in the stomach (IGV2) or elsewhere in the fundus (IGV1); GOV1 represent 75% of GV, GOV2, IVG1 and IGV2 represent respectively 21%, 1% and 4% of GV[57]. GOV1 constitute an extension of esophageal varices[10]. GV bleed less frequently than esophageal varices and with a reported incidence of bleeding of about 25% in 2 years. Fundal varices, however, had a significantly higher bleeding incidence (78% for IGV1 and 55% for GOV2), than GOV1 and IGV2 (10%)[56]. Risk factors for GV bleeding include red color spots, larger nodular GV, fundal location and an advanced Child-Pugh class[56,58].

Primary prophylaxis

Little data have been reported about the primary prophylaxis of GV bleeding. Recently a RCT has compared the injection of cyanoacrylate glue with NSBBs in primary prophylaxis of GV bleeding and showed that cyanoacrylate therapy is more efficacious than NSBBs in preventing gastric variceal bleeding[59].

Acute variceal bleeding

Gastric varices bleeding is less frequent, but more severe than esophageal varices bleeding, therefore it can be more challenging to treat. The management of acute GV bleeding is similarly to the management of esophageal varices bleeding, and include antibiotic prophylaxis, management of euvolemic status and early use of vasoactive drugs[10,11]. The use of cyanoacrylate glue injection resulted in an high percentage of success (*i.e.*, bleeding cessation)[60]. A small RCTs compared cyanoacrylate glue injection with EBL and ES and showed that cyanoacrylate injection is as effective as (or more than) ligation in acute bleeding[61,62]. Leaking of glue (4.4%), sepsis (1.3%), systemic embolism (2%-3%) represent the more common complications related to this treatment[63,64].

A new technique of treatment was introduced in last years, EUS-guided therapy of gastric fundal varices with a combination of cyanoacrylate glue and coil injection that reduced the risk of glue embolization. Coils act as a scaffold to sustain the cyanoacrylate glue within the varix and decrease the amount of glue injection. In a retrospective cohort study this technique was successful in all patients without procedure-related complications[65]. A recently study that compared the treatment of GV by using EUS-guided cyanoacrylate injection or EUS-guided coil application showed that both techniques are effective in the obliteration of localized GV. EUS-guided coil required fewer endoscopies and tended to have fewer adverse events compared with EUS-guided cyanoacrylate injection[66].

TIPS is considered in patients with hemorrhage from fundal varices that can't be controlled or with bleeding that recurs despite the therapy[11]. Fibrin sealant (a solution of fibrinogen and thrombin) has been injected for arrest of variceal bleeding in small uncontrolled series[67,68]. Thrombin has been evaluated for use in endoscopic hemostasis of variceal bleeding. In 2 retrospective studies, thrombin achieved hemostasis in bleeding gastric varices in 75% to 94%[69,70].

Secondary prophylaxis

Cyanoacrylate injection is the most frequent treatment for secondary prophylaxis of GV[10]. Rebleeding rates after an acute GV bleeding episode treated with tissue adhesives range from 7%-65%[71]. After initial hemostasis with tissue adhesives, repeated sessions are performed from two to four weeks until is achieved the endoscopic obliteration. Two RCTs compared cyanoacrylate injection with variceal band ligation, showing that cyanoacrylate injection reduced the rebleeding rates[61,62]. Another study compared cyanoacrylate injection with sclerotherapy and showed a greater control of initial hemostasis and a lower rebleeding rates with cyanoacrylate[72]. TIPS is considered when patients show hemorrhage that can not be controlled or in whom bleeding recurs[11,73].

PHG

The prevalence of PHG, in patients with severe liver disease, ranges between the 11% and 80% and is a potential cause of bleeding[74]. PHG is classified as mild when the only change consists of a snakeskin mosaic pattern, and it is classified as severe when in addition to the mosaic pattern, flat or bulging red or black-brown spots are seen, and/or when there is active hemorrhage[75]. Acute bleeding from PHG is a rare event, with an incidence less than 3%, the incidence of chronic bleeding is around 10%-15%[76]. At the current time, there is not enough data to recommend primary prophylaxis of bleeding from PHG in cirrhotic patients[77].

In the case of acute haemorrhage are administered vasoactive drugs such as vasopressin and its analogue and terlipressin, this drugs are able to control haemorrhage[78-80]. In rare cases, the medical therapy is unable to control bleeding and in this cases limited data suggests the endoscopic thermal therapy[81]. Moreover TIPS is employed in the treatment of PHG with improvement of both mild and severe forms and reduction in endoscopic severity as well as transfusion requirement[82]. Recently haemostatic powder (Hemospray) has been evaluated in patients with acute bleeding due to PHG. This haemostatic powder, which acts by forming a barrier over them bleeding site and enhancing the concentration of clotting factors, was successfully used in four patients actively bleeding from PHG[83]. In patients who have previously experienced clinically significant GI blood loss, NSBBs should be used for prevention of recurrent bleeding[10].

GASTRIC ANTRAL VASCULAR ECTASIA

Gastric antral vascular ectasia (GAVE) is a disorder of the stomach that is characterized by the presence of dilated and fragile blood vessels. In patients with cirrhosis GAVE is less detected compared to PHG[84,85]. There are 2 types of GAVE based on distinctive endoscopic appearances. The classic manifestation consists of appearance of multiple flat, linear, erythematous strips of ectatic vessels radiating from the pylorus to the antrum. The second type is punctate, with punctate red spots scattered throughout the antrum and tends to be more associated with liver cirrhosis[86]. It is reasonable to not treat GAVE lesions that are asymptomatic[77]. Neodymium-yttrium-aluminum garnet laser coagulation is used to control GAVE-related bleeding, in fact is able to reduce the need of blood transfusions in 50%-80% of cases. The disadvantages of this technique are the high cost and the need of a long training period[87-89].

Argon plasma coagulation (APC) is a thermoablative method, which produces thermal coagulation by the use of electric current with high frequency that is passed through with argon gas without contact with the mucosa. APC treatment have an efficacy ranging from 90% to 100%, without the need of blood transfusions with an increase of hemoglobin level in most patients[90,91]. The most frequently complication of APC treatment is the intestinal gas distension, more serious adverse events are antral stenosis and upper GI hemorrhage[91]. Argon plasma coagulation is frequently associated with recurrence of bleeding in 30%-60% of cases, in the medium to long term period[91,92]. The use of EBL has been recently demonstrated for GAVE treatment[93].

EBL may more reliably obliterate vascular structures in the deep mucosa and submucosa, thus reducing the need for further treatments. Ligation bands are applied to abnormal-appearing mucosa in the antrum. First is treated the distal antrum, after the ligation bands are applied more proximally until most of the abnormal mucosa is treated. Wells *et al*[93], in a retrospective study, found that EBL reduced recurrent bleeding and required less treatment sessions and hospital admissions compared to APC treatment[93]. This finding is in accordance with other two studies[94,95].

Recently studies examined the use of radiofrequency ablation (RFA) for the treatment of GAVE[96,97]. These two studies suggests that endoscopic mucosal ablation by using the RFA with HALO system is a viable option for the treatment of chronic bleeding related to GAVE[96,97]. Additional therapy for GAVE includes cryotherapy, cyanoacrylate spray and surgical antrectomy[98-101].

ECTOPIC VARICES

Ectopic varices are those varices which are not located in the gastro-esophageal area, are less common and occur in different sites, such as in the jejunum or ileum (18%),in the duodenum (17%) or in the colon (14%), in the rectum (8%), and finally in the peritoneum (9%)[102,103].

Duodenal varices

Duodenal varices (DV) were reported to be the second cause of ectopic variceal bleeding after the rectal location[104]. They are most commonly noted in the duodenal bulb followed by the second part of the duodenum[102,104]. Bleeding due to DV is usually massive, with a mortality rate around the 40% at the first episode[105,106]. Different sclerosant agents are used for endoscopic injection therapy, for example Seo *et al*[107] have been shown how bleeding duodenal varices can be eradicated with injection of ethanolamine. Liu *et al*[106] in a five-year retrospective study reported the successful treatment with cyanoacrylate injection in 4 patients with bleeding due to DV. Some authors have reported also the successful EBL of DV bleeding[108-110]. If rebleeding occur after endoscopic therapy, and TIPS are used as rescue therapy with good results[111,112].

Small-bowel varices

An uncommon, difficult to treat and sometimes fatal manifestation of portal hypertension is the hemorrhage associated with small-bowel varices. In fact, 8.1% of patients with portal hypertension who underwent to capsule endoscopy present small-bowel varices[113]. When

the terminal ileum is intubated on colonoscopy the 18% of patients with portal hypertension, present terminal ileal varices[114]. Double-balloon enteroscopy (DBE) allows to display whole small bowel and perform endoscopic surgeries in patients with bleeding small-bowel varices. Enteroscopic and colonscopic sclerotherapy of jejunal and ileal varices has been described[115-118]. TIPS is the first line treatment for refractory variceal bleeding[119].

Colonic varices

The most common sites of colonic varices are the rectum and cecum[105]. The rate of colonic variceal bleeding in liver cirrhosis is approximately 1%-8%[120]. Several interventional therapies like endoscopic variceal ligation, glue injection, TIPS, BRTO, colonic resection have been reported[121-126].

Rectal varices

Rectal varices are one of the most important causes of bleeding in portal hypertension, they occur in 44% to 89% of cirrhosis[127-129]. The endoscopic options for treatment of rectal varices are injection therapies using sclerosants or cyanoacrylate glue and band ligation[130-133]. Recently EUS-guided approach has been used in management of rectal varices. The advantages to use EUS-guided therapy are different and include the ability to treat directly the varix and visualize deeper collateral vessels. The EUS-guided therapy with sclerosant or coil embolization showed good results[134-136].

PORTAL HYPERTENSIVE BILIOPATHY

Portal hypertensive biliopathy (PHB) is an abnormalities of all biliary tract including intra-hepatic and extra-hepatic bile ducts, cystic duct and gallbladder. The frequency of PHB in patients with extra-hepatic portal venous obstruction (EHPVO), is greater respect to patients with cirrhosis[137]. EUS could be useful in patients with cirrhosis to identify CBD varices or bile duct stones[138].

The extraction of CBD stones by endoscopic sphincterotomy is the normally treatment applied in patients with CBD stones. Endoscopic treatment is the best treatment for patients with dominant biliary stricture, but without a shuntable vein. Porto-systemic shunt is performed in patients with dominant biliary strictures with a shuntable vein[139,140].

PORTAL HYPERTENSIVE ENTEROPATHY

Portal hypertensive enteropathy (PHE) is defined as the presence of several red spots like arterovenous malformations, patchy hyperemia of the mucosa, diffuse mucosal edema, spontaneous bleeding from the mucosa or small bowel varices[141-143]. Due to the difficult access to the small bowel, in the past the diagnosis of PHE was very difficult, but with the introduction of capsule endoscopy and DBE, PHE seems more common and has been seen that in cirrhotic patients may cause chronic GI bleeding with portal hypertension[144,145]. PHG is mostly asymptomatic, although it may bleed acutely leading to hematemesis and/or melena.

PORTAL HYPERTENSIVE COLOPATHY

Portal hypertensive colopathy (PHC) is characterized by erythema of the colonic mucosa and vascular lesions including telangiectasias, cherry-red spots and angiodysplasia-like lesions. The prevalence of PHC in patients with cirrhosis ranging between 25%-70%[146-148]. Portal hypertension seems to play an important role, and there is an association with a hyperkinetic circulatory state[149]. Lower GI bleeding due to PHC is estimated up to 9%[150-152]. In patients with chronic lower GI bleeding secondary to PHC, as reported the treatment with NSBBs is effective[153]. In patients with acute bleeding, vasoactive medications, such as octreotide or terlipressin, could be effective[153]. TIPS has been used as a rescue therapy in patients with refractory GI bleeding[154].

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REVIEW

Small bowel capsule endoscopy: Where are we after almost 15 years of use?

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Abstract

The development of capsule endoscopy (CE) in 2001 has given gastroenterologists the opportunity to investigate the small bowel in a non-invasive way. CE is most commonly performed for obscure gastrointestinal bleeding, but other indications include diagnosis or follow-up of Crohn's disease, suspicion of a small bowel tumor, diagnosis and surveillance of hereditary polyposis syndromes, Nonsteroidal anti-inflammatory drug-induced small bowel lesions and celiac disease. Almost fifteen years have passed since the release of the small bowel capsule. The purpose of this review is to offer the reader a brief but complete overview on small bowel CE anno 2014, including the technical and procedural aspects, the possible complications and the most important indications. We will end with some future perspectives of CE.

Key words: Capsule endoscopy; Small bowel; Preparation; Procedure; Technology; Complications; Features; Enhancements; Indications; Future

Core tip: This review covers all the relevant aspects of small bowel capsule endoscopy anno 2014. The current techniques, procedures, analyses, indications and future perspectives are discussed thoroughly. Easy-to-use flowcharts are provided to help the readers in their decision-making when confronted with small bowel pathology.

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INTRODUCTION

Wireless Video capsule endoscopy (CE) was invented by Gavriel Iddan[1] in the mid-1990s. Being able to visualize the entire small bowel in a noninvasive, well-tolerated way, CE has closed the diagnostic gap between conventional gastroduodenoscopy and colonoscopy. Since the official release of CE in 2001, almost 15 years have passed, and CE has revolutionized the diagnosis and treatment of

various small intestinal diseases. This review aims to provide state of the art on CE in gastrointestinal diseases. Both the evolution in technique and in indications will be discussed.

TECHNICAL PRINCIPALS, PROCEDURE AND ANALYSIS

Capsule definition

The wireless CE system consists of 4 main parts: (1) the single-use wireless Video Capsule; (2) sensor arrays or a sensor belt attached to the patient; (3) the data recorder attached to the belt; and (4) the computer workstation with the application software[2-4] as can be seen in Figure 1 by Pan *et al*[4].

The capsule weighs less than 4 g and measures about 11 mm in diameter × 26 mm in length. It is made of plastic, biocompatible and resistant to digestive fluids. The capsule contains a short focal lens and a miniature video camera: a charge-coupled device or Complementary Metal Oxide Semiconductor, which focuses the image. The gastrointestinal tract is illuminated by white light LEDs. The capsule is powered by two mercury free silver oxide batteries with a life span of 8-12 h. More than 5000 images are transmitted during this battery life at a rate of 2-6 fps. Capsule features have evolved since the release of the first capsule and nowadays standards are a 156-170° field of view, a high resolution and sharpness with a minimum size of detection of 0.07 mm, a 1:8 magnification, a more homogenous light exposure and a depth of view of at least 20-30 mm[5]. The captured data are sent to the sensor arrays and belt worn by the patients by either ultra-high frequency band radio telemetry or human body communications, using the human body as conductor.

At present, there are three main companies supplying wireless CE systems by approval of the FDA. Given Imaging (Ltd, Yoqneam, Israel) supplying the PillCam® SB 3, Olympus America (Inc, Center Valley, Pennsylvania) supplying the EndoCapsule® and Intromedic Company (Ltd, Seoul, South Korea) manufacturing the MiroCam®. Although not approved by the FDA, another Chinese company, Jianshan Science and Technology (Group) Co., Ltd., Chongqing, has developed its own capsule: the OMOM capsule. The capsule has been approved by the State Food and Drug Administration of the People's Republic of China in March 2004 and is since then being used in China, Southeast Asia and some European countries[6]. The first large clinical trials have reported a yield and completion rate similar to the PillCam, but the major advantage of the OMOM capsule is without doubt its price, which could be reduced by fifty percent[6,7] (Table 1 and Figure 2).

Even though the three main capsules approved by the FDA differ in technical specifications, several trials have shown that they offer a comparable diagnostic yield, image quality and completion rate, as was stated in the systematic review by Koulaouzidis *et al*[8].

Small bowel preparation

To ensure a clear view on CE, the patient is asked to start fasting 12 h before the small bowel CE procedure[2,3]. However, due to bubbles, small intestinal fluid and biliary secretions coming from the major duodenal papilla, the visualization by the VCE can deteriorate. Furthermore, limited battery life span can hamper a complete intestinal examination in patients with delayed gastric emptying and small bowel transit, which necessitates the use of additional small bowel preparation[3]. However, not all patients are eligible for small bowel cleaning. The 2012 Consensus guidelines for the safe prescription and administration of oral bowel-cleansing agents[9] states that small bowel preparation is contraindicated in patients with gastrointestinal obstruction, perforation, ulceration, ileus, gastric retention or inflammatory bowel diseases (IBD), in patients with a reduced level of consciousness, swallowing disorders, hypersensitivity to the used agent and in patients having an ileostomy. The use of small bowel cleansing agents is relatively contraindicated in patients with chronic kidney disease or undergoing dialysis, in patients with a renal transplant, congestive heart failure, liver cirrhosis or ascites and in patients taking Renin-angiotensin blockers, diuretics or nonsteroidal anti-inflammatory drugs (NSAIDs). In these patients the utility of small bowel cleaning should be reconsidered and the choice of cleaning agent is of main importance: polyethylene glycol (PEG) is normally preferred over Sodium Phosphate. Patients taking Renin-angiotensin blockers, diuretics or NSAIDs are advised to discontinue their medication temporarily and their hydration and electrolyte status should be checked prior to the small bowel preparation. In a recent systematic review, Kotwal *et al*[10] compared the results of various randomized-controlled trials regarding improvement of vision quality (VQ), diagnostic yield (DY) and completion rate (CR) by small bowel preparation. In this review, administration of 2L polyethylene glycol (PEG) the evening before VCE was found to be superior to two doses of 45 mL Sodium Phosphate before VCE regarding VQ and DY improvements. Another study by Kantianis *et al*[11] showed that 2 L as well as 4 L PEG did not differ in small bowel cleansing and CR. Therefore 2 L should be preferred as regimen before VCE. Furthermore Kotwal *et al*[10] stated that simethicone, an antifoaming agent, significantly improved the VQ by decreasing the bubbles without implications on CR. Yet no significant improvement in VQ and DY were observed by combining Simethicone with PEG. After meta-analysis prokinetics did not show a significant improvement in CR, so they are not recommended.

Procedure

After bowel preparation, the patient gets eight sensor arrays attached to his body and a sensor belt fastened around his waist. The data recorder is attached to the belt before capsule ingestion. The capsule is ingested with a glass of water and fluid restriction is needed till 2

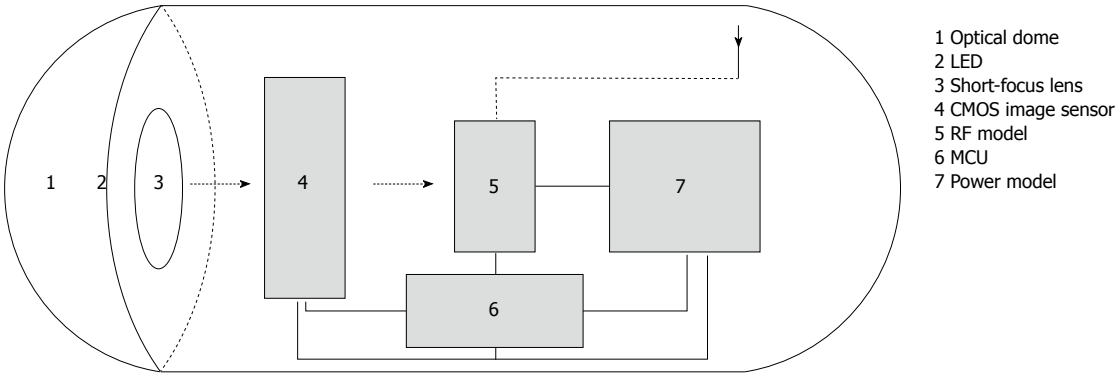

Figure 1 Main parts of the wireless capsule endoscope.

Table 1 Comparison between commercially available capsule endoscopy devices

Capsule	PillCam® SB 3 Given Imaging	EndoCapsule® Olympus America	MiroCam® Intromedic Company	OMOM® Jianshan Science and Technology
Size	Length: 26.2 mm Diameter: 11.4 mm	Length: 26 mm Diameter: 11 mm	Length: 24.5 mm Diameter: 10.8 mm	Length: 27.9 mm Diameter: 13 mm
Weight	3.00 g	3.50 g	3.25-4.70 g	6.00 g
Battery life	8 h or longer	8 h or longer	11 h or longer	6-8 h or longer
Resolution	340 x 340 30% better than SB2	512 x 512	320 x 320	640 x 480
Frames per second	2 fps or 2-6 fps	2 fps	3 fps	2 fps
Field of view	156°	145°	170°	140°
Communication	Radio Frequency Communication	Radio Frequency Communication	Human Body Communication	Radio Frequency Communication
FDA approval	Yes	Yes	Yes	No
Price per capsule	$500	$500	$500	$250

h after ingestion. After 4 h, fasting can be stopped. Daily activities do not need to be interrupted during CE.

Capsule propulsion needs to be followed by real-time viewing during the first hour to make sure the capsule passes the stomach. If not, gastroscopy is performed to deposit the capsule in the duodenum.

The sensor arrays and belt are removed once the capsule has been expelled into the colon (as verified by real-time viewing), or when the battery life has expired. Images can be downloaded from the recorder to the workstation. The capsule itself passes naturally with bowel movement and is usually excreted within 24 to 72 h.

Analysis

After downloading the data from the recorder to the workstation, images can be reviewed by gastroenterologists using the application software. Reading time and interpretation are around 40-120 min[2,12] which can be, compared to conventional endoscopy, a time-consuming activity. A solution to this problem might be to train nonphysicians in pre reading the images. A study by Bossa *et al*[12] found that a nurse with expertise in endoscopy might be able to shorten the time needed by the endoscopist to read a capsule. Moreover the pre reading of the CE by the nurse endoscopist led to a more careful approach of the physician in the flagged areas, which enhanced the accuracy of the CE investigation. Another recent study by Dokoutsidou *et al*[13] confirmed these findings and stated that despite a longer reading time, a nurse is perfectly capable of pre reading and subsequently flagging aberrant images. However, another possibility to lower reading time is the use of special software to select aberrant images, which can be revised afterwards. With the introduction of Quickview by Given Imaging, reading time could be reduced significantly. The Quickview software samples sites of interest for review at a chosen rate, but unfortunately missed lesions occur far more often, which is unacceptable[14]. However, in certain clinical settings, such as overt obscure gastrointestinal bleeding (OGIB) in an urgent inpatient setting and suspected Crohn Disease or occult OGIB in outpatient setting, Koualouzidis *et al*[15] found that Quickview could be used confidently without clinical consequences. To enhance the yield of CE, virtual chromoendoscopy was developed by adding colour filters to the images. Fuji Intelligent Colour Enhancement (FICE) was seen to be superior in detecting small bowel lesions and in particular angioectasias compared to conventional CE[16]. In another trial by Krystallis *et al*[17] Blue Mode (BM) was found superior to FICE in detecting lesions of the small bowel. Adding BM to Quickview studies however did not show any diagnostic advantage and is therefore not recommended[15].

Figure 2 Types of small bowel capsule endoscopes. A: PillCam SB 3 (Given Imaging, Yoqneam, Israel); B: MiroCam (IntroMedic, Seoul, South Korea); C: Endo Capsule (Olympus America, Center Valley, PA); D: OMOM (Jinshan Science and Technology, Chongqing, China).

COMPLICATIONS AFTER CE

Capsule retention

Although very popular for its non-invasive character, CE can be the cause of unnecessary treatment due to complications. One of the most feared complications is capsule retention. It is defined as the presence of the capsule in the bowel lumen for a minimum of 2 wk after ingestion, or when the capsule is retained for an unspecified period of time unless targeted medical, endoscopic or surgical intervention is started[18].

According to a systematic review by Liao *et al*[19] overall retention rates are as low as 1.4%, which makes the procedure acceptable, regarding the high overall diagnostic yield of 59.4%. Furthermore, the retention rate differs according to the underlying pathology, with up to 2.6% in known Crohn's disease (CD) and 2.1% in patients with Neoplastic Lesions[19]. This can be explained by the fact that capsule retention is usually caused by masses, strictures and stenotic areas resulting from neoplastic lesions, CD, NSAID consumption or post-operative adhesions, which narrow the small bowel lumen and favors retention[20]. In this regard, known small bowel obstruction, strictures and extensive CD are a contraindication for CE[21]. In a large study by Höög *et al*[22] risk factors for capsule retention were identified. OGIB and suspected CD were associated with the lowest chance of capsule retention, whereas known CD and small bowel tumors had a higher chance of retention. These findings were also confirmed by other authors[19,23].

Most of the time, retained capsules are asymptomatic, but intestinal obstruction, partial or complete, may occur, especially in case of known CD or neoplastic lesions. In the 2009 consensus by the European Society of Gastrointestinal Endoscopy it is recommended with a grade B evidence level to precede the CE by small bowel imaging or a patency capsule (PC) (cf. infra) in patients with suspected or established CD to rule out potential strictures. As said earlier, known small bowel obstruction is a contraindication for CE and patients at risk for a small bowel obstruction should therefore be carefully investigated by their physician before a CE procedure[24].

Evacuation of the retained capsule can be spontaneously, medically or by surgery. The latter is unfortunately the most frequent intervention, but is on the other hand safe and can be seen as a required diagnostic and therapeutic tool for treating the underlying small bowel condition. With the surgery, not only the capsule is removed, but also the responsible lesion can be resected, which reliefs the patient's symptoms. However retention can also lead to unnecessary surgery of lesions caused by, *e.g.*, NSAID or CD, for which a medical solution would also have been an option[25].

In recent years, an endoscopic approach of capsule retention has become more popular as a less invasive alternative for surgery. Before capsule retrieval a radiographic localization of the capsule is done to determine whether an upper or lower gastro-intestinal and a standard (gastroduodenoscopy, Push Enteroscopy or colonoscopy) or advanced endoscopic approach

(device assisted enteroscopy) is needed. In this regard, surgery can be considered when endoscopic approaches did not manage to retrieve the capsule or when the patient presents with symptoms of toxicity[26]. In a study by Van Weyenberg *et al*[27] DBE showed to be an adequate tool to retrieve a retained capsule. Moreover the DBE was capable to aid in pre-operative staging by histological sampling. In conclusion DBE can prevent unnecessary surgery as well as determine the cause of the capsule retention before the operation, which is beneficial both for physician and patient.

Capsule perforation

Another yet very rare complication is perforation of the small bowel. Usually it results from capsule retention. In the few cases that are reported, CD was the most frequent underlying pathology causing the perforation[20,28-31]. In a study by Repici *et al*[28] a possible explanation for this complication is given. CD affects the tissue of the small bowel wall and makes it vulnerable. By the complete luminal occlusion due to the entrapment of the capsule and the high peristaltic activity the fragile tissue of the small bowel wall distends just above the capsule and leads to fissuration and possible perforation of this area. One study by Gonzalez Carro *et al*[32] reported perforation after CE in a patient with a history of surgery with subsequent adhesions. Because of the major implications, perforation should be acknowledged as a possible complication after CE in patients with known or suspected CD.

Capsule interference

One of the relative contra-indications for CE is the presence of implantable cardiac devices, such as pacemakers, ICDs, pulsatile and nonpulsatile LVADs. Interference may arise during the CE procedure resulting in an alteration of atrial or ventricular assistance[33]. This is however a theoretical assumption without clinical significance, because few studies show actual interference between cardiac devices and CE. Moreover, previous studies have already suggested that CE can be used safely in patients with these devices[34-41]. Only one study by Dubner *et al*[42] reported oversensing of an ICD due to interference with the CE procedure, which resulted in an inappropriate shock by the cardiac device. In another case report by Guyomar *et al*[37] interference between pacemaker and video capsule occurred, resulting in a failure of recording by the capsule when close to the pulse generator. Harris *et al*[43] found similar results in a 2013 study: all implantable devices proved to be safe for the patient, but LVAD had the tendency to interfere with image capture and therefore a CE lead position as far away from the LVAD as possible is required. On the other hand, in the article by Cuschieri *et al*[40] no loss of images was observed. In conclusion, close monitoring is recommended in patients with implantable cardiac devices but the risk for complications seems to be extremely low.

Capsule aspiration

Some cases have reported the existence of bronchial aspiration of the capsule. It is a very rare complication, which occurs in one out of every 800 investigations and can be asymptomatic[44]. CE aspiration can resolve spontaneously[45], but often necessitates immediate radiological investigations to localize the capsule, followed by bronchoscopy to retrieve it with the aid of a Roth Net[44]. To prevent this unnecessary invasive procedure, screening for patients at risk should be done. Risk factors include aging, neurological or swallowing disorders and patients with a weak or absent cough[46,47]. Direct placement of the capsule in the gastrointestinal tract should be considered in these patients[44-46,48]. If not, the Real Time Viewer should be used during the ingestion of the capsule to make sure that the capsule reaches the gastrointestinal tract[46-48].

Until now, only one fatality has been reported due to intracerebral haemorrhage resulting from capsule aspiration[47]. The reason for this low mortality rate is hypothesized in a study by Lucendo *et al*[44] stating that the size of the capsule is not capable to block the total lumen of the trachea and therefore still allows adequate oxygenation after capsule aspiration. However Koulaouzidis *et al*[49] found that the CE size might be correlated with the chance of aspiration.

ADDITIONAL FEATURES AND ENHANCEMENTS IN THE FIELD OF CE

Suspected blood indicator

In 2003 Given Imaging introduced the Suspected Blood Indicator (SBI) as an aid in diagnostics. The new feature highlights images suspected for redness or blood, which makes it easier for physicians to identify possible bleeding sites accurately. The software is activated when the capsule has reached the duodenum and operates only during its stay in the small bowel[50].

Sensitivity of the SBI software is determined by the presence of active bleeding. In studies, sensitivity ranges from 20% to 56.4% and increases up to 58.3% to 93% in case of active bleeding[50-52]. However, sensitivity and specificity of SBI remains too low, so complete review by a gastroenterologist is still required and the SBI only serves as rapid screening tool for actively bleeding lesions[51,52].

The detection rate of the SBI is affected by background color of the small bowel as by velocity of the capsule[50]. This is also a possible explanation for the variation in sensitivity observed among different studies. The background of the small bowel differs according to patient's condition and small bowel preparation[50]. In experimental small intestine models, a very pale magenta background showed the highest detection rate, followed by burnt sierra and yellow. Lowest detection rates were observed in small bowel sites with colors significantly different from the normal small bowel color or when the capsule reached a high velocity. In an interesting study by

Buscaglia *et al*[53] SBI was found to be an inferior screening tool for sites of potential bleeding with a sensitivity below 60% even in active bleeding. Yet they found that in CD the SBI could be used as a screening tool for detection of aberrant mucosa with high sensitivity. Another study by D'Halluin *et al*[54] also rejected the SBI software as a useful tool for screening the small bowel stating that the detection rate was poor, independent of the type of lesion. Furthermore they found that the SBI missed certain lesions while tagging few others and that irrelevant flagging might unnecessarily prolong the reading time of the CE. However, in a recent study Tal *et al*[55] stated that SBI is a reliable aid in excluding active bleeding or major lesions, but that the role of the endoscopist could not be neglected. In summary we can conclude that SBI might improve the interpretation and thereby the yield of CE by tagging areas for a second review, but can certainly not replace the gastroenterologist's review.

PC

To address the problem of capsule retention, the Agile PC was developed by Given Imaging. The PC with the same size as a video capsule, serves as dummy to assess the patency of the small bowel prior to CE examination. As one of the major contraindications for CE is suspicion of small bowel stenosis, routine administration of PCs could enable safe CE use in a larger patient population by ruling out possible stenoses[56]. The PC system consists of two main parts: the capsule itself with a radiofrequency identification tag (RFID tag) and an external detector system to capture radio-frequency signals.

The PC is made of lactose and 10% barium, which dissolves when coming into contact with intestinal fluids through the window at the edge of the capsule, also known as timer plug. To insure that the timer plug is not blocked by capsule impaction in a stricture, the second generation PCs consist of two timer plugs. If excretion does not occur, dissolution starts at 30 h. After 35 h, 38 percent of the capsules are dissolved and all are dissolved within 72 h[57]. After dissolution, the remains of the capsule encounter no difficulties to pass the small bowel strictures.

The detector system receives the radio-frequency signals coming from the RFID tag and reconstructs the exact capsule position. This can also be done by using radiography, which visualizes the PC by its radiopaque RFID tag or 10% barium[56]. Localization can be complicated by overlap of intestines so subsequent fluoroscopy or CT scan can be warranted. One drawback of the RFID tag system is the probability of impaction in a stricture, which can lead to small bowel ileus[58]. Recently a new tag-less PC was developed by Given Imaging to overcome this issue and proved its usefulness as found by Nakamura *et al*[58].

The PC procedure is not as strict as the CE procedure. The capsule can be swallowed without previous food restrictions. If the capsule is not excreted in 33 h, further examination is warranted to localize the PC and make a distinction between a small bowel and a colonic localization. The latter is still an indication for VCE. The subsequent CE has to be done quickly after PC so a possible change of stricture status and subsequent capsule retention is avoided[56].

The use of the PC still remains controversial. Although some authors have reported its utility[59-61], others have found that the capsule was not capable of confirming stenoses, which were found on CT or small bowel follow through[62]. In conclusion, patients still benefit from a CT investigation prior to CE to exclude possible stenosis and strictures.

CapsoCam capsule

Over the last decade, a new player entered the field of CE. CapsoCam by Capsovision renewed the concept of CE by offering a capsule with a 360° view and on-board storage, which enables the retrieval of images wire-free after interception of the capsule in the feces. The capsule contains four cameras, which offer high resolution images and a frame rate up to 20 fps max. Furthermore, two new technologies were developed, Smart Motion Sense Technology and Auto Illumination Technology. Smart Motion Sense Technology enables the capsule to activate its cameras only during capsule motion. When the capsule is stationary, a sensor is used to compare the current frame with the previous frame to control reactivation. Auto Illumination Technology controls the 16 white LEDs to provide the optimal level of illumination. When the capsule is located nearby the walls, a low light intensity is optimal to capture the best images. A position further away from the wall necessitates a higher light intensity. By adding these software features, battery life is sustained up to 15 h. The first clinical trial that used the CapsoCam accepted it as a safe and efficient tool in small bowel evaluation[63]. In a recent French study by Pioche *et al*[64] the concordance between the PillCam SB2 and CapsoCam was evaluated in terms of diagnostic yield and image quality. A kappa value of 0.63 was obtained, which confirms the good concordance between the two capsules. Although the reading time of the CapsoCam was longer, the CapsoCam detected significantly more lesions in a per lesion analysis.

Three-dimensional representation

In recent years, three-dimensional representation is becoming a hot issue. By reproducing the depth information lost by camera recording, diagnosis can be facilitated, because the texture and the abnormalities of the mucosa are highlighted. 3-D rendering can be software- or hardware-based. The latter is limited by the technological possibilities of the capsule, so software based 2-D to 3-D conversion is used[65,66]. Software-based 3-D rendering uses algorithms to recreate the third dimension. In a study by Karargyris *et al*[67] four Shape-from-Shading (SfS) algorithms were compared. The Tsai's SfS algorithm excelled the other algorithms in

visualization improvements, but we may not forget that the evaluation criterion was subjective in origin. However, the Tsai's SfS algorithm is especially adapted to bright and round surfaces, therefore perfectly applicable in small bowel endoscopy.

Lesion localization

Apart from the image quality, accurate lesion localization is one of the key elements of CE, because further therapeutic steps, non-invasive and invasive, can depend on the exact localization of the lesion[68]. Lesion localization is currently estimated according to the transit time and the use of pylorus and caecum as landmarks, but lacks precision.

Exact localization can be determined by using a capsule emitting a magnetic field or electromagnetic waves. Both methods have their advantages and drawbacks. Magnetic-field-strength-based localization is not attenuated by the human body and the capsule does not have to be aligned with the detectors to be detected. As a drawback, interference of the magnetic fields for capsule localization and the magnetic fields for active capsule movement in the future (cf. infra) may occur. On the other hand electromagnetic waves localization, such as the previously mentioned RFID tag, is based on radio-frequency waves, which are attenuated by the human body and therefore may lose precision. A promising step forward in capsule localization is the development of a new software by Olympus Medical Systems Corporation (Tokyo, Japan), which uses a 3D-triangulation. The exact capsule position is calculated by determining its distance from the 6 radiofrequency sensors using radiofrequency signal strength. In the study by Marya *et al*[69] an average localization error of 13.26 cm^3 by attenuation was observed, especially in patients with an increased BMI.

Finally, in 2010 the Capsule-odometer, a conceptual CE design, was proposed by Karargyris *et al*[70] which in theory offers a more accurate lesion localization. The capsule has two protruding wheels attached to a spring-mechanism, so the wheels can adapt to the diameter of the intestinal lumen, serving as a micro-odometer with subsequent accurate lesion localization, calculated from the onset of the capsule investigation. This design also offered a greater stability, avoiding non-forward movement through the gastrointestinal tract. Further experiments and research are needed on this subject.

MAJOR INDICATIONS FOR SMALL BOWEL CE

CE has been approved for various indications. These include (1) overt and occult obscure gastrointestinal bleeding; (2) suspected CD; (3) surveillance in patients with polyposis syndromes and detection of small bowel tumors; (4) screening and evaluation of NSAID side-effects; and (5) suspected malabsorptive syndromes such as celiac disease. These indications will be explained further on in this paper. Relative contra-indications for CE include, like mentioned before: (1) known or suspected GI obstruction, strictures or fistulas; (2) cardiac devices; (3) swallowing disorders; and also (4) pregnancy.

Obscure gastrointestinal bleeding

Obscure gastro intestinal bleeding (OGIB) is defined as bleeding of unknown origin that persists or recurs following a bidirectional negative endoscopic evaluation of the gastrointestinal tract. OGIB is a common problem encountered by gastroenterologists, and accounts for approximately 5% of all GI bleedings[71]. OGIB can be overt (melena, hematochezia, hematemesis) or occult (iron-deficiency anaemia, IDA, with or without a positive fecal occult blood test). OGIB is mostly caused by a lesion located in the small bowel, but can also originate from a lesion in the other parts of the GI tract as well, missed with conventional endoscopy because of intermittent bleeding or by human error[72]. The underlying pathology is age dependent. Under the age of 40, the most frequently detected lesion is a small bowel tumor, followed by Meckel's diverticulum, Dieulafoy's lesion and CD. Above the age of 40, vascular lesions such as angiodysplasia are most frequently observed, counting for up to 40% of the underlying lesions. NSAID-induced lesions (cf. infra) are the second most frequent finding on CE[71].

Since its development in 2000, CE has mainly been used for the indication of OGIB, accounting for 60%-70% of the patients[8]. CE has proven superiority to all other diagnostic modalities in OGIB, such as barium contrast radiology, small bowel computed tomography (CT), magnetic resonance imaging (MRI), push enteroscopy and angiography, as can be seen in Table 2. The American Society for Gastrointestinal Endoscopy (ASGE) confirmed these findings in their guidelines presented in 2007[71]. Before using CE as a diagnostic tool, at least one gastroduodenoscopy and ileocolonoscopy have to be performed to rule out upper and lower gastrointestinal tract abnormalities. Repeating gastroscopies or colonoscopies immediately prior to CE in patients who have not had endoscopic investigations for more than 6 mo, tends to have a low diagnostic yield and is not cost-effective[73]. Therefore, CE is recommended as the first-line investigation after negative bidirectional endoscopies. Younger patients however have a higher chance of IBD or tumours and a CT abdomen is indicated prior to CE to rule out stenosis[20]. A gynaecological etiology has to be considered in young females.

The overall yield of CE is between 35% and 83% for OGIB[19,71,72,74-80] with its mean around 60%[81,82]. Diagnostic yield is influenced by the type of bleeding. Patients with ongoing overt bleeding usually present with a higher diagnostic yield than patients with obscure-occult bleeding, presenting as IDA[72,83]. More factors associated with a higher diagnostic yield have been identified, including low hemoglobin measurements, transfusion need, older age and a short interval of less

Table 2 Comparison of different diagnostic modalities in obscure gastrointestinal bleeding

Ref.	Country	Design	No. of patients	Comparator	Yield of CE, (%)	Yield of Comparator, (%)	Significant difference? (yes/no)	CE superior? (yes/no)	Other
Triester *et al*[80]	United States	Meta-analysis and Systematic review	396	PE	63	28	Yes	Yes	NNT = 3 to yield one additional clinically significant finding with CE
			88	SB radiography (barium contrast and enteroclysis)	67	8	Yes	Yes	NNT = 3 to yield one additional clinically significant finding with CE
Leighton *et al*[82]	United States	Meta-analysis and Systematic review	396	PE	63	28	Yes	Yes	Yield of significant findings: CE = 56% *vs* PE = 26%, NNT = 3 to yield one additional clinically significant finding with CE
			88	Barium radiography	67	8	Yes	Yes	Yield of significant findings: CE = 42% *vs* SB barium radiography = 6%, NNT = 3 to yield one additional clinically significant finding with CE
			42	Intraoperative enteroscopy	83	83	No	No	
			17	Mesenteric angiography	47	53	No	No	
Chen *et al*[205]	China	Meta-analysis and Systematic review	277	DBE	61	56	No	No	CE was superior if no combination of oral + anal approach <-> DBE was superior when a combination of the two insertion approaches was done
Pasha *et al*[95]	United States	Meta-analysis and Systematic review	397	DBE	24	24	No	No	CE should be the initial diagnostic test for determining insertion route of DBE
Arakawa *et al*[76]	Japan	Retrospective Study	162	DBE	54	64	No	No	
Teshima *et al*[77]	Canada, The Netherlands	Meta-analysis and Systematic review	651	DBE	62	56	No	Yes	Yield of DBE after positive CE = 75.0% <-> yield after negative CE = 27.5%
Leung *et al*[206]	China	RCT	60	Mesenteric angiography	53	20	Yes	Yes	No significant difference in the long-term outcomes (transfusion need, hospitalization for rebleeding,mortality)
Wang *et al*[207]	China	Meta-analysis and Systematic review	279	CT	53	34	Yes	Yes	Complementary role to CE and can be used as a triage tool prior to DBE in evaluating OGIB

PE: Push enteroscopy; CE: Capsule endoscopy; SB: Small bowel; NNT: Number needed to treat; DBE: Double balloon enteroscopy; RCT: Randomized controlled trial.

than 3 d between admission and the CE procedure[84-88]. CE is recommended in all cases of OGIB because of its diagnostic value and its impact on further management. A study by Albert *et al*[75] found that CE was able to determine the therapy in 66% of the cases and led to an alteration in management in 32.3% of the cases. This is in line of previous studies, which reported that CE could alter subsequent management in 23%-66% of the cases[79,85,89-91]. Sidhu *et al*[84] found that this management alteration could be predicted by patient comorbidity or angiodysplasia findings on CE.

The reason why CE has been recommended as first-line examination tool over DBE after initial negative upper and lower endoscopies is its noninvasive nature and ease of use, which makes it well-tolerated and feasible in an outpatient setting[92]. Furthermore its ability to visualize the whole small bowel in more than 80%-85% of the cases[93,94] and the ability to determine the initial DBE approach makes it a helpful tool in OGIB diagnostics[92,95]. However, CE often fails to visualize lesions in the proximal small bowel, in a Roux-en-y loop and in patients presenting with diverticula[76].

If necessary, a CE procedure can be followed by a double balloon enteroscopy (DBE) procedure[72]. DBE is the only diagnostic tool showing a similar diagnostic yield for OGIB as VCE, as can be seen in Table 2. However, the DBE procedure is more invasive, can be time-consuming, requires training, needs sedation or general

anesthesia and can have a complication rate of up to 4.3% in therapeutic procedures as was reported by Mensink *et al*[96]. Moreover DBE is not always able to visualize the whole small bowel. A completion rate of only 62.5% was achieved in DBE, compared to 90.6% in CE as reported by Nakamura *et al*[94]. Yet, DBE is preferred over CE in patients requiring a biopsy or a therapeutic intervention such as argon plasma coagulation (APC). Also DBE tends to have an acceptable yield in patients with an initial negative CE and suspicion of a small bowel lesion[95,97], although it has been reported being much lower than the yield of DBE following a positive CE, respectively 28% and 75%[77].

Not only clinically, but also economically is CE recommended as first line investigation of OGIB. It has shown to be more cost-effective than DBE when only visualization of the small bowel is needed[98]. Negative CE investigations usually do not require further diagnostic work-up, which saves money in the long term, because reimbursement for CE is less than for DBE[93]. A mean cost-saving of €1738.07 was reported by Marmo *et al*[99] when CE was preferred over other modalities in OGIB and turned out to be positive. However, only reimbursement costs were evaluated, so the cost of the hospital and the personnel was not taken into account.

If a therapeutic intervention is needed with a probability of more than 25%, gastroenterologists should consider the use of DBE as initial therapeutic option to minimize costs[93]. Furthermore, cost equalization of DBE and CE was reached at 100 procedures for diagnostic DBE and 79 procedures for therapeutic DBE, which suggests that DBE is especially cost-effective in large-scale hospitals, with a substantial number of DBE procedures per year. Another study by Gerson *et al*[100] found that, regardless of the cost, DBE procedure was more cost-effective than CE-guided DBE procedure, because no additional costs were charged regarding further examinations and therapy could be given instantly. However, the workload for physicians would significantly increase if an initial DBE would be done and we may not forget that DBE is correlated with a higher rate of complications compared to CE. CE-guided DBE was associated with better outcomes in the long term because of fewer potential complications and fewer utilization of endoscopic resources. This can be explained by the high negative predictive value of CE, which leads to a reduction in the subsequent DBE procedures[92,100].

When CE is negative, the chance of rebleeding is low, so that further investigations can be deferred, even when a second test might be diagnostic[101-103]. Rebleeding was reported to be higher in CE-positive patients and patients using anticoagulants[103]. Nonetheless, gastroenterologists should consider close monitoring, alternative modalities in suspicious cases because the chance of rebleeding has been reported up to 28.4% and 35.3% during a median follow-up of respectively 23.7 mo and 31.7 mo[104,105]. Repeating the CE procedure however should only be considered if the bleeding presentation switches from occult to overt bleeding or the hemoglobin level drops with more than 4 g/dL[106]. Diagnostic yield of a repeated CE was reported to be between 35% and 75% and a subsequent management change was reported in 39% to 62.5% of the patients[107,108].

To conclude this chapter about OGIB, we have made a flow-chart to represent the current knowledge in this field. For this purpose we included the reviewed articles in previous flow charts[18,109] (Figure 3).

CD

Non-stricturing CD is the second main indication for CE. CD is a type of chronic IBD which may affect the whole gastrointestinal tract and lead to mucosal and transmural damage. Categorization of patients with CD is done based on the disease presentation: solely the small bowel (30%-35% of the patients), the small bowel and the large bowel (45%-50%) or only the large bowel (20%)[110]. So even though it primarily affects the terminal ileum, the ileocecal region and the large bowel, one third of the patients presents with only small bowel inflammation which challenges gastroenterologists to diagnose the disease. Traditionally small bowel involvement was diagnosed by radiological procedures, small bowel barium radiography, CT, colonoscopy with ileoscopy or enteroscopy. But with the invention of CE, new possibilities in CD diagnostics have become available.

CE can be very helpful in the diagnosis of new cases of Crohn and in the evaluation of known CD, with regard to the activity and extent of the disease. CE is reserved however for cases with unexplained symptoms, when other investigations remain inconclusive or when CE would affect the management of the patient[111]. So both in suspected as established CD, CE usually is performed third after a negative colonoscopy and ileoscopy, thereby replacing the traditional modalities. CE is considered positive for CD when more than 3 ulcerations are identified in the absence of NSAID use[111-113] or when 4 or more obvious clear ulcers, erosions, or a region with clear exudate and mucosal hyperemia and edema are seen[114].

Like in OGIB, CE also has shown a superior yield for detecting early inflammatory lesions in the small bowel comparing to all other modalities as can be seen in Table 3. The yield of CE in non-stricturing CD has been reported to be between 18% and 96%[81,95,115-119]. Triester *et al*[81] only found a significant difference in yield between CE and other modalities for diagnosing non-stricturing small bowel CD. However, a distinction should be made between suspected and established CD. The reported superior yield was only significant for evaluating established CD and was not reported for diagnosis of small bowel CD in patients with a suspected initial presentation of the disease. This was contradicted by Dionisio *et al*[115], who found that CE has a superior yield compared to small bowel radiography (SBR), CT enterography (CTE) and colonoscopy with ileoscopy in the diagnosis of suspected CD patients. Although the

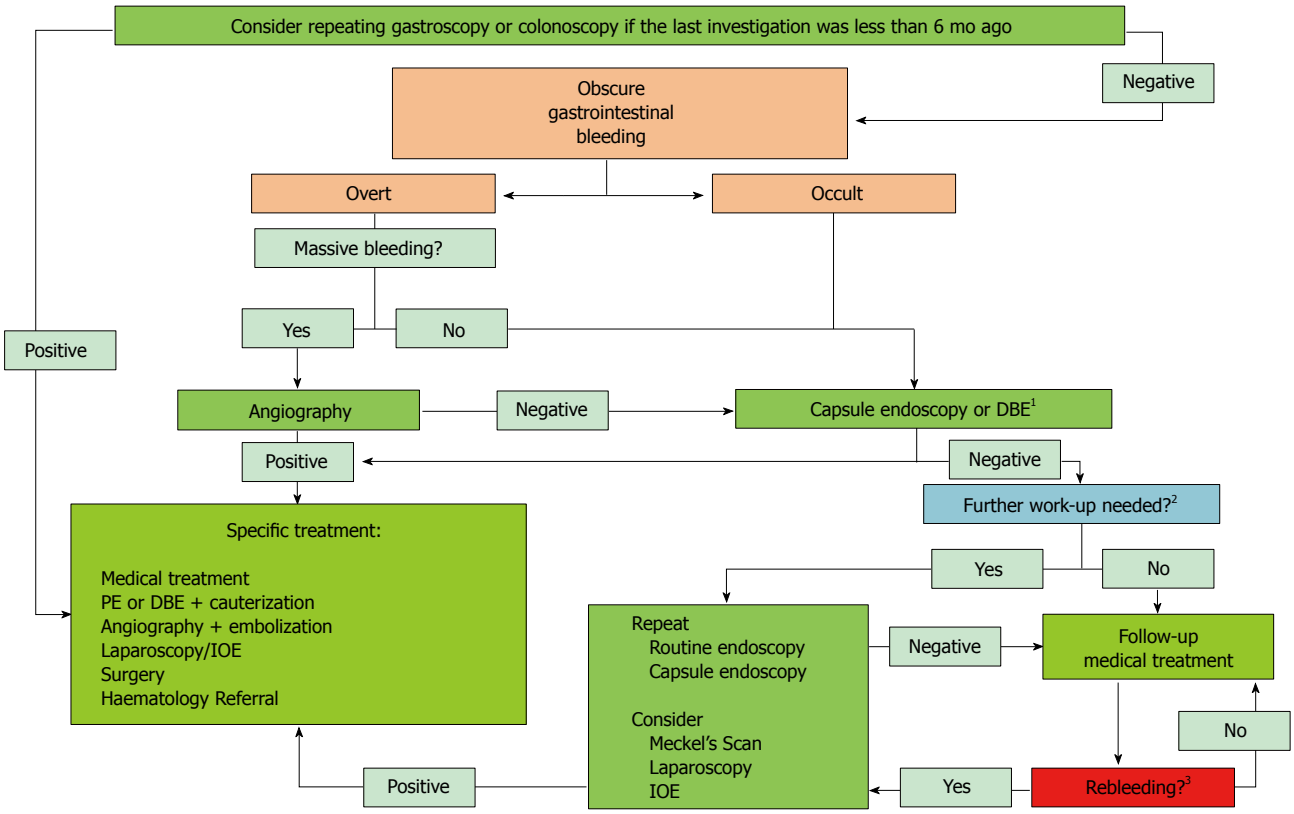

Figure 3 Recommended approaches for diagnosis and treatment of obscure gastrointestinal bleeding. [1]DBE is recommended in (1) patients requiring a biopsy or a therapeutic intervention (2) patients with an initial negative CE and suspicion of a small bowel lesion (3) large scale hospitals or (4) hospitals where CE is not available; [2]If a lesion is suspected, further work-up is needed; [3]Rebleeding was defined as a change from occult to overt bleeding or a hemoglobin level drop more than 4 g/dL. DBE: Double balloon enteroscopy; PE: Push enteroscopy; IOE: Intraoperative enteroscopy; Routine endoscopy: Uni/bidirectional endoscopy.

yield of CE in CD is high, the proportion of CD patients diagnosed with CE is rather low (0%-4%). Only in young patients presenting with abdominal pain plus diarrhea a 30% chance of diagnosing CD was achieved[114]. In established CD patients, CE was reported to be superior compared to SBR, CTE and PE, which was the same according to previous findings[115]. When compared to CT enterography and MR enterography, CE shows superior yields in the first two-thirds of the small bowel, but loses this superiority in the last portion of the small bowel by showing a yield similar to the comparators[120,121]. However, we may not forget that MR enterography is also capable of visualizing the small bowel surroundings, so that transmural and extra-intestinal manifestations can be diagnosed[122]. A recent study by Leighton *et al*[123] found that a combination of colonoscopy with ileoscopy and CE achieved a far more high yield than patients investigated with a combination of colonoscopy with ileoscopy and small-bowel follow-through (SBFT). They confirmed the role of CE as valuable third diagnostic option in diagnosis of suspected CD, when colonoscopy and ileoscopy turned out to be negative or inconclusive.

In patients with suspected CD, Girelli *et al*[119] found that, presuming a pre-test probability of CD of 50%, a positive CE was capable to raise the post-test probability up to 85% and if the CE was negative, it was capable to lower the probability to only 5%. In patients with established CD, the use of small bowel CE in monitoring therapy response is still a controversial issue. Many reports found that the clinical and biological response to treatment is not correlated with mucosal healing, which is monitored on CE, so it has not proven useful in this respect[124].

Caution should be taken when evaluating CEs positive for small bowel lesions. Because of the potential of CE to detect early lesions, CD-induced lesions are often non-specific and can be confused with NSAID-induced lesions. Both CD and NSAID-induced small bowel injury show endoscopically similar lesions and because of the inability of CE to take biopsies, the differential diagnosis remains inconclusive. Pathognomonic however for NSAID-induced lesions are the concentric diaphragmatic strictures in the ileum seen on endoscopy, which can lead to small bowel obstruction[125]. According to Doherty *et al*[126] the problem of false positive capsules also overestimates the incremental yield of CE compared to other modalities, necessitating a diagnostic golden standard to overcome the problem of premature CD diagnoses. Currently, there are two scores available to assess and monitor mucosal disease activity on CE. The CE CD Activity Index (CECDAI or Niv score) and the Lewis score are only recently developed and still have to prove their usefulness in standardizing the diagnosis of CD on CE before being widely accepted in clinical

Table 3 Comparison of different diagnostic modalities in Crohn's disease

Ref.	Country	Design	No. of patients	Comparator	Yield of CE, (%)	Yield of Comparator, (%)	Significant difference? (yes/no)	CE superior? (yes/no)	Other
Marmo *et al*[117]	Italy	RCT	31	SB radiography (enteroclysis)	71	26	Yes	Yes	Terminal ileum: yield 89% *vs* 37% Proximal SB: yield only 46% *vs* 13%
Chong *et al*[208]	Australia	Blinded prospective trial	43	SB enteroclysis	77	19	Yes	Yes	Results are in patients with a history of CD
				PE	77	14	Yes	Yes	
Triester *et al*[81]	United States	Meta-analysis and Systematic review	250	SB barium radiography	63	23	Yes	Yes	NNT = 3 to yield one additional diagnosis with CE
			114	Colonoscopy with ileoscopy	61	46	Yes	Yes	NNT = 7 to yield one additional diagnosis with CE
			93	CT enterography/CT enteroclysis	69	30	Yes	Yes	
			84	PE	46	8	Yes	Yes	
			18	MR enterography	72	50	No	Yes	
Solem *et al*[118]	United States	Blinded prospective trial	41	CT enterography	83	83	No	No	Specificity of CE (53%) was significantly lower than the other tests
				Colonoscopy with ileoscopy	83	74	No	Yes	
				Small bowel follow-through	83	65	No	Yes	
Pasha *et al*[95]	United States	Meta-analysis and Systematic review	343	DBE	18	16	No	No	
Dionisio *et al*[115]	United States	Meta-analysis and Systematic review	428	SB barium radiography	52	16	Yes	Yes	
			236	Colonoscopy with ileoscopy	47 (71)[1]	25 (36)	Yes	Yes	Suspected CD (Established CD)
			119	CT enterography	68 (71)	21 (39)	Yes	Yes	Suspected CD (Established CD)
			102	PE	66	9	Yes	Yes	Established CD
			123	MR enterography	55 (70)	45 (79)	No	Yes (no)	Suspected CD (Established CD)
Lu *et al*[116]	China	Retrospective Study	50	Colonoscopy with ileoscopy	96	66	Yes	Yes	Combination of two methods showed a higher yield, but no significant differences were reported between each two examinations
			34	CT enterography	96	85	Yes	Yes	
			39	Small bowel follow-through	96	67	Yes	Yes	

[1]Extra information between brackets is specific for Established Crohn's disease. PE: Push enteroscopy; CE: Capsule endoscopy; SB: Small bowel; NNT: Number needed to treat; DBE: Double balloon enteroscopy; RCT: Randomized controlled trial.

practice as an objective tool of mucosal inflammation measurement[127,128]. Although the yield of CE has been questioned by these diagnostic problems, CE still remains a valuable tool in the diagnosis of CD: a recent study by Hall *et al*[129] found a very high negative predictive value in the long term despite the questioned yield in patients with suspected CD, which makes it capable of safely ruling out suspected CD.

As mentioned before, capsule retention is especially feared in patients with CD because of possible strictures and stenosis. The reported 2.6% by Sharaf *et al*[130] has made small bowel imaging a standard exam previous to the CE procedure[19]. MR is a useful tool to asses patency of the small bowel[131]. Another possibility is the use of the previously discussed Pillcam PC (Given Imaging, Yoqneam, Israel), which indicates patency if the capsule is excreted intact or the scan has lost the RFID tag signal 30 h after ingestion[132], so the CE procedure can be done to evaluate the mucosal surface of the small bowel.

Cost analyses for CE in CD have been made and showed that colonoscopy with ileoscopy followed by a CT enterography was the most cost-effective choice

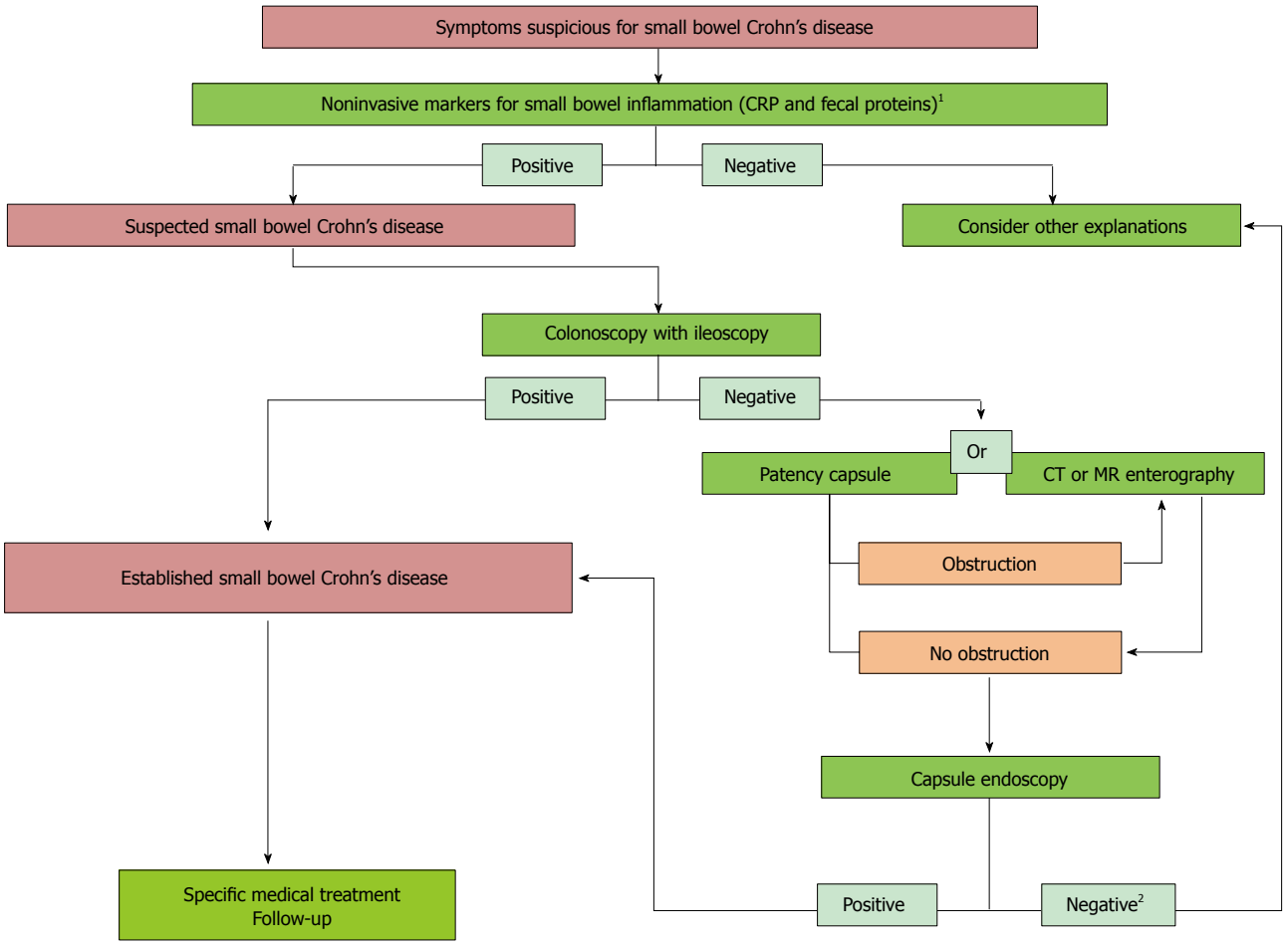

Figure 4 Recommended approaches for diagnosis and treatment of Crohn's disease. [1]Non-invasive markers have proven to be useful in giving baseline information about the presence of small bowel inflammation; [2]If capsule endoscopy (CE) is negative, Crohn's disease can be ruled out due to the high negative predictive value of CE. In that case, other explanations should be considered. CRP: C reactive protein.

among the different diagnostic options in patients suspected of CD[133]. Moreover, CE was proven to be not cost-effective as third diagnostic option, because of the high false positive rate, the diagnostic yield and the low pre-test probability of CD. Sharaf *et al*[130] confirmed these findings and concluded that CE is not a valuable option in patients with suspected CD. However, Leighton *et al*[134] found that CE did play a significant role in early diagnostics of CD, because it did not necessitate repeated procedures, physician visits and hospital stays, so direct costs could be reduced. Further investigation on this matter is needed.

In summary, CE has a superior diagnostic yield when compared to other modalities in suspected as well as established small intestinal CD. However, the question if this superior yield is due to false positive results remains unanswered. With the development of two scoring systems, this problem might be solved in the near future. Still, CE is a promising tool in CD diagnostics because of its capability to early diagnose small bowel lesions. We conclude with a flow chart based on the ICCE flowchart[131] and Mergener *et al*[109] with incorporation of new evidence[124,129] (Figure 4).

Surveillance of polyposis syndromes and detection of small bowel tumors

Small bowel tumors make up only 3%-6% of the gastrointestinal neoplasm cases despite the 90% of the gastrointestinal tract surface the small bowel covers, which makes it a difficult entity to diagnose[135,136]. The most frequently observed tumors are adenocarcinoma, gastrointestinal stromal tumor, carcinoid, lymphoma and sarcoma[137-140]. Symptoms are rather unspecific and include anaemia or overt OGIB and later abdominal pain, nausea, vomiting, weight loss and anorexia[141,142]. Thereby tumors are mostly found on CE or DBE when investigating patients with OGIB[80,139,140,143]. A study by Singeap *et al*[137] reported a detection rate for small bowel tumors of 4.9% in patients presenting with OGIB or other nonspecific symptoms. Other studies have found a tumor detection rate of 6%-12% on CEs done for OGIB[144]. The insidious process often is responsible for the delayed diagnosis of a patient, which impacts the further management of the patient[145]. Fast tumor detection is therefore very important, since management can be changed accordingly and outcomes can be improved even in malignant lesions if metastasis is

absent[146]. Small bowel tumors can be benign, potentially malignant, malignant or metastatic. However the majority, 60%, of these tumors are malignant[144], and differentiation between benignant and malignant cannot be made on CE. Tumors mostly appear as masses or polyps, but also can present as ulcers and stenoses in a minority of the cases. Hereditary polyposis syndromes like Familial Adenomatous Polyposis (FAP) and Peutz-Jeghers Syndrome (PJS), are another entity and apart from the colon polyposis, patients often develop benignant small bowel pathology with a high tendency to evolve into cancer[147].

CE was evaluated for small bowel tumors and hereditary polyposis syndromes and turned out to be a valuable diagnostic tool[148,149]. The pooled detection rate of CE was 55.9%[19]. Therefore, In patients with suspected small bowel tumors, CE can be the first choice in diagnostics[137]. In a study by Schulmann *et al*[147] it was stated that CE was capable of detecting small bowel polyposis, located in the distal jejunum and ileum beyond the reach of PE. These polyps could subsequently be removed by DBE, so surgery was avoided. However, most FAP patients with distal polyposis also presented with proximal polyposis, which was equally detected by CE as well as PE. Proximal jejunal polyposis is significantly correlated with the presence and severity of duodenal disease, which is one of the main locations for adenocarcinoma and subsequent mortality. Because CE was capable of detecting proximal small bowel polyposis and given its superior sensitivity and non-invasive nature, it was recommended as a surveillance tool in a subgroup of FAP patients with severe duodenal polyposis[147]. Duodenal polyposis itself is difficult to detect by CE, due to the rapid transit of the capsule in this part of the gastrointestinal tract. Another study by Plum *et al*[150] confirmed the superiority of CE compared to other modalities such as PE, ileoscopy and enteroclysis in patients with FAP. However, they also stressed on the fact that CE did not replace the other modalities, because CE sometimes missed lesions and did not manage to precisely localize the small bowel lesions. Also a study by Wong *et al*[151] confirmed the fact that CE could underestimate the number of small bowel polyps in FAP and a review by Koornstra[152] stated that CE cannot totally replace standard endoscopy in the surveillance of the proximal small bowel. A tool to overcome missed lesions might be the recently developed CICE tool, which enhances the contrast of the CE images and thereby improves the visibility in patients with small bowel polyposis. Although further evaluation is needed, a first trial showed that half of the adenomatous polyps could be better visualized and hamartomatous polyposis was better visible[153].

In PJS, CE was capable of detecting lesions with direct impact on further management. CE is the most accurate diagnostic tool to detect small bowel polyposis throughout the whole small bowel and can be seen as a safe alternative for the traditional modalities, such as PE and MR enteroclysis used in PJS and FAP[147]. The superiority of CE over MR enterography was also confirmed by Liao *et al*[19] who found that CE was capable of detecting smaller small bowel lesions. Urgesi *et al*[143] stated that CE could detect more lesions than the traditional endoscopy and radiological imaging in patients suspected for small bowel tumors. They concluded that CE played an important role in the diagnostic work-up of these patients[143]. Similarly another very recent study by Urquhart *et al*[154] found that CE was able to identify significantly more small bowel polyps compared with MRE in patients with PJS. Furthermore, Rahmi *et al*[155] found that CE was also useful in planning the DBE approach in patients in need of polypectomy. DBE, which achieves a similar yield as CE, is useful when biopsy, exact pre-operative localization or local therapy, such as stenting or balloon dilatation is needed[156].

CE also has its limitations in the detection of small bowel tumors. First of all it is not useful in an emergency setting, such as obstruction and peritonitis, because of the risk of capsule retention[145]. Furthermore, CE is not capable of treating locally or taking biopsies, needed to differentiate between benignant and malignant[157]. Finally CE is not able to differentiate a mucosal bulge from a smooth-walled tumor. To overcome the latter problem, the scoring system SPICE (Smooth, Protruding lesion Index on CE) has been developed. A score greater than 2 is suggestive of small bowel malignancy, but further validation is needed[158].

Just like in CD, the risk of capsule retention is present. Yet the rate is lower in patients with intestinal tumors compared to patients with CD[19]. Moreover, Bailey *et al*[146] stated that obstructions due to neoplasms were a positive complication because, since the tumor anyway needed to be treated by enteroscopy or surgery, the impacted capsule could serve as a guide. Like in CD, if the patient is suspicious for obstruction, imaging should be done before CE. Management of malignant small bowel tumors is primarily surgical. In selected cases, this can be performed laparoscopically. Adjuvant chemotherapy and radiotherapy may be needed, depending on the histology of the tumor[135].

We can conclude by stating that CE is a diagnostic tool with a big value regarding its yield in diagnosis and surveillance of small bowel tumors/polyps. However, it is complementary to the traditional modalities and can not substitute them. CE is recommended third after negative bidirectional endoscopy in patients with OGIB or other unspecific symptoms indicating a possible small bowel tumor. It can be used first as a complementary diagnostic tool in patients with established hereditary polyposis syndromes. We summarized the evidence in two flow-charts based on the Consensus statements for small–bowel CE, 2006/2007 by Mergener *et al*[109] and a study by Plum *et al*[150] (Figures 5 and 6).

NSAID side-effects

NSAIDs can inflict injury along the whole gastrointestinal tract, when used for a prolonged time. Although many

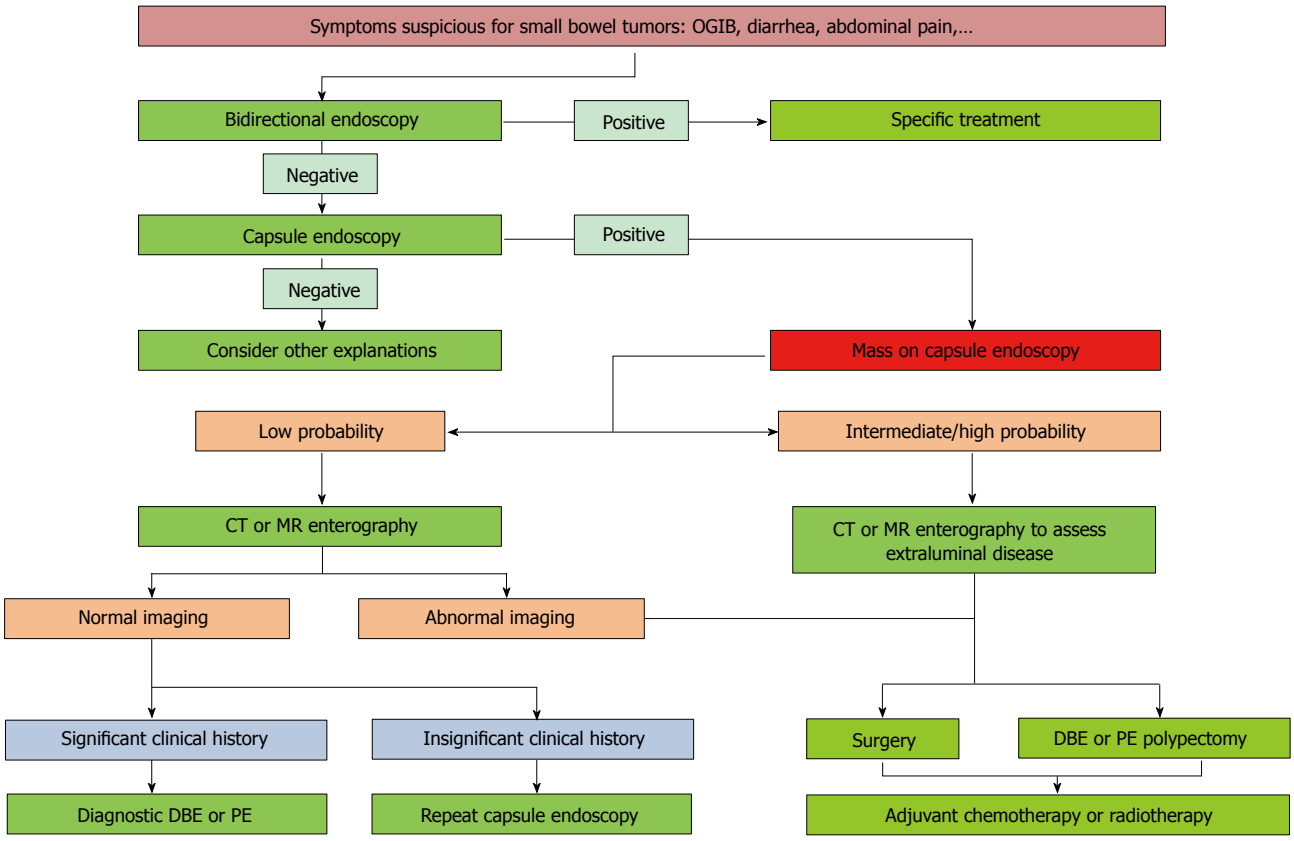

Figure 5 Recommended approaches for diagnosis and treatment of small bowel tumors. DBE: Double balloon enteroscopy; PE: Push enteroscopy; OGIB: Obscure gastrointestinal bleeding.

publications have emphasized on the incidence of upper gastrointestinal lesions, fewer have mentioned lower gastrointestinal ones. However, as mentioned before, NSAIDs can also induce small bowel lesions, which can be observed on CE. In fact, these lesions are far more common than the NSAID-induced gastropathy[159]. Furthermore, complications in the lower gastrointestinal tract, such as perforation, bleeding, or obstruction are currently increasing while upper GI complications are decreasing[160], which necessitates the need of small bowel diagnostics in the field of NSAID side-effects.

In seventy percent of the patients using NSAIDs continuously, mucosal damage of the small intestine has been reported on CE or DBE[161,162]. Even a two-week NSAID-regimen with slow-release diclofenac resulted already in macroscopic injury of the small intestine in 68%-75% of the volunteers[163]. Different types of lesions have been observed ranging from mucosal redness and multiple petechiae to erosions, ulcers, loss of villi, diaphragm-like strictures, which are pathognomonic for NSAID-induced enteropathy, and even severe bleeding[164,165]. Most symptomatic patients present with OGIB with or without obstruction symptoms and are accordingly diagnosed[166,167].

Both CE and DBE have been evaluated for NSAID-induced lesions. They show a similar yield of 60% in diagnosis[166,168]. CE however is preferred for screening of NSAID-induced lesions and evaluation of further treatment because of its non-invasive character. DBE on the other hand is the first choice in patients suspicious of strictures. NSAID-use has been recognized as a risk factor for capsule retention and CE should therefore be avoided in these patients[19]. Furthermore DBE is preferred when further examination of the lesion, endoscopic or histologically, is needed or when local therapy has to be given, such as balloon dilatation of a stricture or endoscopic coagulation, clipping or injection of the bleeding site. Balloon dilatation of a stricture seems to be safe, since the muscularis propria remains intact and perforation is subsequently rarely observed[156]. A recent study by Tacheci *et al*[169] confirmed the high sensitivity of CE and further stated that subclinical small bowel damage also could be observed on CE. If NSAID enteropathy is found on CE or DBE, further investigation can be done using other modalities such as radiological examination, the permeability test, scintigraphy, the fecal excretion with ^{111}In white blood cells and measurement of the calprotectin concentration in the feces[164].

Just like in CD, scoring systems are available to classify lesions and to consider and evaluate further treatment[127,161,163,168]. However, no standard scoring system is thoroughly evaluated. Different therapeutic options are available. The first choice of therapy is a discontinuation in the use of NSAIDs, which in most cases is not possible due to the underlying pathology[161]. Cyclooxygenase-2 (COX-2) selective inhibitors, prostaglandin derivatives, a combination of NSAIDs and

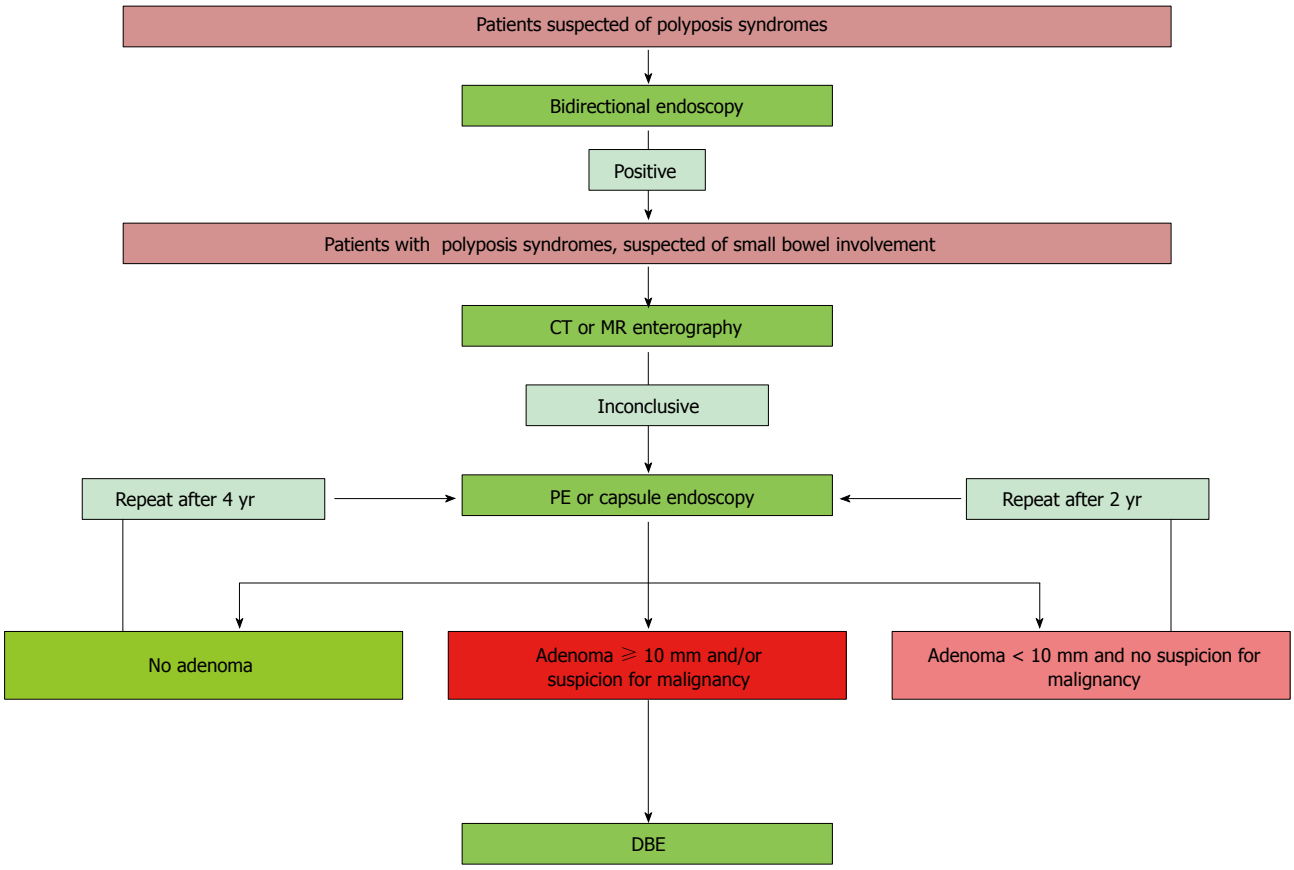

Figure 6 Recommended approaches or diagnosis of small bowel hereditary polyposis. DBE: Double balloon enteroscopy; PE: Push enteroscopy.

phosphatidylcholine, cytoprotective drugs and probiotics are all useful for the treatment of NSAID-induced small intestinal injuries[159]. Yet controversy remains around the use of selective COX-2 agents. A trial by Goldstein *et al*[170] reported that a 2-wk regimen of selective COX-2 agents caused fewer small intestine injuries than treatment with a nonspecific NSAID. This was confirmed in a big RCT by Chan *et al*[171]. However, Maiden *et al*[172] showed that COX-2 selective inhibitors caused the same amount of small bowel damage as long-term NSAIDs, which is interesting given the fact that they affect the gastroduodenal mucosa to a lesser extent[170]. So COX-2 might play a significant role in the maintenance of the small bowel integrity. We can conclude that it remains unclear whether selective COX-2 inhibitors truly prevent NSAID-induced enteropathy.

Also chronic Low-dose aspirin (LDA) users are at risk of small bowel enteropathy. The phenomenon was first described by Leung *et al*[171] in 2007 and the study by Endo *et al*[165] was the first to report the characteristics of the small bowel damage associated with long-term LDA use. The use of LDA however was less harmful than other types of NSAIDs[166]. These findings may have implications on treatment of the large group of patients requiring anti-inflammatory or antithrombotic drugs.

Celiac disease

Celiac disease is caused by an chronic auto-immune response of the intestines to gliadins in the diet and occurs in approximately 1% of the population in genetically susceptible persons[174]. It is characterized by duodenal folds, scalloping of folds, mucosal fissures, crevices or grooves, visible submucosal vessels, micronodules in the duodenal bulb and a mosaic pattern in the small bowel mucosa[175]. The lesions are visible on CE, which makes CE therefore a perfect tool to assess small bowel damage in these patients. In a large meta-analysis by Rokkas *et al*[176] sensitivity and specificity of CE in celiac disease have been reported up to 89% and 95% respectively. This was similar to a previous meta-analysis by El-Matary *et al*[177] which reported a sensitivity of 83% and a specificity of 98%. However, to confirm celiac disease in patients with positive serologic markers, a biopsy is needed, which is not possible with the current capsules. Therefore, the gold standard for the diagnosis of celiac disease remains the histological findings of a small bowel specimen obtained through gastroduodenoscopy.

The main indications to use CE are serological positive patients, who are unwilling to undergo gastroduodenoscopy or patients with antibody-negative villous atrophy. The latter group showed a higher yield on CE, compared with CE in serological positive patients with biopsy-proven celiac disease and persisting symptoms as was found by Kurien *et al*[178]. Also in patients with non-responsive celiac disease, defined by persistent or recurrent symptoms under treatment with a gluten-free diet, CE showed to be of use to detect

complications, such as multiple erosions, ulcerations, ulcerative jejunitis and adenocarcinoma[179]. Tennyson *et al*[180] confirmed these findings, but emphasized that CE was not a necessary tool in the evaluation of non-responsive celiac disease when no alarm symptoms are present, such as weight loss and abdominal pain, or when no loss of T-cell antigens on intraepithelial lymphocytes or loss of clonality of the T-cell receptor gene was observed. In the latter situations, a combination of CE and CT or MR enterography should be performed. In all other cases, upper gastroduodenoscopy with biopsy remains the gold standard. A recent study by Van Weyenberg *et al*[181] found similar results stating that CE could be used in patients with non-responsive celiac disease to identify the cases who are at risk of complications. CE might also be useful in the follow-up of patients with celiac disease under treatment with a gluten-free diet, regarding mucosal healing, because the follow-up of duodenal histology is not representative for the mucosal healing more distally[182]. Finally, Akin *et al*[183] confirmed other authors by stating that CE was useful as an alternative to duodenal biopsy in patients unable or unwilling to undergo gastroduodenoscopy and further stated that CE could be of use in the diagnosis of celiac disease in elderly patients with unspecific symptoms.

In conclusion, gastroduodenoscopy remains the diagnostic tool of choice for celiac disease, but CE shows to be a useful adjunctive tool in specific situations.

UPCOMING CHALLENGES

To conclude this paper about the current knowledge of CE, we would like to offer an insight in its bright future. Since its release in 2001, optics, battery life, visualization and software have been improved, with consequences on yield, completion rate and reading time. We have already discussed some technological advances in CE, but we will now shortly focus on future expectations of this technology.

One major field of advancement will be the maneuverability. If a capsule endoscope would be steerable and could approach a site of interest, this could be a big step forward in the diagnosis and treatment of diseases of the whole gastrointestinal tract. With efficient movement, battery life could sustain during movement through the whole gastrointestinal tract and thereby could increase completion rate. Various studies have been done and many prototype active capsules, using different locomotion techniques are currently under investigation for human use[184-188]. However, in the near future, remote manipulation using magnetic forces will be the first to be commercially available. These capsules contain a magnet, which can then be mobilized with an externally handled magnetic paddle or with a joystick. Perspective of the camera also can be adjusted with this magnet, rendering the desired image[189]. Swain *et al*[190] was the first to document the use of a magnetic field to guide a capsule through the human oesophagus and stomach. Since this article, many studies have followed, especially focusing on investigation of the stomach[191-194]. To overcome the problem of capsule impaction and to improve mucosal visualization, especially in the colon, insufflation techniques have recently been described by several authors using a capsule with a magnetic controlled drug release system to create a basic chemical reaction forming CO_2 in the lumen[195-197]. Another very interesting topic is a novel wireless platform able to measure and locate the force opposing capsule motion as a reflection of the gastrointestinal tract resistance[198]. It is the first platform for magnetic control of CEs that implemented this intermagnetic force measurement feature.

Another advancement might be the availability of a controlled drug release feature. This could help gastroenterologists in the local treatment of various gastrointestinal diseases, such as medical treatment of CD or even hemostasis in OGIB. Only one study introduced a capsule able to microposition a needle and to deliver 1 mL of a targeted medication, while resisting peristalsis with its holding mechanism[199].

The inability of taking biopsies is a third challenge CE faces. Together with an accurate maneuverability, this could enable CE to completely take the place of DBE in diagnostic and even therapeutic endoscopy of the small bowel. In 2008, Valdastri *et al*[200] was the first to successfully report an *in vivo* experiment with a capsule with built-in clip-releasing mechanism. The VECTOR project by the European Commission is currently developing a capsule for diagnosis and treatment of gastrointestinal cancer[201]. Another study also investigated the use of a large number of thermo-sensitive microgrippers in CE for this purpose of grabbing and retrieving tissue samples, which showed promising results[202].

Finally, to end this paper, we would like to reflect on the environmental consequences of capsule endoscopies, a subject that will become more important in the future, given the growing importance of CE. Although the ASGE consensus states that the capsule is "disposable and designed to be excreted"[3], considerations around this topic should be made, since the capsule contains many particles with potential biohazards[203]. Pezzoli *et al*[204] was the first to publish a small article on this matter in 2011. They found that it was possible, after retrieval and cleaning, to reactivate used capsules with a 10 min procedure and a new battery cost of only 2 euro. Recycled capsules could then be given a second life in, *e.g.*, veterinary procedures[205].

CONCLUSION

This paper gives a brief but complete overview on small bowel CE anno 2014. As the technology is still evolving and new insights are still being published every year, we emphasize that healthcare-providers should continue to monitor the medical literature for recent data, in order to provide the best evidence-based care for their patients.

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REVIEW

Endoscopic ultrasound-guided biliary drainage as an alternative to percutaneous drainage and surgical bypass

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Abstract

Endoscopic retrograde cholangiopancreatography had been a treatment modality of choice for both benign and malignant biliary tract obstruction for more than half century, with a very high clinical success rate and low complications. But in certain circumstances, such as advanced and locally advanced pancreatobiliary malignancies (pancreatic cancer, cholangiocarcinoma, ampullary tumor) and tight benign strictures, endoscopic retrograde cholangiopancreatography (ERCP) fails. Up to this point, the only alternative interventions for these conditions were percutaneous transhepatic biliary drainage or surgery. Endoscopic ultrasound guided interventions was introduced for a couple decades with the better visualization and achievement of the pancreatobiliary tract. And it's still in the process of ongoing development. The inventions of new techniques and accessories lead to more feasibility of high-ended procedures. Endoscopic ultrasound guided biliary drainage was a novel treatment modality for the patient who failed ERCP with the less invasive technique comparing to surgical bypass. The technical and clinical success was high with acceptable complications. Regarded the ability to drain the biliary tract internally without an exploratory laparotomy, this treatment modality became a very interesting procedures for many endosonographers, worldwide, in a short period. We have reviewed the literature and suggest that endoscopic ultrasound-guided biliary drainage is also an option, and one with a high probability of success, for biliary drainage in the patients who failed conventional endoscopic drainage.

Key words: Endoscopic ultrasound; Endoscopic ultrasound; Biliary drainage; Choledochoduodenostomy; Hepaticogastrostomy; Technique

Core tip: Failure of endoscopic retrograde cholangiopancreatography occurs in 5%-10% of the cases from many etiologies. However, there are few alternative options for biliary drainage up to the present time. Percutaneous biliary drainage and surgical bypass have their own drawbacks. Endoscopic ultrasound guided biliary drainage (EUS-BD) is a new platform with a very high technical and clinical success rate with

an acceptable complications. This review focused on the techniques, instruments including tips and tricks of this treatment modality. EUS-BD would become another alternative options for biliary drainage for both benign and malignant conditions in the future.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) was first introduced by Demling and Classen[1] in 1970 and is now the treatment of choice for pancreatobiliary diseases. It was originally used as a diagnostic tool, but since the development of magnetic resonance imaging (MRI) and computed tomography (CT), which provide superior soft tissue details of the pancreatobiliary tract, ERCP has been used exclusively for therapeutic purposes. Pancreaticobiliary obstructions are the most common cause of pancreatobiliary disease. Because of the development of ever better endoscopy instruments and technologies, the overall success rate of ERCP is now 90% to 95% with a complication rate of 5% to 7%[2-16]. Selective bile duct cannulation, if performed by experienced endoscopists, is an effective treatment for over 90% of cases of pancreatobiliary disease without anatomical obstructions. It is not effective in only 3% to 5% of cases, usually due to gastroduodenal obstruction, failed cannulation, distorted ampullae, altered anatomy, a periampullary diverticulum, or previous enteral stents. In cases of failed ERCP, patients are usually referred for either percutaneous transhepatic biliary drainage (PTBD) or surgical bypass. Both these procedures have high rates of undesirable complications. Endoscopic ultrasound-guided biliary drainage (EUS-BD) is a new technique that was developed within the last decade. It is an attractive alternative to PTBD or surgery when ERCP fails, but there is no strong evidence-based data on which procedure is best in this setting. We have reviewed the literature and summarize the advantages and disadvantages of PTBD, surgical bypass, and EUS-BD, including which technique is best for different clinical situations and how to maximize procedural success and reduce complications for each method.

Percutaneous transhepatic biliary drainage

Percutaneous transhepatic biliary drainage (PTBD) is a treatment option for patients for whom ERCP was not successful. The first report on PTBD was in 1961 by Catalano *et al*[17], and it was the treatment of choice for biliary drainage for more than two decades. The technical success rate for PTBD ranges from 75% to 100% and the clinical success rate ranges from 65% to 92%. The complication rate ranges from 9% to 31%[18-21]. Ho *et al*[22] published a review article on why PTBD should be considered first-line treatment for biliary drainage. Data showed that PTBD was superior than endoscopic biliary drainage in malignant hilar biliary obstruction with a technical success rate of 89% *vs* 41%, respectively ($P < 0.001$) and complication rates of 52% and 18%, respectively ($P = 0.04$). The data on the best type of drainage for distal CBD obstruction was inconclusive. PTBD is successful even in patients who have poor performance status. It also takes less procedural time and has few complications. The drawbacks are that it cannot be used in the presence of moderate to marked ascites and the fact that bile drainage is external, which impairs the patient's quality of life and involves difficulty in taking care of the catheter.

Surgical bypass

Surgical bypass is another treatment option after failed ERCP or unresectable hilar cholangiocarcinoma. Glazer *et al*[23] published a meta-analysis of randomized controlled trials of immediate stent placement *vs* surgical bypass in the palliative management of malignant biliary obstruction and found that there was significantly less recurrent biliary obstruction after surgical bypass than after stent placement (RR 0.14, 95%CI: 0.03-0.63, $P < 0.01$). The technical success rates (RR 0.99, 95%CI: 0.93-1.05; $P = 0.67$) and complication rates (RR 1.54, 95%CI: 0.87-2.71; $P = 0.14$) were not significantly different. Despite the more invasive approach, surgery produced better drainage; the drainage was internal, which had less effect on the patient's quality of life; and the interval to recurrent biliary occlusion was longer. Unfortunately, this technique is only suitable for patients who are good surgical candidates, which limits its use in cases of advanced malignant biliary obstruction.

EUS-BD

EUS-BD has been increasingly used as a minimally invasive alternative to surgery or radiologic intervention for biliary drainage after failed ERCP. EUS-BD can be performed *via* the papillary or gastrointestinal lumen. In the transpapillary route, rendezvous retrograde or antegrade stenting is used. For gastrointestinal luminal access, choledochoduodenostomy or hepaticogastrostomy is used, depending on the desired site of access. Artifon *et al*[24] conducted a randomized trial of EUS-guided choledochoduodenostomy or percutaneous drainage for unresectable distal biliary obstruction after failed ERCP. Technical success and clinical success were 100% in both groups. The complication rate for PTBD was 15.3% and the complication rate for EUD-BD was 25% ($P = 0.2$), and the cost of the procedures was similar (7570 USD and 5573 USD respectively, $P = 0.39$). Khashab *et al*[25] also conducted a trial of PTBD ($n = 51$) and EUS-BD ($n = 22$) after failed ERCP. Their technical success rate was higher in the PTBD group than the EUS-BD

Table 1 Advanvtage and disadvantage of puncturing sites

Route of access	
Extrahepatic route	Intrahepatic route
Easy approach (especially for large-caliber CBD)	The duct to be punctured is far from the scope
The puncture site is close to the scope	Easier scope positioning to achieve desired direction from the punctured duct
More difficult scope positioning to achieve desired direction from the punctured duct (rendezvous)	Easy scope handling
Easy guidewire negotiation and neo-tract creation (EUS-BD)	Difficult guidewire negotiation and neo-tract creation
Difficult scope handling	Higher risk of bleeding
	Higher risk of bile leakage

CBD: Common bile duct; EUS-BD: Endoscopic ultrasound guided biliary drainage.

group (100% *vs* 86.4%, $P = 0.007$), and their clinical success rates were 92.2% *vs* 86.4%, $P = 0.40$. PTBD was associated with higher adverse events (index procedure: 39.2% *vs* 15.7%), but stent patency and survival rate were equivalent in both groups. PTBD cost more than twice as much to perform as EUS-BD ($P = 0.004$), mainly because the re-intervention rate was higher (80.4% *vs* 15.7%, $P < 0.001$). Multicenter studies and other cases reports and case series[26-41] have confirmed the safety and efficacy of EUS-BD alone. In the authors' opinions, there was no one best approach among these three platforms for patients who failed ERCP. We recommend surgical bypass for patients with both duodenal and biliary obstructions who are good surgical candidates, but EUS-BD might be better than PTBD in patients with a large volume of ascites or patients who refuse external drainage. First-line treatment options depend on each institution's facilities, the clinician's expertise, and the patient's preferences after receiving enough information to accurately evaluate each procedure's strengths, weaknesses, and impact on quality of life.

EUS-guided biliary drainage

The use of endoscopic ultrasound-guided cholangiography was initially described by Wiersema *et al*[42] in 1996. The first EUS-guided biliary drainage was reported by Giovannini *et al*[43] in 2001. In 2004, Mallory *et al*[44] reported the first case of EUS-guided ERCP using the rendezvous technique.

Endoscopic ultrasound-guided biliary drainage can be classified into two major groups: the transpapillary approach (rendezvous retrograde and antegrade stent insertion) and the transmural approach (choledochoduodenostomy and hepaticogastrostomy)[45-48].

When to use the transpapillary rendezvous route

EUS-guided biliary drainage should be reserved for patients for whom ERCP was not successful. Some experts recommend the transpapillary (rendezvous) approach before the transmural approach[49-51]. Rendezvous technique is impossible if the ampulla is not accessible; but, even in patients with accessible ampullae, the rendezvous procedure can be difficult because it is necessary to change from the echoscope to the duodenoscope and the railroad technique during guide wire grasping is not always easy. In the authors' opinion, the advantage of the procedure is that it's not necessary to create a bilo-entereic tract, which can sometimes produce leakage and bleeding. In patients with surgically altered anatomy in which the anastomotic opening could not initially be seen and the access to the opening was not too difficult. When the position of the echoscope is good enough and dilatation and the guidewire can be passed down to the duodenum easily, rendezvous is a good option. If access is through the intrahepatic ducts (left lobe segments Ⅱ or Ⅲ) or extra-hepatic duct [common bile duct, (CBD)] the route depends on the location of the obstruction and the expertise of the endoscopist. If the site of obstruction is located above the proximal to mid-CBD, the intra-hepatic route is best. For distal obstruction with large CBD caliber, the extrahepatic route is the ideal choice.

Each route has advantages and disadvantages. It is easier to make the puncture using the extra-hepatic route, but the echoscope is in an upward curving position that makes it more difficult to control and easier to slip out. The puncture and guidewire placement are more difficult in the transmural route, but handling the scope is easier.

When to use the transmural route

The transmural route of EUS-guided biliary drainage can be achieved through an EUS-guided choledochoduodenostomy or an EUS-guided hepaticogastrostomy. The site of puncture depends on the location of the obstruction. If the obstruction site is distally located, choledochoduodenostomy is procedure of choice, while hilar obstructions are best served by a hepaticogastrostomy. It is easier to perform the puncture and handle the scope in segment Ⅱ of the left lobe of the liver[52,53] and the endoscopist who performed the procedure has to confirm that the puncture site is not in the esophagus in order to avoid higher risk of mediastinitis. Even though some experts use the right lobe[54], it is not yet standard of practice.

Tips for EUS-guided biliary drainage

Where to puncture: We summarized the advantages and disadvantages of extrahepatic and intrahepatic duct puncture in Table 1.

Table 2 Compare the two neo-tract creation methods

Neo-tract creation methods	
Cauterization	Non-cauterization
Easy neo-tract creation with no need for forceful manipulation	More difficult and forceful manipulation, especially when the intervening tissue is thick or the direction is inappropriate
More tissue injury from thermal burn	Less injury, smaller diameter of the neo-tract
The procedure takes less time	Lower risk of bile leakage or bleeding
More complications, especially bile leakage or perforation	

Table 3 Compare the two neo-tract dilation methods

Dilatation methods	
Balloon dilation	Graded dilation
Radial force leads to bigger neo-tract diameter (easier but greater risk for bile leakage, bleeding and perforation)	Axial force creates a smaller neo-tract. More difficult, but less leakage and less bleeding)
Easier stent insertion	Stent insertion can be more difficult
Only a single dilation session is needed and there are fewer guidewire exchanges	More sessions of dilation are needed and there are more frequent guidewire exchanges

How to create the bilo-enteric tract

There are two major ways to create a bilo-enteric tract: cauterization with a needle knife or small caliber cystotome especially 6 Fr in diameter[55-66] and non-cauterization with a tapered-tip catheter[67] or Soehendra stent retriever[68]. Neo-tract creation is followed by neo-tract dilation. The advantages and disadvantages of these two approaches are summarized in Table 2.

Neo-tract dilation can also be performed two ways: balloon dilation or graded dilation. Both methods are evaluated in Table 3.

There is no best approach. The technique of choice depends on the individual endoscopist's expertise. If balloon dilation must be used, the authors recommend the small size (4 mm diameter) balloon dilator.

What is the best stent?

In the early years of EUS-guided biliary drainage, the most commonly used stent was plastic; but many experts used fully covered, self-expandable metal stents (FCSEMS) instead of plastic stents and reported good outcomes[69-71]. Many types of metallic stents were developed for this purpose. Even though metal stents create a wider lumen with better drainage ability, they are more expensive and there is a risk of migration. Recently, Galasso *et al*[72] developed a stent suitable for EUS-guided hepaticogastrostomy called the Gio-Bor stent. It is a half-covered SEMS stent (Figure 1). The authors recommend an FCSEMS or partial CSEMS stent 40 to 60 mm in length for EUS-CD and 80 to 100 mm in length for EUS-HG. The small introducer (7 Fr) FCSEMS and partial CSEMS are shorter procedures and need fewer guidewire exchanges. However, there was a multicenter Japanese study[38] demonstrate that higher bile leakage was associated with plastic stent placement, therefore there was a trend towards to preference of using covered SEMS to prevent this complication.

What are the commonly encountered problems?

How to locate the puncture site: The site of puncture should be evaluated both endosonographically and fluoroscopically. Endosonographic tracing of the left intrahepatic bile duct was important in guiding the tip of needle and helping the endoscopist select the segment most suitable for puncture and easy guidewire negotiation. The fluoroscopic view can also help the endoscopist assess the best angle for bile duct puncture and easy neo-tract creation. Interestingly, if the scope's tip is perpendicular to the gastroduodenal wall, it will make the dilation process more difficult, so we recommend a slightly tangential angle. If the tip of the scope is too angulated, it will make the puncture more difficult. The distance between the punctured duct and the probe should be no more than 1-2 cm. Before starting the puncture, check Doppler color flow to avoid the intervening vessel.

DIFFICULT GUIDEWIRE NEGOTIATION

Using a 0.025 stiff guidewire (VisiGlide) or a 0.035 hydrophilic tip guidewire will make guidewire negotiation easier. The direction of the needle tip will directly affect guidewire manipulation. If the direction of the needle is opposite to the desired guidewire direction, manipulation will be really difficult. Moving the guidewire back and forth just a little bit (jiggling maneuver) will help change the guidewire direction. Using guidewires designed for manual twisting maneuvers or that have accessories, such as Terumo or ViziGlide guidewires, will make guidewire manipulation easier.

Guidewire shearing or knotting

Most endoscopists who perform EUS-guided biliary drainage have experience with guidewire shearing or knotting during the procedure. Saxena *et al*[73] and

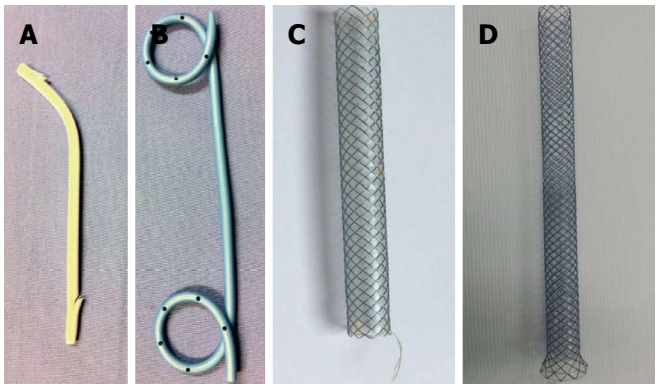

Figure 1 The different types of stents used in Endoscopic ultrasound guided biliary drainage. A: Plastic stent; B: Double-pigtail plastic stent; C: Fully covered, self-expandable metal stent; D: The Gio-Bor stent.

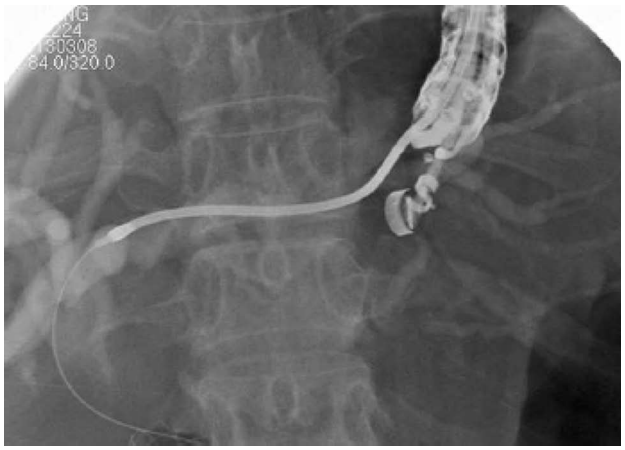

Figure 2 The Soehendra stent retriever was used in neo-tract creation.

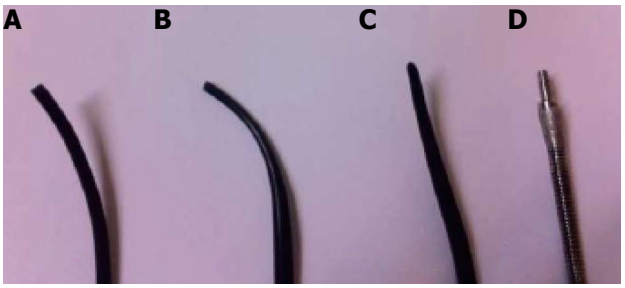

Figure 3 Different types of catheter tips. A: Soehendra stent dilator; B: Tapered tip catheter; C: Sharp tip catheter (self-made); D: Soehendra stent retriever.

Khashub *et al*[74] recommend flushing the channel with water and using a special type of needle, such as an access needle, which is designed to resolve these problems. However, in the authors' experience, this specially designed needle was not sharp enough in some situations and did not prevent guidewire shearing. We found that the way to prevent shearing and knotting was to push, not pull, the guidewire back, even if the desired duct was not yet punctured, and to exchange the needle for the small-sized dilator or tapered-tip catheter after the guidewire was looped and continue the guidewire negotiation later on. We have had no problem with shearing or knotting if we followed these guidelines.

How to deal with thickened soft tissue between the puncture site and bile duct

The distance between the puncture site and the desired duct is a very important factor in neo-tract creation. If the distance is longer, it is more difficult to penetrate through the tissue and pierce the bile duct. Another factor is the stiffness of the tissue between the puncture site and the bile duct. If the patient has liver fibrosis, the tissue is stiffer and this can make creation of a neo-tract more difficult. If difficulty is encountered, we recommended that the endoscopist should, firstly, re-check the position of the scope tip to make sure it is not perpendicular to the gastric wall. If graded dilation is being performed, change the dilating catheter to a smaller size or a catheter with a tapered tip, use a tapered-tip cannulation catheter, or re-shape the tip of the catheter by cutting it to a needle shape. Dilating with a Soehendra stent retriever, which has a drilling effect, might also be useful (Figure 2). If all of the above methods fail, cauterization may be necessary. Different types of catheter tips are shown in Figure 3.

Complications can occur if the needle knife is used with the Odd ratio of 12.4[75]. To minimize possible tissue damage during neo-tract creation, only open the knife half of its full length and cauterize until it enters the duct. In process of dilation, the dilator should be inserted after the knife is used. For cystotome usage, it very important to push the cystotome catheter against the mural and bile duct wall firmly, before starting the cauterization (this technique would help to enter the bile duct easily).

HOW TO MINIMIZE THE COMPLICATIONS DURING NEO-TRACT DILATION

Generally, the least chance of bile leakage and bleeding if the diameter of neotract is as small as possible. Therefore, the authors recommend not to dilate the neo-tract larger than the size of stent introducer (always not more than 8.5 Fr). For graded dilation technique, 8.5 Fr size is suitable for Soehendra dilator and only 7 Fr size is suitable for Soehendra stent retriever whereas smaller balloon especially not more than 4 mm in diameter is suitable for balloon dilation.

FUTURE RESEARCH AND DEVELOPMENT

The development of single step device which might be more suitable to each specific procedure would be helpful the help endoscopist to overcome the cubersome techniques such as multiple guidewire exchanges and would make the procedure time shorter; Smaller introducer (7 Fr) of smaller sized covered SEMSs (6 or 8 mm in diameter) would be benefit for less complications and shorter procedure time; Randomized control trial that EUS-BD as the treatment of choice in some particular conditions such as surgical altered anatomy would be interesting; The possibility of using EUS-BD as the preferable options than transpapillary drainage should be widely discussed and prospective study should be conducted.

CONCLUSION

EUS-guided biliary drainage is safe and effective when performed by an experienced endoscopist, and is an alternative to PTBD and surgical bypass after failed ERCP. Unfortunately, it use is still limited to tertiary care hospitals with advanced-complex endoscopy units. Clinicians will need to choose a treatment method based on each patient's status, preferences, and the facilities of the hospitals in their area.

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Self-expandable metal stents for achalasia: Thinking out of the box!

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Abstract

Achalasia is a primary motor disorder of the esophagus diagnosed manometrically in the clinical setting of dysphagia to both solids and liquids. Currently established treatment options include pneumatic dilation, laparoscopic Heller myotomy, botulinum toxin injection performed endoscopically, oral agents that relax the lower esophageal sphincter and esophagectomy for refractory, end-stage disease. Despite their effectiveness, a significant proportion of patients eventually relapses and needs retreatment. In this setting, several new techniques are under investigation promising future enrichment of our therapeutic armamentarium for achalasic patients. Among them, peroral endoscopic myotomy and self-expandable metal stents placed across the gastro-esophageal junction represent the most encouraging modalities, as initial studies assessing their efficacy and safety indicate. This review highlights the role of self-expandable metal stents in the management of patients with achalasia. Their possible position in the therapeutic algorithm of achalasia along with established and novel techniques is also assessed. Finally, the need for large prospective randomized trials is underlined in order to elucidate the numerous relevant issues.

Key words: Achalasia; Self-expandable metal stents; Dysphagia; Endoscopy; Treatment

Core tip: Recommended treatment of patients with achalasia are associated with significant clinical relapse over subsequent months or years. Therefore, numerous innovative techniques are under evaluation. Self-expandable metal stents may represent a promising alternative according to initial studies. They may gain a place in the therapeutic algorithm of achalasia in the view of its different types and stages, patients' characteristics and other emerging modalities.

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INTRODUCTION

Achalasia is a primary esophageal motility disorder characterized by aperistalsis in the distal portion of the esophageal body and incomplete or absent relaxation of the lower esophageal sphincter (LES). It is a disease of unknown cause; it pathophysiologically results primarily from the degeneration of ganglion cells in the myenteric plexus of the esophageal wall[1,2].

Achalasia is a rare clinical entity with annual incidence and prevalence of approximately 1.6 and 10 cases per 100000 individuals, respectively. Both sexes are affected equally, there is no racial predilection and the age of diagnosis ranges between 25 and 60 years[3,4]. Onset is rather insidious and disease progression gradual accounting for high rates of delayed diagnosis. The predominant symptom of achalasia is dysphagia to solids and liquids. Other symptoms include regurgitation of undigested food or saliva occasionally leading to aspiration and pneumonia, sub sternal chest pain, weight loss and heartburn[5].

The diagnosis of achalasia when clinically suspected is suggested by barium esophagram and established by manometry. On barium swallow supporting findings include aperistalsis, dilation of the esophagus, bird-beak appearance of the gastro-esophageal junction and delayed contrast medium emptying[6]. Manometry typically reveals incomplete or absent LES relaxation in response to a swallow and aperistalsis in the distal 2/3 of the esophagus[7]. Recently high resolution manometry classifies achalasia in 3 subtypes namely I (classic), II (with panesophageal pressurization) and III (spastic or vigorous)[8]. This classification possibly correlates with the final outcome of treatment[9,10]. Endoscopy may be normal or reveals a dilated esophagus with retained saliva and undigested food particles along with difficulty in passing the gastro-esophageal junction. Of importance, endoscopic examination and, when indicated, imaging studies are mandatory to exclude focal malignancy mimicking primary achalasia[11,12].

CURRENT TREATMENT OPTIONS AND THEIR LIMITATIONS

Treatment modalities for achalasia aim at reducing LES resting pressure thus relieving dysphagia and regurgitation and preventing the long-term development or mega-esophagus. This goal is accomplished by either mechanical disruption of the LES muscular fibers (*e.g.*, pneumatic dilation, myotomy either laparoscopic or peroral endoscopic) or by pharmacological decrease in LES pressure (*e.g.*, botulinum toxin injection, oral nitrates and calcium-channel blockers)[13,14].

Pneumatic dilation (PD) represents a highly-accepted first-line therapy for primary achalasia due to its cost-effectiveness and low complication rates. PD is performed in a gradual fashion by experienced endoscopists using standard-diameter balloons. Initial success rates are high and up to 90% of patients report symptomatic relief. Favorable predictors include older age (> 45 years), female gender, narrow esophageal lumen, post-dilation pressure < 10 mmHg and type II pattern on high-resolution manometry[10,15,16]. However, improvement is often not sustainable in the medium - to long-term period, since prospective studies suggest that approximately two thirds of patients eventually relapse and need additional dilations and possibly surgery[17]. Moreover, subsequent dilations seem less effective and patients referred for myotomy are at increased risk for intra-operative complications. Mostly feared complication is esophageal perforation with an overall median rate of 1.9% (range 0%-16%)[18]. Additionally gastroesophageal reflux disease occurs in 15%-35% of patients necessitating antisecretory medications[19].

Laparoscopic Heller myotomy (LHM) coupled with Dor fundoplication is the primary alternative to PD for achalasia. Initial clinical remission is achieved to nearly 90% of patients but this excellent outcome seems to wane over time[18,20]. Long-term studies show that 18% of patients require PD and 5%-10% of them repeat myotomy or esophagectomy 5-11 years post-operatively[21,22]. Nevertheless, a meta-analysis published in 2013 favored LHM over PD in terms of both short- and long-term efficacy[23]. Being more invasive, surgery is associated with a protracted recovery period and numerous complications including gastro-esophageal reflux disease (GERD), dysphagia associated with the fundoplication that may require dilations, perforation, bleeding, leaks and infections which affect negatively its cost-effectiveness[20]. Despite these imperfections, LHM is preferred over PD for patients younger than 40 years as they frequently need more re-dilations than older subjects[5]. To note, very recently, Nau *et al*[24] suggested that LHM should be used as a benchmark against which other treatments for achalasia are judged, given its outstanding results[24].

Developed by Inoue in Japan peroral endoscopic myotomy (POEM) is the most fascinating new treatment option for achalasia currently being extensively studied in the United States and in Europe. This approach involves endoscopic dissection of the esophageal submucosal space and the creation of a tunnel eventually allowing LES circular muscle bundles dissection[25,26]. Initial studies in a total of 1000 procedures with a mean follow-up from 3 to 12 mo report excellent short term results (clinical success 82%-100%) and only minor self-limited adverse events (mainly tense capnoperitoneum) in less than 10% of patients[27]. The most serious complication is mediastinitis due to esophageal leak, although its incidence seems remarkably low. On the other hand, recent studies show that objectively-measured gastroesophageal reflux disease prevalence after POEM varies from 20% to 46%, higher than that in early reports and similar to those following LHM with Dor fundoplication[28,29]. No procedure-related death has been reported. In all circumstances, further studies with long-term follow-up, as well as randomized trials comparing POEM with LHM and PD are warranted before POEM

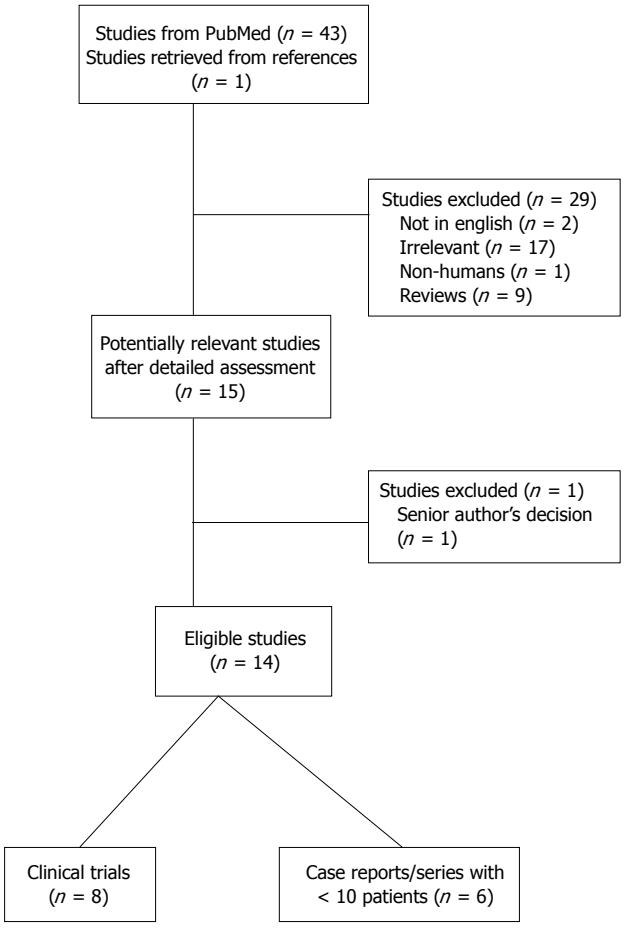

Figure 1 Flow diagram of the literature search strategy and valuation of studies identified for review.

can be recommended[25] as the procedure of choice.

Intrasphincteric botulinum toxin injection (BTI) can be easily performed during routine endoscopy in poor surgical candidates. Using a sclerotherapy needle, 100 units of the toxin are administered just above the squamocolumnar junction in at least 4 quadrants. Its initial efficacy reaches those of PD and LHM. Unfortunately, symptoms relapse in more than 50% of patients necessitating additional injections at 6-24-mo intervals[30]. Main complications are post-procedural chest pain, heartburn and allergic reactions[19]. In addition, BTI may increase the technical difficulty of subsequent myotomy either surgical or endoscopic[31].

Oral pharmacologic agents indicated for primary achalasia include calcium-channel blockers and nitrates. They represent the least effective means of treatment[32]. Traditionally, they are administered 30 to 60 min prior to meals and act by decreasing basal LES pressure and tone. Their efficacy is variable and their use is limited to those who are not suitable to receive invasive therapies. Moreover, side effects such as headache, hypotension and peripheral edema, as well as tachyphylaxis, diminish their application[19].

Finally, for patients with end-stage achalasia (megaesophagus, or sigmoid-esophagus) who have failed PD and/or LHM, esophagectomy should be considered[33]. Esophageal resection results in symptomatic improvement in more than 80% of patients; however, it is associated with significant mortality reaching 5.4% in uncontrolled studies and recurrence of dysphagia in up to 50% of patients[34].

As shown, all currently available therapeutic modalities for primary achalasia remain of palliative nature, given that the underlying mechanism cannot be reversed. Moreover, a good proportion of patients will experience symptom recurrence and require retreatment. In this context, several new endoscopic treatments are under evaluation over the last years. This review aims to highlight the role of self-expandable metal stents (SEMS) in the management of patients with achalasia.

USED MATERIALS AND METHODS

Using PubMed we carried out a thorough review of the literature to identify all articles published between January 1995 and July 2014 referring to the use of SEMS in achalasia. The search was initially performed using the term "achalasia and stents" as a free text. A total of 43 studies were retrieved and one additional was identified by a manual search of the references cited in the key articles. Each manuscript was subsequently cross-checked by two authors (AS, CM) to achieve a maximum completeness of the reports chosen for inclusion. In case of disagreement, a third senior author (KT) made the final decision. Eventually, 14 studies were considered suitable for review. The article selection process is presented in Figure 1.

SEMS FOR ACHALASIA TREATMENT

Early reports regarding the use of SEMS in the treatment of achalasia were published in 1998 by De Palma *et al*[35] A nitinol coil stent (InStent Inc., Eden, Praire, United States), 10 cm long, was placed in 4 patients with long-standing disease who were unresponsive to conventional treatment such as LHM, PD and BTI. Stent placement was successful in all cases and the patients achieved clinical remission during the follow-up period up to 12 mo. One of them developed reflux esophagitis treated medically[35].

Three years later the same authors presented their extended experience in 8 patients followed for a period ranging from 29 to 44 mo. Nitinol coil and Ultraflex (Microvasive, Boston Scientific, Natick, MA, United States) stents were placed across the gastro-esophageal junction. Although stent implantation was technically successful and all patients experienced complete remission of dysphagia, a significant complication rate was noted both in the early (within 30 d) and in the late (after 30 d) phase. In particular, 62.5% of patients had early complications (mainly stent migration, 37.5%) and 57.1% late complications (mainly chest pain, 28.5%). As a result the investigators concluded that the use of SEMS in achalasia should not be generalized but reserved only for carefully selected cases[36].

Unlike the rather promising experience of De Palma *et al*[35], a case series published in 2000 announced extremely disappointing results. Three different SEMS types, namely Gianturco Rosch Z stent (Wilson Cook Medical, Winston Salem, NC, United States) and Wallstent I and Ⅱ (Schneider USA, Plymouth, MN, United States) were inserted in 4 achalasic patients. Placement was technically feasible and uneventful. Symptomatic remission before further intervention varied between 2 wk and 10 mo. However, complications such as stent migration and dysphagia recurrence secondary to either food bolus impaction or inflammatory stricture occurred in all cases. Most serious, one patient died from bleeding due to an aorta-enteric fistula developed from a penetrating gastro-esophageal junction ulcer adjacent to the stent. The authors recommended that alternative to SEMS options should be preferred in the management of patient with refractory achalasia[37].

Thereafter, a center from the United States and one from Spain reported few cases of achalasic patients treated with SEMS insertion. The former used metal coil stents (Esophacoil, InStent Inc., MN, United States) in 2 patients with complicated refractory achalasia. Technical and clinical success was achieved; nevertheless, hematemesis secondary to severe erosive esophagitis and small bowel obstruction due to stent migration were encountered a few months after stent placement[38]. The Spanish center announced the use of SEMS (Hanarostent, MI Tech, IZASA, Seoul, South Korea) as an effective short-term bridging therapy in 2 achalasic patients, one pregnant and one with newly diagnosed pituitary tumor[39].

In 2009 Zhao *et al*[40] reported the results of a prospective study assessing the long term efficacy and safety of a specifically designed partially-covered SEMS, 30 mm in diameter, placed for 3-7 d in 75 achalasic patients. Both technical and post-procedural clinical success was 100%. During the long follow-up period (up to 13 years) the overall remission rates remained extremely high reaching 100% and 83.3% at > 5 and > 10 years, respectively. These excellent results, as well as the low rates of complications including stent migration and perforation (5.3% and 0%, respectively) were attributed to the large-diameter stent that had been used. On the other hand, the same factor was possibly responsible for the relative high rates of chest pain (38.7%), gastro-esophageal reflux (20%) and bleeding (12%). It was therefore suggested that temporary SEMS placement is effective and safe and could serve as an alternative or complementary method in the management of esophageal achalasia[40].

The importance of stent diameter in terms of clinical efficacy was evaluated in a prospective study with long-term follow-up conducted by Cheng *et al*[41] As the results indicate, the overall cumulative clinical remission rate was significantly higher for patients who underwent a 30 mm stent placement as compared with those who received a 25 mm and 20 mm one (87% *vs* 73% *vs* 47%, respectively). Similarly, the wider the stent, the lower the migration rate (6.6% *vs* 13.3% *vs* 26.7%) and the higher the chest pain rate (40% *vs* 33% *vs* 17%, respectively)[41].

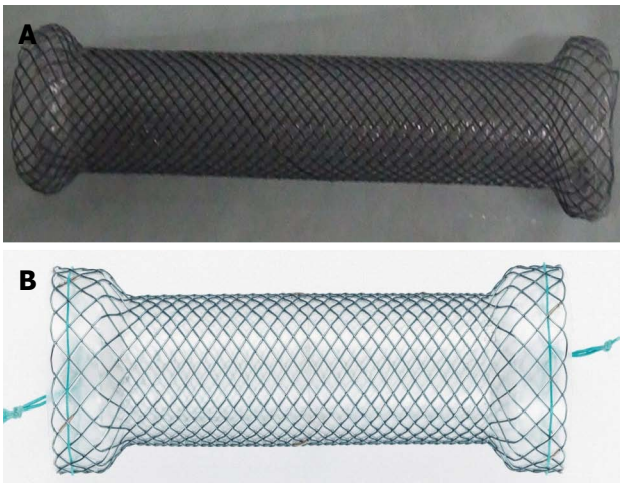

Figure 2 Large-diameter self-expandable metallic stent for achalasia. A: Self-expandable metal stents similar to that used by Coppola *et al*[43]. Picture is provided by courtesy of Mr. Kuhn D, Micro-Tech Europe GmbH, Dusseldorf, Germany; B: Niti-S stent. Picture is provided by courtesy of Mr. Bekzat M, TaeWoong Medical, Seoul, South Korea.

A recent study by Zeng *et al*[42] assessed for the first time the efficacy of fully-covered SEMS, 20-25 mm in diameter, in achalasia (Z-stent, Sigma, Huaian, China). Fifty-nine patients with no prior treatment were enrolled and underwent stent placement for a 1 mo period. The cumulative remission rates after 6, 12, 18, 24, 30 and 36 mo were 90.9%, 81.8%, 76.4%, 69.1%, 65.%% and 49.1%, respectively. Sub sternal chest pain was the most common complication (25.5%), followed by heartburn (10.6%) and stent migration (8.5%)[42].

Apart from Eastern countries, a study from Italy published a few months ago evaluated the safety and efficacy of SEMS as a temporary treatment in patients with achalasia. Seven patients underwent a 30 mm partially-covered stent (Micro-Tech, Nanjin, China) placement for 6 d and were followed thereafter for a mean period of 19 mo. Beneficial effects on dysphagia were excellent in 5 and good in 2 patients during the follow-up. No serious complication was observed. The authors concluded that large stent placement may permanently disrupt the muscular fibers of the cardia and possibly represents a safe and effective option for patients not fit for more invasive interventions[43]. A stent similar to the one used in this study as well as, a nitinol-covered stent are illustrated in Figure 2. Major points of the above mentioned studies are presented in Table 1.

SEMS *VS* PD AND BTI IN THE TREATMENT OF ACHALASIA

Several studies compare SEMS *vs* established treatment options such as PD and BTI in the management of patients with achalasia, as presented in Table 2. Of note,

Table 1 Published series using self-expandable metallic stents for achalasia treatment

Ref.	Coppola *et al*[43] (2014)	Zeng *et al*[42] (2014)	Cheng *et al*[41] (2010)	Zhao *et al*[40] (2009)	De Palma *et al*[36] (2001)	Mukherjee *et al*[37] (2000)	De Palma *et al*[35] (1998)
Baseline characteristics and effectiveness							
Patients, *n*	7	59	90	75	8	4	4
SEMS diameter, mm	30	20/25	20/25/30	30	18	18/20	18
Time to removal, d	6	30	4-5	3-7	?	?	?
Technical success, %	100	100	100	100	100	100	100
Initial remission, %	100	100	100	100	100	100	100
Major complications							
Stent migration, *n*	0	4	14	4	4	1	0
Perforation, *n*	0	0	0	0	0	1	0
Bleeding, *n*	0	0	14	9	0	1	0
30-d mortality, *n*	0	0	0	0	0	1	0

Table 2 Published comparison studies

Ref.	Li *et al*[47] (2010)	Li *et al*[46] (2010)	Zhu *et al*[45] (2010)	Cheng *et al*[44] (2003)	Cai *et al*[48] (2013)
Compared methods	PD *vs* SEMS (20, 25, 30 mm)	PD *vs* SEMS (30 mm)	PD *vs* SEMS (30 mm)	PD *vs* SEMS (permanent, temporary)	BTI *vs* SEMS (25 mm)
Patients, *n*	30/30/30/30	80/75	38/63	60/8/65	51/59
Technical success, %	100/100/100/100	100/100	100	100/100/100	100/100
Initial remission, %	100/100/100/100	100/100	100	100/100/100	94.1/100
Remission at maximum follow-up, %	0/0/28.6/83.3	0/83.3	42.1/88.9	10/33.3/85.5	4.17/49.1
Major complications					
Migration, *n*	NA/8/4/2	NA/4	NA/2	NA/0/0	NA/4
Perforation, *n*	0/0/0/0	0/0	0/0	0/0/0	0/0
Bleeding, *n*	2/3/5/6	4/9	3/10	6/3/8	0/0
30-d mortality, *n*	0/0/0/0	0/0	0/0	0/0/0	0/0

PD: Pneumatic dilation; SEMS: Self-expandable metallic stent; NA: Not applicable.

no randomized trials are currently available.

In 2003 Cheng *et al*[44] compared PD with permanent uncovered or ant reflux covered SEMS and temporary partially-covered SEMS. The latter stents, sized 20-30 mm in diameter, were inserted and withdrawn successfully after 3-7 d. According to the results, temporary partially-covered SEMS exhibited significantly superior long-term therapeutic efficacy as compared to the rest interventions, although immediate symptomatic relief was equally excellent. Interestingly, permanently uncovered metal stent dilation proved to be unsuitable for patients with achalasia due to high rates of gastro-esophageal reflux and stent occlusion secondary to hyperplasia of granulation tissue[44].

To overcome the limitations of their previous study (*e.g.*, relatively short follow-up and great variety in stent diameters) the same investigators reported the results of a retrospective trial comparing PD and temporary partially-covered SEMS (Zhiye Medical Instruments, Guangzhou, China and Youyan Yijin Advanced Materials, Beijing, China). The diameter of the balloon or stent used was 30 mm. The stent was removed within 7 d after placement and the patients were followed both clinically and manometrically for more than 10 years. The results showed that both interventions are very efficacious in the immediate post-procedural period. However, the total symptom scores in patients treated with SEMS were statistically better than those treated with PD throughout the follow-up period ($P < 0.05$). LES pressure did not exhibit significant differences apart from one time frame (after 8-10 years). As expected, complications such as pain and bleeding occurred more frequently in the stent group compared to the balloon one (42.9% *vs* 23.6% and 15.9% *vs* 8%, respectively)[45].

Similar results were obtained by an uncontrolled prospective study with a long-term follow-up comparing SEMS and PD of the same diameter (30 mm). Temporary (3-7 d) SEMS placement was associated with significantly higher clinical remission rates in all follow-up periods (up to > 10 years). Notably, the long-term efficacy of SEMS seems to be comparable with that of LHM. Although of no statistical significance, complications like chest pain and bleeding were more common in the SEMS group, whereas stent migration occurred in 5.3% of patients[46]. Additionally, the same medical group showed prospectively that temporary SEMS with a diameter of 30 mm achieved significantly higher clinical remission rates after more than 10 years of follow-up as compared to patients treated with PD with a 30 mm balloon or SEMS with diameters of 20 or 25 mm (83.3% *vs* 0%, 0% and 28.6%, respectively). Surprisingly, the clinical remission rate with PD in the long-term was extremely poor suggesting a possible study limitation[47].

The only study that compares BTI and SEMS for

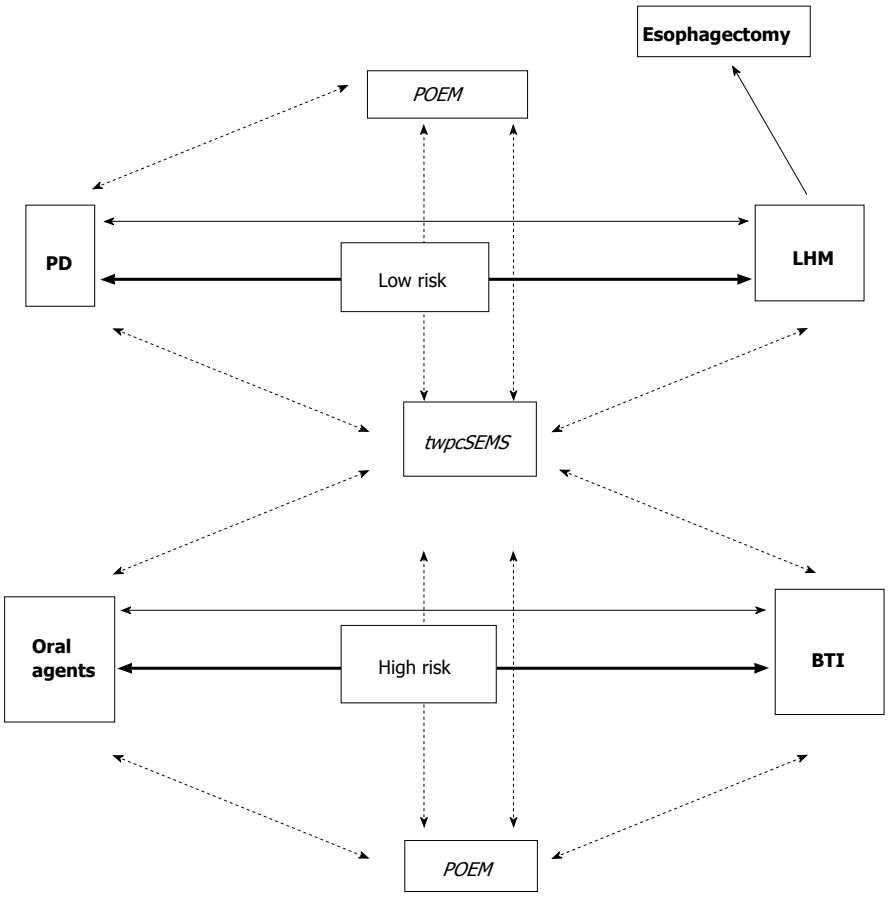

Figure 3 Proposed therapeutic algorithm for achalasia based on surgical risk. Currently established treatments are in bold. Investigational ones are in italics. Arrows indicate current first-line treatments. Lines binding different treatments indicate management of failures. Dotted lines indicate assumed steps in management, while solid lines the to-date recommended[11]. PD: Pneumatic dilation; LHM: Laparoscopic Heller myotomy; BTI: Botulinum toxin injection; twpcSEMS: Temporal, wide, partially covered, self-expandable metallic stent; POEM: Peroral endoscopic myotomy.

the treatment of achalasia has been published by Cai and colleagues in 2013. A partially-covered SEMS 25 mm in width was applied and retrieved after 4 wk. The mean duration of follow-up was 28 mo (range 10-36 mo). Based on the results, the patients in the SEMS group achieved significantly better improvements regarding global symptoms scores, dysphagia and LES pressure. Moreover, differences in remission rates after 12 mo gained statistical significance favoring SEMS placement. No adverse events were observed in the BTI group, whereas 13 episodes of chest pain, 9 cases of regurgitation and 4 stent migrations were captured in the SEMS group[48].

SEMS IN THE NEW ERA

Achalasia treatment should be individualized taking into account both patients characteristics and available expertise. Although current established treatments are effective, emerging techniques such as SEMS placement are being developed, as presented. Nevertheless, what could be the exact position of SEMS in the therapeutic plan of achalasia, especially in the era of very promising interventions like POEM?

As shown in Figure 3, temporal placement of wide, partially covered SEMS could potentially serve as an alternative first-line treatment in both low and high surgical risk patients. This could be of great value mainly for the latter ones, given that the unique currently recommended treatment option (*e.g.*, BTI) exhibits short-term, only, efficacy. Temporal wide partially covered SEMS may also be preferred for all cases of treatment failures, irrespective of the initial therapy, offering an efficacious, well-tolerated choice. It may be hypothesized, that SEMS could possibly serve on a short-term basis as a bridging therapy until surgery is performed.

One could argue that POEM will eventually predominate in achalasia treatment due to its efficacy and safety profile according to initial studies. However, POEM is still a quite invasive procedure compared to SEMS placement. Additionally, it is by far more technically demanding, requires specific training and can be feasible only in centers of excellence worldwide[49,50]. General anesthesia requirements, time consumption and cost should be undoubtedly considered. Long-term results and adverse events in patients who have undergone POEM are still pending. Given the above, temporal placement of wide, partially covered SEMS seems able to maintain a role in the management of achalasic patients, even in the advent of POEM. Comparative randomized trials are

surely appreciated before achalasia therapeutic algorithm takes its definite form.

CONCLUSION

Treatment remains palliative since its neuronal defect seems to be irreversible. In this setting, temporal, wide, partially covered SEMS placement may represent a safe and effective alternative therapy for carefully selected patients. Several technical issues including stent type, stent diameter and length, optimal time for removal and prevention of complications are still open for discussion. Small size of treated population, low quality of studies' design and the majority of studies performed in Asia also preclude the generalizability of the reviewed evidence.

Additionally, the advent of self-expandable biodegradable stents used in the management of refractory benign esophageal strictures, as well as drug-eluting stents could provide an area for further innovation, in the field of stents in achalasia. Large, multicenter, randomized trials are warranted - while not always feasible - to elucidate the exact position of stent placement in the therapeutic armamentarium for the different profiles of achalasic patients.

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Intragastric surgery using laparoscopy and oral endoscopy for gastric submucosal tumors

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Abstract

We review the techniques and outcomes of the intragastric resection for gastric submucosal tumors (GSTs) using laparoscope and oral endoscope. In the literature, the mean operation time, intraoperative blood loss, pathological size of the tumor and postoperative hospital stay were 134 min, minimal, 31 mm and 6.4 d, respectively. There were no particular perioperative complications during the follow-up period (mean: 121.3 mo). Intragastric surgery using laparoscopy and oral endoscopy can be considerably beneficial for patients with GSTs locating in the upper third of the stomach between 2-5 cm in diameter and < 8 cm^2 in cross-sectional area and located in the upper third of the stomach.

Key words: Laparoscopic surgery; Intragastric resection; Gastric submucosal tumor; Oral endoscopy

Core tip: The laparoscopic approach for gastric submucosal tumors (GSTs) depends on the characteristics of the submucosal tumors including its location or size. In particular, GSTs located close to the esophagogastric junction or pyloric ring cannot be easily applied the laparoscopic local resection. Therefore, the intragastric approach is adopted for those tumors. This review evaluates the technique and outcomes of the intragastric resection for GSTs using laparoscopy and oral endoscopy. Intragastric surgery using laparoscopy and oral endoscopy can be considerably beneficial for patients with GSTs less than 5 cm in diameter and locating in the upper third of the stomach.

Tagaya N, Tatsuoka T, Kubota Y, Takegami M, Sugamata N, Saito K, Okuyama T, Sugamata Y, Oya M. Intragastric surgery using laparoscopy and oral endoscopy for gastric submucosal tumors. *World J Gastrointest Endosc* 2015; 7(1): 53-58 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i1/53.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i1.53

INTRODUCTION

Techniques for the resection of gastric submucosal tumors (GSTs) have seen a shift from an open to an endoscopic approach, and from gastrectomy to local resection[1]. Endoscopic approaches can be divided into oral endoscopic resection and laparoscopic resection. The latter may include the resection from outside, inside or both side, depending on the characteristics of the GST, including its location or size. In particular, GSTs located close to the esophagogastric junction (EGJ) or pyloric ring are not amenable to laparoscopic local resection, and instead an intragastric approach is adopted[2-5]. This review evaluates the techniques and outcomes of intragastric resection for GSTs using laparoscopy and oral endoscopy in a series of patients treated at our institution.

PREOPERATIVE EVALUATIONS

We preoperatively investigated the tumor conditions including the size, location and distance from the EGJ to proximal side of the tumor using an upper gastrointestinal radiological series and endoscopy. Furthermore, endoscopic ultrasound (EUS) was also added to evaluate the location and growing formation of the tumor within the gastric wall[6]. And, EUS-guided fine-needle aspiration biopsy examination was performed when necessary. Computed tomography with contrast medium was added to clarify whether there was any liver metastasis, dissemination, ascites, lymphadenopathy or other comorbidities, as well as the relationship between the tumor and the whole stomach.

INDICATION

The criteria for the use of laparoscopy and oral endoscopy for intragastric resection of GSTs were a tumor between 2-5 cm in diameter and < 8 cm^2 in cross-sectional area with the aim of possible removal *via* the mouth, or an endoscopically evident tendency of the tumor to grow in size during follow-up, and location of the tumor on the posterior wall of the upper third stomach or close to the EGJ[4].

SURGICAL TECHNIQUES

Standard technique[4,5]

The patient was placed in the supine position under general anesthesia. Initially a 12-mm port was initially introduced into the peritoneal cavity at the umbilicus, using the open laparotomy method. After creating a pneumoperitoneum by Carbon dioxide (CO_2) insufflation, and the operative field was kept at 8-10 mmHg of intra-abdominal pressure. The stomach was inflated to confirm the tumor condition using an oral endoscope. When we approached an intragastric technique, the anterior wall of the stomach was lifted up to the abdominal wall using a double-straight needle device (Ideal Lifting: Olympus Medical Systems Co., Tokyo, Japan) to insert the port easily. After this preparation, 5-mm and 12-mm ports were directly inserted into the stomach at the left upper quadrant of the abdominal wall, depending on the tumor location, under the observation of oral endoscope. To obtain the better intragastric operative field, CO_2 insufflation was added into the stomach. A linear stapler to minimize the deformity of the stomach and avoid the stenosis of EGJ carried out local resection of the stomach including the lesion with an adequate margin in all directions. The first fire of linear stapler was put on the normal gastric wall near the distal side of the tumor. The direction of the resection line was modified so as not to close the EGJ. The resected specimen with a plastic bag was removed from the mouth by an oral endoscope. If the tumor removal is complicated orally, we made a small gastrostomy enlarging 12-mm port site, and then the specimen extracted from the stomach. We immediately ensured the free margins around the lesion. The entry holes in the stomach were closed using a linear stapler or hand sewing intracorporeally. Finally, the stomach was re-inflated to check the air leakage or bleeding from the closed sites and confirm no stenosis at the EGJ. Abdominal port sites were closed without drainage tube.

In a modified technique, an initial 12-mm port was introduced at the umbilicus. After checking the intra-abdominal cavity by laparoscope during stomach inflation, the anterior wall of the stomach was pulled out through an umbilical incision, and a 12-mm gastric opening was made. This hole was used for insertion of an Endo-GIA linear stapler or a 10-mm laparoscope. Subsequently a 3-mm port was inserted into the stomach at the left upper quadrant to allow manipulation of the normal gastric mucosa near the tumor (Figure 1). The tumor was resected using a linear stapler under endoscopic guidance (Figure 2). The specimen was retrieved *via* the mouth. The entry hole in the stomach was directly closed extracorporeally, and the 3-mm hole of the stomach was closed inside the stomach by clipping using an oral endoscope (Figure 3). The skin was only closed at the umbilicus.

Single-site technique[7,8]

Initially a 2.5 cm vertical skin incision was made at the umbilicus, and a X small Alexis Wound Protector (Applied Medical, Rancho Santa Margarita, CA, United States) was attached to the incision. The stomach was pulled out through that incision, and a 2-cm opening was made in the anterior wall of the stomach by laparoscopic coagulating shears. A single port device or surgical glove with 3 or 4 working ports was introduced into the gastric orifice. After the stomach was inflated with CO_2 gas, intragastric pressure was maintained between 8 and 10 mmHg. A 10- or 5-mm laparoscope was inserted, and the target tumor was identified. The normal mucosa adjacent to the tumor was initially pulled up with a curved grasper

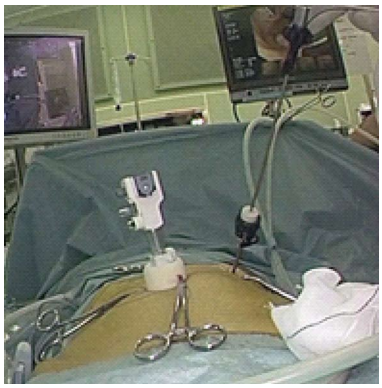

Figure 1 Intraoperative outside view of one 12-mm port and 3-mm port.

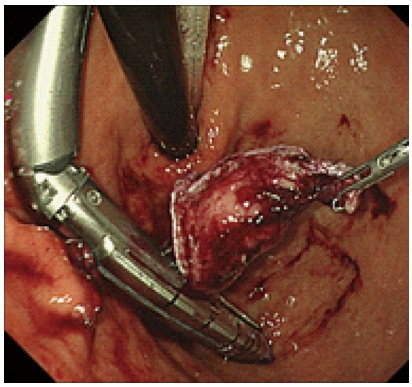

Figure 2 The tumor was resected by an Endo-GIA stapler under the guidance of oral endoscope.

and resected using a 30-mm linear stapler not to expose the tumor itself. Subsequently, the remaining main tumor area was resected continuously using a 45- or 60-mm linear stapler. The specimen was put into the plastic bag and retrieved from the single port site. After the single port device or surgical glove had been removed, the gastric orifice was closed using absorbable sutures. The stomach was re-inflated to confirm no bleeding or air leakage from the repaired site. The umbilical wound was closed without drainage tube.

POSTOPERATIVE EVALUATION

We postoperatively evaluated the passage condition at the EGJ and the deformity of the residual stomach in all patients on the postoperative day 1 by an upper gastrointestinal radiological series, and followed by gastroscopy every 6 mo thereafter. Further treatment for gastrointestinal stromal tumors (GISTs) was considered according to the results of immunohistochemical tumor staging.

DISCUSSION

Surgical resections for GSTs are classified into open, endoscopic or laparoscopic procedures. The selection

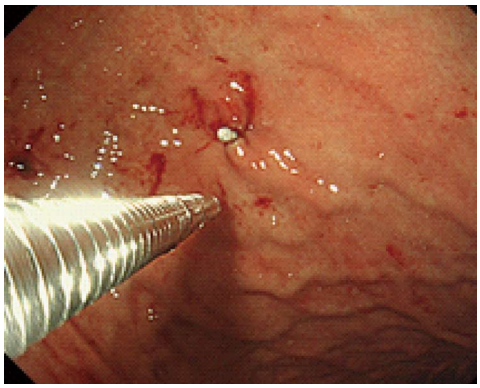

Figure 3 The hole of 3-mm port site was closed by a clip from the inside of the stomach.

of the procedure depends on the characteristics of the tumor, including its size, location and growth condition. In particular, laparoscopic intragastric resection can be modified for tumors located near the EGJ or pyloric ring, in order to avoid gastrectomy or stomach deformity after resection. From the viewpoint of minimal surgical invasiveness, several laparoscopic intragastric approaches have been reported, but the role of oral endoscopy for intragastric resection of GSTs has been emphasized.

The indications for intragastric resection also depend on the characteristics of the tumor. In general, tumors amenable to this technique are 2-5 cm in size and located on the posterior wall of the upper third of stomach, or close to the EGJ. In our experience, tumors more than 5 cm in size or 8 cm^2 in cross-sectional area require an additional gastrostomy for removal of the specimen from the stomach, because those sizes cannot be passed through the EGJ using an oral endoscope. However, when the tumor is less than 2 cm in size, resection depends on the results of FNA. Furthermore, when the tumor is more than 5 cm in size, a transgastric approach is selected for removal[4,5].

The actual resection method involved the use of an endo-linear stapler, coagulating shears or electrocautery. Stapled resection is more beneficial to provide with less operation time and blood loss, and can omit the suture of the resected area. In the resection process using an endo-linear stapler, if the 12-mm port is relatively close to the tumor, or if a tumor is larger than 5 cm, application of an endo-linear stapler is not easy, even if the stomach is inflated, because of the practical movable length of the stapler or the small opening of the stapler jaw[4,5]. Therefore we often use a minimum-length (30-mm) linear stapler, and place the 12-mm port on the greater curvature of the distal stomach under the guidance of oral endoscope. However, for any tumor located on the level of Z-line, submucosal dissection is applied circumferentially using electrocautery to prevent stenosis of the EGJ[9].

For successful intragastric resection of a GST, the use of an oral endoscope is mandatory for defining

Table 1 Basic data of the literature

Ref.	Year	Case	Gender (M/F)	Age (mean)	Location (U/M/L)	Distant from EGJ (mm)	Size (mm)
Choi and Oh[12]	2000	9	NA	NA	9/0/0	NA	NA
Matthews *et al*[13]	2002	3	NA	NA	3/0/0	NA	NA
Walsh *et al*[14]	2003	11	NA	NA	11/0/0	NA	24-85
Pross *et al*[15]	2003	5	NA	NA	5/0/0	NA	34 (28-41)
Uchikoshi *et al*[16]	2004	7	NA	NA	7/0/0	NA	27-75
Li *et al*[17]	2008	3	0/3	77	2/1/0	37 (30-50)	28 (20-40)
Na *et al*[7]	2011	7	3/4	65	6/1/0	NA	27 (23-38)
Sahm *et al*[18]	2011	7	NA	NA	NA	NA	38 (28-48)
Shim *et al*[9]	2011	6	3/3	48	7/0/0	NA	27 (15-40)
Tagaya *et al*[5]	2013	13	5/8	61	10/3/0	40 (10-70)	27 (10-65)
de Vogelaere *et al*[19]	2013	3	NA	68	3/0/0	NA	38 (27-68)
Dong *et al*[20]	2014	8	3/5	51	6/2/0	NA	28 (15-45)

NA: Not available.

Table 2 Clinical data of the literature

Ref.	Year	Operation time (min)	Complication	POHS (d)	Recurrence	Follow up (mo)
Choi and Oh[12]	2000	100-140	Open conversion: 1	5.9	None	Up to 42
Matthews *et al*[13]	2002	NA	NA	NA	NA	NA
Walsh *et al*[14]	2003	186 (120-320)	None	3.0-8.0	None	16.2 (1-32)
Pross *et al*[15]	2003	85-105	None	4.0-7.0	None	NA
Uchikoshi *et al*[16]	2004	141 (95-200)	Open conversion: 1	7.6	1 in 2 yr	14-99
Li *et al*[17]	2008	192 (140-240)	Staple line bleeding: 1	7.7	None	8-57
Na *et al*[7]	2011	86 (70-105)	Wound bleeding: 1	5.7	None	8.5 (1-23.3)
Sahm *et al*[18]	2011	NA	None	6.1	NA	NA
Shim *et al*[9]	2011	128 (105-145)	None	4.3	NA	NA
Tagaya *et al*[5]	2013	176 (132-217)	None	7.5	None	121.7 (1-192)
de Vogelaere *et al*[19]	2013	75 (67-82)	None	5.0	None	NA
Dong *et al*[20]	2014	85 (60-130)	None	7.4	None	NA

POHS: Postoperative hospital stay; NA: Not available.

precisely the location of the tumor, for determining the port placement site in the stomach, for assisting intragastric resection, for confirming hemostasis at the staple line, for retrieval of the specimen *via* the mouth, and for checking the presence of any air leakage from the resected area after re-inflation of the stomach. Schubert *et al*[10] have also reported that intraoperative flexible endoscopy has several advantages including facilitation of the trans-illumination of the gastric lesion during laparoscopic observation, elimination of preoperative tattooing of the lesion, and evaluation of the repaired gastric opening for any leakage after resection. Recently, Hiki *et al*[11] have reported laparoscopic and endoscopic cooperative surgery (LECS) for resection of GISTs. This method makes it possible to obtain an adequate cutting line independently of tumor location, eliminate an unnecessary resection of the gastric wall around the tumor in the setting of exogastric resection, and minimize any deformity of the stomach after resection. However, its indications are limited to intragastric growth-type tumors less than 5 cm in size, those with no direct tumor exposure, and those with no ulceration, in view of the attendant risk of dissemination. It is anticipated that oral endoscopy during laparoscopic procedures will become increasingly important in order to achieve minimal surgical invasiveness.

There are 18 reports covering laparoscopic intragastric resection of GSTs published between 2000 and 2014[5-10,12-23]. Six of them were excluded because their data were mixed with those for exogastric and transgastric procedures, or for single cases. We reviewed previous reports describing laparoscopic intragastric surgery (LIS) for GSTs (Tables 1 and 2)[5,7,9,12-20]. The number of cases ranged from 3 to 13, with a mean of 7 cases. The mean patient age was 62 years (range: 48-77 years). The tumor was located in the upper stomach in almost all cases (96.3%), with the exception of 3 cases. The mean size of the tumor was 31 mm (range: 27-38 mm). The common indications for intragastric resection of GSTs were a tumor location in the upper third of the stomach and posterior wall, intragastric growth, and a tumor diameter of less than 5 cm. The mean operation time was 134 min (range: 75-192 min). There were 4 complications (5.2%), including conversion to open laparotomy in 2 cases, bleeding from the staple line and wound in one case each, respectively. The mean postoperative hospital stay was 6.4 d (range: 4.3-7.7 d). The mean follow-up period was 48.8 mo (range: 8.5-121.7 mo), and only one case of tumor recurrence was recorded. However, the recurrence rate appears to depend on the size of the tumor: Nakamori

et al[22] reported that the recurrence rate increased with tumor size, and that the average period until recurrence was 23.6 mo. Evaluation of recurrence required a follow-up period of more than 2 years. This procedure has one limitation of consuming the number of linear staples, approximately 3 being necessary per procedure. When considering the possibility of recurrence, intragastric resection of GSTs using laparoscopy and oral endoscopy is suitable for tumors less than 5 cm in size and located in the upper third of the stomach.

Transumbilical single-incision laparoscopic abdominal surgery was introduced in 2007 and has since become disseminated worldwide. We have also applied single-incision laparoscopic local resection of the stomach for GSTs showing extragastric growth. There are a few reports[7,8] describing single-port access using a single port devices for tumors showing intragastric growth. Na *et al*[7] reported that a single-incision intragastric approach did not require the use of intraoperative oral endoscopy or pneumoperitoneum, and that the technique differed in three ways from the conventional approach: the operation time was reduced because of the use of a single gastrostomy and extracorporeal repair, the specimen was easily retrieved from the gastric opening without using an endoscope, and a better cosmetic outcome was achieved at the umbilicus. Morales-Conde *et al*[8] also reported intragastric endoscopically assisted single-incision surgery for GST at the EGJ. The single-site approach avoids multiple punctures of the stomach, and allows retrieval of larger specimens. However, this approach should be limited to selected cases involving tumors less than 5 cm in diameter without ulceration because of possible tumor rapture due to the complicated procedures employed.

In conclusion, intragastric surgery using laparoscopy and oral endoscopy can be considerably beneficial for patients with GSTs located in the upper third of the stomach. From the viewpoint of minimal surgical invasiveness, the significance of oral endoscopy during laparoscopic procedures is expected to increase for tumors in the stomach.

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MINIREVIEWS

Current status of single-balloon enteroscopy: Insertability and clinical applications

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Abstract

The single-balloon enteroscopy (SBE) system was launched in 2007, proposed as a simpler method than double-balloon enteroscopy (DBE). Controversy surrounds whether the SBE system has the same insertability as DBE. However, many methods have been proposed to improve the depth of insertion with the SBE system, involving several techniques and endoscopic accessories. SBE is used for investigating not only small bowel diseases, but also diseases of the pancreatobiliary and colonic structures. SBE is a necessary advancement for many endoscopic procedures and applications in modern clinical practice. In our review, we summarized the current literature concerning the insertability of SBE and described the technical aspects of improving the rate of deep insertion in SBE procedures. In addition, the recent applications of SBE to diseases besides those of the small bowel are described.

Key words: Single-balloon enteroscopy; Double-balloon enteroscopy; Small-bowel endoscopy; Endoscopic retrograde cholangiopancreatography; Endoscopic submucosal dissection

Core tip: The insertability of the single-balloon enteroscopy (SBE) system can be improved by technical innovations and by using endoscopic accessories such as carbon dioxide insufflation equipment. SBE is used not only useful for small bowel diseases, but also for colonic lesions and pancreatobiliary diseases. The SBE system is a necessary advancement for many endoscopic procedures in modern clinical practice.

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INTRODUCTION

Double-balloon enteroscopy (DBE) was developed by Yamamoto *et al*[1]. Since then, endoscopic observation of the entire small intestine has been possible without surgical intervention. The single-balloon enteroscopy

(SBE) system was launched in 2007 by Olympus Medical Systems (Tokyo, Japan) as an alternative to DBE[2-5]. SBE is a simpler method because the second balloon at the tip of the enteroscope is not present. However, controversy surrounds whether the SBE system offers the same insertability and diagnostic yield as DBE.

The purpose of this review was to summarize the current literature concerning the insertability and diagnostic yield of SBE and to describe the technical aspects of improving the depth of insertion in SBE procedures. In addition, recent applications to diseases besides those of the small bowel are described. While spiral enteroscopy is another alternative method of DBE[6-8], this method is not widely used in Japan; therefore, we did not discuss spiral enteroscopy in the present article. Details of the instruments used, and the basic principles of the insertion technique of SBE, have already been reviewed by Manno *et al*[9] in 2012.

INSERTABILITY OF SBE

Insertability compared with DBE

Total enteroscopy can be achieved using SBE. Usually, total small bowel visualization is confirmed by inserting the enteroscope through both the oral and anal routes and marking the midway point with an Indian ink tattoo or endoscopic clipping (Figures 1 and 2). The initial experience reports of SBE in Japan have been characterized by total enteroscopy rates of 12.5% to 71.4% (Table 1)[2-5].

Three randomized, controlled trials thus far have compared the rates of total small bowel visualization by DBE and SBE[10-12]. May *et al*[10] reported that complete enteroscopy was achieved with the DBE technique in 66% (33/50) of cases and only 22% (11/50) with the SBE technique ($P < 0.0001$). However, this study had a number of significant limitations. One was that the SBE system used in this study was not the original system produced by Olympus, but a DBE system made by Fujifilm Corporation (Tokyo, Japan) without the tip balloon attached. In 2011, Takano *et al*[12] also reported worse results for the insertability of the SBE system developed by Olympus compared to those for the DBE system developed by Fujifilm. The total enteroscopy rate was 0% in the SBE group and 57.1% in the DBE group ($P = 0.002$). This result suggested that the insertability of SBE might be inferior to that of DBE. However, Domagk *et al*[11] reported that DBE and SBE have comparable performance in the evaluation of the small bowel. Their study revealed that complete visualization of the small bowel was achieved in 18% and 11% of procedures in the DBE and SBE groups, respectively. These randomized control studies yielded conflicting results concerning the insertability of SBE compared to that of DBE.

We have discussed the insertability of SBE using total enteroscopy rate as a comparative parameter, because none of the currently known methods of estimating insertion depth are ideal[13]. However, the clinical impact of total enteroscopy rate is controversial, because in majority of the patients the fact whether total enteroscopy is achieved is not necessary to diagnose small bowel diseases[14]. Lenz *et al*[8] indicated that the first-choice enteroscope should be selected according to availability, physicians' experience, and clinical implications.

In the next section, the many methods of improving the insertability of SBE will be discussed.

Methods of improving the depth of insertion

The most important difference between SBE and DBE is the manner in which the small intestine is held by the tip of the enteroscope during sliding tube insertion. If the holding force is not sufficient, the enteroscope will slip back. Ohtsuka *et al*[15] discussed the method of improving the holding force in the small intestine using the SBE technique. To prevent the scope from slipping back during sliding tube insertion, it is important to use both upward and left angulation, as this helps to increase the holding force applied by the tip of the enteroscope. Furthermore, they recommended the use of a distal attachment to assist the fixation of folds in the small intestine.

A recent study suggested the usefulness of carbon dioxide insufflation during the SBE procedure in improving intubation depth[16,17]. Li *et al*[17] reported that the total enteroscopy rate of the carbon dioxide insufflation group was significantly higher than that of the air insufflation group (34.9% *vs* 17.6%; $P = 0.006$). Lenz *et al*[16] reported that oral intubation depth was significantly higher in the carbon dioxide group than in the air group (258 ± 84 cm *vs* 192 ± 42 cm; $P < 0.05$) in patients with previous abdominal surgery.

By using the techniques described above alongside carbon dioxide insufflation, the depth of SBE insertion devices can be improved. Interestingly, Ohtsuka *et al*[15] reported several cases of total enteroscopy using only the anal approach.

Complications

SBE is a safe diagnostic endoscopic procedure. However, serious complications such as acute pancreatitis[18,19] and perforation[20] could occur, although the rates of these complications are very low. Aktas *et al*[21] reported that while post-SBE hyperamylasemia occurred in 16% (13/81) patients, no acute pancreatitis was observed in 105 consecutive patients undergoing peroral approach SBE. Lenz *et al*[22] reported that the rate of severe adverse events after SBE procedures was only 0.6% (2/298) and did not differ significantly from that after DBE procedures in their large case series.

CLINICAL APPLICATIONS OF SBE

SBE for small bowel diseases

Parikh *et al*[23] summarized the clinical applications of SBE for small bowel diseases in 615 patients reported

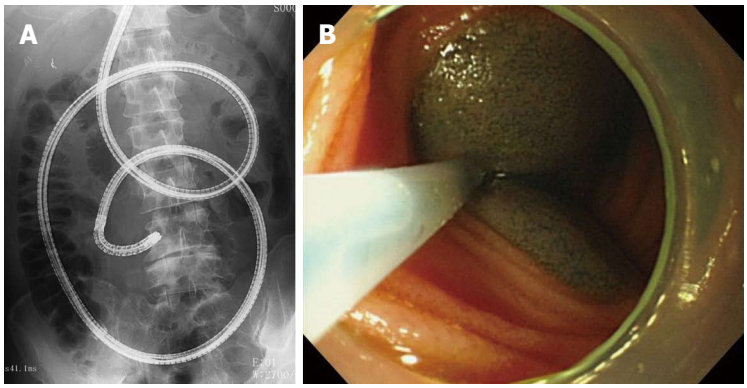

Figure 1 Case of total enteroscopy. A: Single-balloon enteroscope inserted orally; B: Indian ink was used as a tattoo in the deepest part of the intestine.

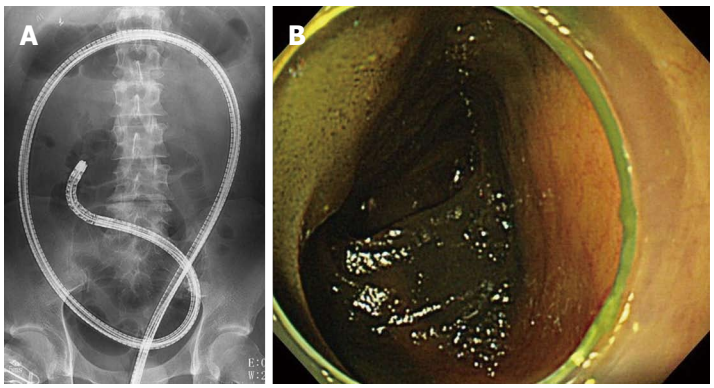

Figure 2 Case of total enteroscopy (continued). A: Single-balloon enteroscope inserted anally; B: Tattoo marked when enteroscope was inserted orally was confirmed.

Table 1 Rates of total enteroscopy using the single-balloon enteroscope

Ref.	Study design	No. of cases	Rate of total enteroscopy	Year
Tsujikawa *et al*[5]	Case series	78 exams in 41 pts	6/24 (25%)	2008
Kawamura *et al*[2]	Case series	37 exams in 27 pts	1/8 (12.5%)	2008
Ohtsuka *et al*[4]	Case series	48 exams in 30 pts	5/7 (71.4%)	2008
Kobayashi *et al*[3]	Case series	50 exams in 40 pts	3/5 (60%)	2008
Ramchandani *et al*[24]	Case series	131 exams in 106 pts	5/20 (25%)	2009
May *et al*[10]	RCT	50 pts	11/50 (22%)	2010
Domagk *et al*[11]	RCT	65 pts	7/65 (11%)	2011
Takano *et al*[12]	RCT	14 pts	0/14 (0%)	2011
Li *et al*[17]	RCT (CO_2 use)	106 pts	37/106 (34.9%)	2014
Li *et al*[17]	RCT (air use)	108 pts	19/108 (17.6%)	2014

RCT: Randomized controlled trial; pts: Patients.

thus far in their review article. The most common indication of SBE was obscure gastrointestinal bleeding (51%), followed by evaluation for Crohn disease (13%) and polyp/mass (8%). The most common lesions of the small bowel were angioectasias (22%), ulcers (15%), and polyp/mass (10%), and the most common interventions included hemostasis with argon plasma coagulation (22%), followed by polypectomy (3%) and dilation (3%).

Although there were conflicting results regarding the insertability of SBE compared with that of DBE, the diagnostic yield of small intestinal lesions using SBE was reported as equal to that of DBE. Diagnostic yields were 41%-65% in initial experience reports[2,5,24] and 37%-50% in randomized control studies[10-12], which were almost same as the rates of the DBE system.

Recently, SBE for disease in regions other than the small bowel has been reported. In the next session, the clinical applications of SBE for colonic and pancreatobiliary lesions are discussed.

SBE for colonic lesions

There are two main reasons for performing SBE for colonic lesions: One is when colonoscopy fails, and another is when endoscopic submucosal dissection (ESD) is required in difficult positions.

An elongated colon and adhesion would make it

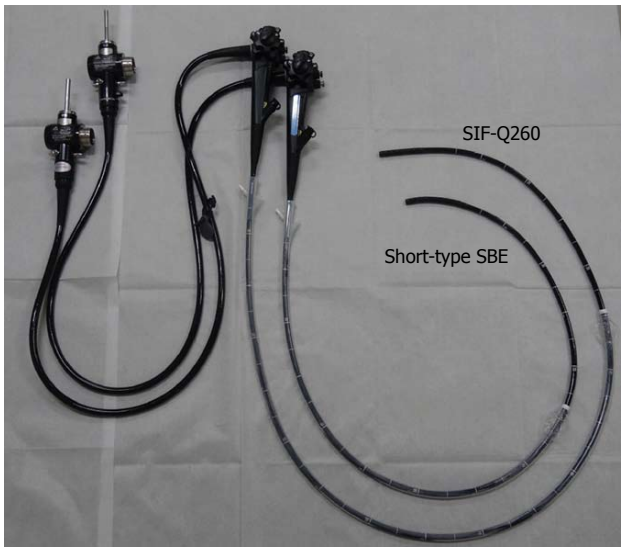

Figure 3 Short-type prototype single-balloon enteroscope. This scope has a working length of 1520 mm and an inner channel of 3.2 mm, which are compatible with those of many endoscopic accessories. SBE: Single-balloon enteroscopy.

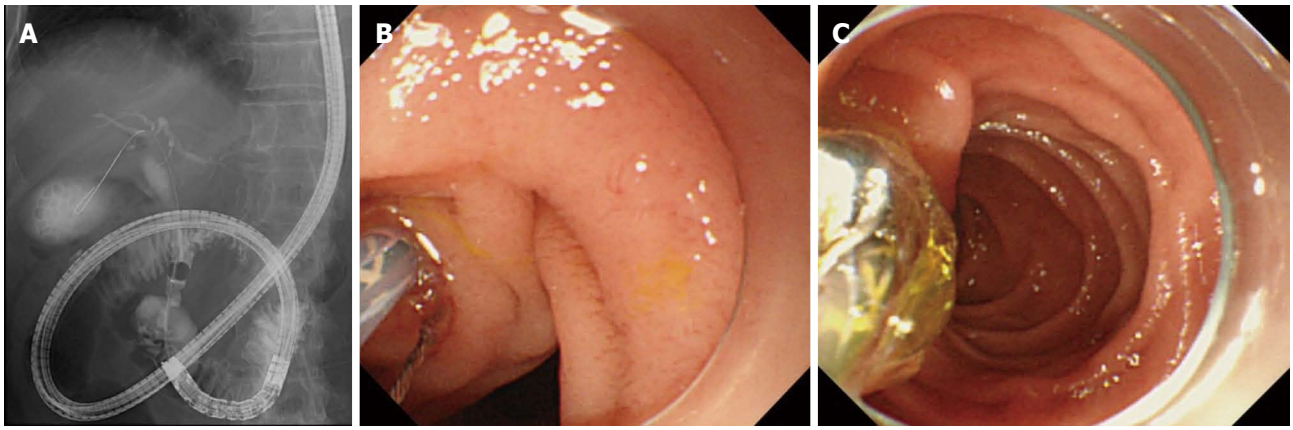

Figure 4 Case of common bile duct stones treated using a short-type prototype single-balloon enteroscope. Conventional endoscopic accessories such as retrieval balloon catheter (A), endoscopic sphincterotomy catheter (B), and endoscopic balloon dilation catheter (C), were used in this procedure.

difficult to achieve total colonoscopy. SBE is used to prevent stretching of the intestine. A case series suggested that the SBE system is successful in almost all patients in whom the cecum cannot be reached[25-27]. A randomized control trial revealed that the utility of SBE and DBE for colonoscopy seemed comparable in patients with incomplete previous colonoscopy using a conventional colonoscope[28].

ESD for colonic neoplasm is a technically challenging procedure, especially if the target neoplasm resides in a difficult to reach position. An overtube with a balloon is used to stabilize the endoscope during the ESD procedure. Ohya *et al*[29] reported the usefulness of a therapeutic gastroscope (GIF-Q260J; Olympus Medical systems, Tokyo) with an SBE overtube for colonic ESD. The SBE overtube was too long to use with the gastroscope, so a modified and shortened overtube of 70 cm from the distal end was used.

Endoscopic retrograde cholangiopancreatography for patients with surgically altered gastrointestinal anatomy

SBE is useful for both small bowel diseases and pancreatobiliary diseases in patients with altered gastrointestinal anatomy. Many studies have reported the usefulness of the SBE system for endoscopic retrograde cholangiopancreatography (ERCP) with altered gastrointestinal anatomy, especially in patients with Roux-en-Y anastomosis[30-43]. However, a limited number of ERCP accessories are compatible with the SBE system because of its narrow inner channel diameter and working length compared to those of a conventional duodenoscope. Recently, the usefulness of the short-type SBE prototype (SIF-Y0004; Olympus medical systems, Tokyo) has been reported[44-49]. The short-type SBE has a working length of 1520 mm and an inner channel diameter of 3.2 mm (Figure 3), which are both compatible with many conventional ERCP accessories (Figure 4). In the future, this short-type SBE system may become the first-choice endoscope for ERCP in patients with altered gastrointestinal anatomy.

Other applications of SBE

Recently, the efficacy and safety of SBE for children with Crohn disease and Peutz-Jeghers syndrome have been

reported[50-52]. SBE is expected to be as useful in children as in adult patients.

Endoscopic removal of foreign objects, diagnosis of parasite infestation, and SBE-assisted direct percutaneous endoscopic jejunostomy are reported as uncommon uses of SBE[53-56]. In cases in which the target regions lies in the small bowel, not far from the ligament of Treitz or the terminal ileum, the balloon at the tip of the enteroscope may not be needed. SBE might have advantages compared to DBE in such cases because of SBE involves a greater ease of preparation.

FUTURE PERSPECTIVES

In the future, detailed diagnosis will become more important and the optimal therapy after reaching the target region will be essential. For example, the usefulness of high-resolution enteroscopy, image-enhanced enteroscopy, magnified enteroscopy, and endoscopic ultrasonography[57-59] by using SBE will need to be discussed. Furthermore, several endoscopic accessories for ERCP and ESD performed using SBE will be required. Endoscopic procedures and applications using the SBE system are promising.

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ORIGINAL ARTICLE

Observational Study

Treatment of dysplastic Barrett's Oesophagus in lower volume centres after structured training

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Author contributions: Hoare J designed the study; Vlavianos P and Hoare J performed all the endoscopies, and collected all the specimens; Goldin R analysed all the specimens; Chadwick G, Faulkner J and Ley-Greaves R extracted all the results from the endoscopy database for analysis; Chadwick G wrote the manuscript with input from Faulkner J and Ley-Greaves R; the manuscript was critically reviewed and edited by Hoare J, Vlavianos P and Goldin R; all authors approved the final manuscript.
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Abstract

AIM: To investigate whether dysplastic Barrett's Oesophagus can be safely and effectively treated endoscopically in low volume centres after structured training.

METHODS: After attending a structured training program in Amsterdam on the endoscopic treatment of dysplastic Barrett's Oesophagus, treatment of these patients was initiated at St Marys Hospital. This is a retrospective case series conducted at a United Kingdom teaching Hospital, of patients referred for endoscopic treatment of Barrett's oesophagus with high grade dysplasia or early cancer, who were diagnosed between January 2008 and February 2012. Data was collected on treatment provided (radiofrequency ablation and endoscopic resection), and success of treatment both at the end of treatment and at follow up. Rates of immediate and long term complications were assessed.

RESULTS: Thirty-two patients were referred to St Marys with high grade dysplasia or intramucosal cancer within a segment of Barrett's Oesophagus. Twenty-seven met the study inclusion criteria, 16 of these had a visible nodule at initial endoscopy. Treatment was given over a median of 5 mo, and patients received a median of 3 treatment sessions over this time. At the end of treatment dysplasia was successfully eradicated in 96% and intestinal metaplasia in 88%, on per protocol analysis. Patients were followed up for a median of 18 mo. At which time complete eradication of dysplasia was maintained in 86%. Complications were rare: 2 patients suffered from post-procedural

bleeding, 4 cases were complicated by oesophageal stenosis. Recurrence of cancer was seen in 1 case.

CONCLUSION: With structured training good outcomes can be achieved in low volume centres treating dysplastic Barrett's Oesophagus.

Key words: Barrett's Oesophagus; Oesophageal cancer; Endoscopic treatment; Radiofrequency ablation; Endoscopic resection

Core tip: With structured training endoscopic treatment of dysplastic Barrett's Oesophagus with endoscopic resection and radiofrequency ablation can be provided in lower volume centres with good safety and efficacy outcomes.

Chadwick G, Faulkner J, Ley-Greaves R, Vlavianos P, Goldin R, Hoare J. Treatment of dysplastic Barrett's Oesophagus in lower volume centres after structured training. *World J Gastrointest Endosc* 2015; 7(1): 66-72 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i1/66.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i1.66

INTRODUCTION

Barrett's Oesophagus is a significant risk factor for oesophageal cancer[1], with studies suggesting it develops through a dysplasia-carcinoma sequence[2]. As it does the risk of progression to cancer increases from 0.1% per year for a non-dysplastic segment of Barrett's Oesophagus[3], to 5.6% per year if high grade dysplasia (HGD) is present[4].

United Kingdom guidelines recommend that Barrett's Oesophagus should be regularly surveyed, with prompt intervention if there is progression to HGD or cancer[5]. Until recently esophagectomy has been considered the treatment of choice, but this is associated with significant morbidity and mortality even in high volume centres[6]. Over recent years significant progress has been made in the endoscopic treatment of Barrett's Oesophagus with dysplastic changes. This has resulted in the most recent United Kingdom guidelines recommending endoscopic treatment of HGD in preference to oesophagectomy, given the lower treatment related morbidity[5].

Endoscopic treatment of dysplastic Barrett's oesophagus has two important stages. First, removal of any visible dysplastic lesions. This is usually achieved by endoscopic mucosal resection (EMR) of the lesion; this provides definitive staging information and ensures that lesions extending into the submucosa are not missed. Once this is done, it is recommended that any remaining segment of Barrett's Oesophagus is treated, this minimises the risk development of cancer in the future in the remaining Barrett's segment[7]. Two distinct approaches can be taken to do this, stepwise radical endoscopic resection (SRER) or ablation of the affected mucosa. Over the last five years radiofrequency ablation (RFA) has become the most widely used ablative technique. A recent systematic review demonstrated that while SRER and RFA have similar efficacy in treating dysplastic Barrett's Oesophagus, RFA is associated with a significantly lower rate of complications[8]. Furthermore while SRER appears to be a relatively complex technique to learn[9], learning to perform RFA does not appear to be associated with such a significant learning curve[10]. Ablation is therefore generally accepted as the preferred treatment modality in Europe.

To date most of the studies looking at the endoscopic treatment of Barrett's Oesophagus have come from high volume research centres, with only one small retrospective study coming from a community hospital in the United States[11]. This study reported 100% success in eradication of dysplasia at follow up in 10 patients with HGD, suggesting that dysplastic Barrett's Oesophagus can be managed successfully outside of large volume research centres. But larger studies performed outside high volume research centres are still needed.

Given the rapidly rising incidence of oesophageal cancer and Barrett's Oesophagus in the United Kingdom[12,13], several smaller centres have established treatment programs for dysplastic Barrett's Oesophagus. Recognising this fact the Academic Medical Centre in Amsterdam (AMC) created a multidisciplinary European Training Program for the treatment of neoplasia within Barrett's Oesophagus[14]. The aim of this course was to improve the quality of detection and treatment of dysplastic Barrett's Oesophagus in these lower volume centres.

This study aims to assess whether with the structured training, endoscopists with little experience in ablative techniques can be taught to manage dysplastic Barrett's Oesophagus safely and effectively in lower volume centres.

MATERIALS AND METHODS

Study design and patient population

In 2008 a centre for the treatment of dysplastic Barrett's oesophagus was established at St Mary's, a United Kingdom teaching hospital and regional centre for upper gastro-intestinal surgery. Patients were included in this retrospective consecutive case series, if they were diagnosed with Barrett's Oesophagus with HGD or intramucosal cancer (IMC) between January 2008 and February 2012 and were referred to St Marys for endoscopic treatment.

All patients had their pre-treatment histological diagnosis confirmed by a specialist pathologist (RG), and were discussed at the local specialist multi-disciplinary team (MDT) meeting, to determine the most appropriate treatment course. Any further staging investigations including CT and EUS recommended by the MDT to rule out invasive cancer, were performed at this stage.

Patients were identified for inclusion in the study by searching the hospital's electronic endoscopy database (Ascribe), records were cross checked against pathology

records and MDT meeting reports to ensure no cases were missed. Patients were excluded from this study if there was evidence of sub-mucosal invasion on resection of any visible nodules, or if they were considered unfit for repeated therapeutic endoscopies.

Teaching program at the AMC

Prior to the commencement of the study period, a multi-disciplinary team from St Marys, consisting of an endoscopist (JH), a pathologist (RG) and an endoscopy nurse attended the European training program for Barrett's Oesophagus with neoplasia at the AMC. The course consisted of three two day workshops, these combined theoretical lectures, live demonstrations by experts and finally hands on supervised training sessions. The hands on sessions were staged, starting treatment on explanted pig tissue, before progressing to live pigs and then human cases. A variety of different endoscopic techniques were taught including EMR-cap, multiband mucosectomy and RFA.

Endoscopic procedures

All endoscopic procedures were performed by one of two experienced endoscopists (JH, PV) on an outpatient basis under conscious sedation. All procedures were performed using an Olympus H260Z series endoscope, with narrow band imaging and zoom features used at the operators discretion.

Visible areas of dysplasia were resected first, using the Duette™ Multiband Mucosectomy (Cook Medical, Winston-Salem, NC). Patients with evidence of sub-mucosal invasion on the resected specimen were referred back to the MDT, and excluded from the study at this stage. Remaining patients had a repeat endoscopy two months later, where a further resection was performed if required. Otherwise patients were considered for ablation of any residual Barrett's Oesophagus using RFA. Patients with dysplasia detected within a segment of flat Barrett's Oesophagus on initial endoscopy started treatment with RFA immediately.

RFA was performed using the HALO system (BARRX Medical, Sunnyvale, CA). Circumferential RFA (HALO^{360}) was usually applied first, using standard energy settings (12 J/cm^2, 40 W/cm^2). This was repeated after repositioning the balloon, until the entire Barrett's Oesophagus segment was ablated. The catheter was then removed, so debris could be scraped off the balloon and coagulum could be removed from the ablation zone. The process was then repeated, before ablating the segment a second time. If there was only a short segment of non-circumferential Barrett's Oesophagus present initially or on follow up procedures, focal ablation was applied using the HALO^{90} device. RFA was then delivered twice in quick succession to each area (12-15 J/cm^2, 40 W/cm^2), then the probe and the mucosa were cleaned, the area was then ablated again twice. In the interest of costs, argon plasma coagulation (APC) was used at the endoscopist's discretion to treat small islands (< 5 mm) of residual Barrett's Oesophagus. Patients received treatment at 2-3 monthly intervals until all visible Barrett's Oesophagus was eradicated.

At this stage treatment was considered complete and targeted biopsies were taken of any endoscopic abnormalities in the oesophagus, and quadrantic biopsies were taken from just distal (< 5 mm) to the neo-squamocolumnar junction (NSCJ).

Histological analysis

All histological specimens were analysed by a specialist gastrointestinal pathologist (RG), and if there was evidence of dysplasia the diagnosis was confirmed by a second pathologist. Biopsies were assessed using the revised Vienna classification[15].

Data collection

Data was collected retrospectively from endoscopy reports and pathology records, up to August 2013. Information was collected on patient demographics, length of the Barrett's Oesophagus segment treated, the number and type of procedures each patient had had, duration of follow up and complications related to the procedure. Histology records provided information on pre and post treatment histology.

Endpoints

The primary outcome assessed was success of complete eradication of dysplasia (CE-D) and intestinal metaplasia (CE-IM) after completion of treatment. This was defined as absence of any endoscopically visible Barrett's Oesophagus (confirmed on available oesophageal biopsies), combined with the absence of dysplasia on biopsies taken from just distal to the NSCJ.

Secondary endpoints: (1) Rate of CE-D/CE-IM at most recent follow-up endoscopy, more than 6 mo after completion of treatment. Follow-up duration was defined as the time between completion of treatment and the most recent follow up endoscopy; (2) Rates of short term complications, related to initial endoscopic procedure, *e.g.*, bleeding or perforation; and (3) Rates of long term complications associated with the endoscopic treatment, *e.g.*, oesophageal stenosis.

Results are presented on both a per protocol (PP) and an intention to treat (ITT) basis, for the primary outcome and complication rates. But follow up results are presented on intention to follow up basis, after excluding patients who did not complete endoscopic treatment (due to patient choice or failure of endoscopic treatment) and patients who had not completed 6 mo follow up.

Statistical analysis

The study did not use any biostatistics mathods.

RESULTS

Between January 2008 and February 2012, 32 patients were referred for endoscopic treatment of Barrett's Oesophagus with HGD or IMC.

Twenty-one of these patients had a nodule visible

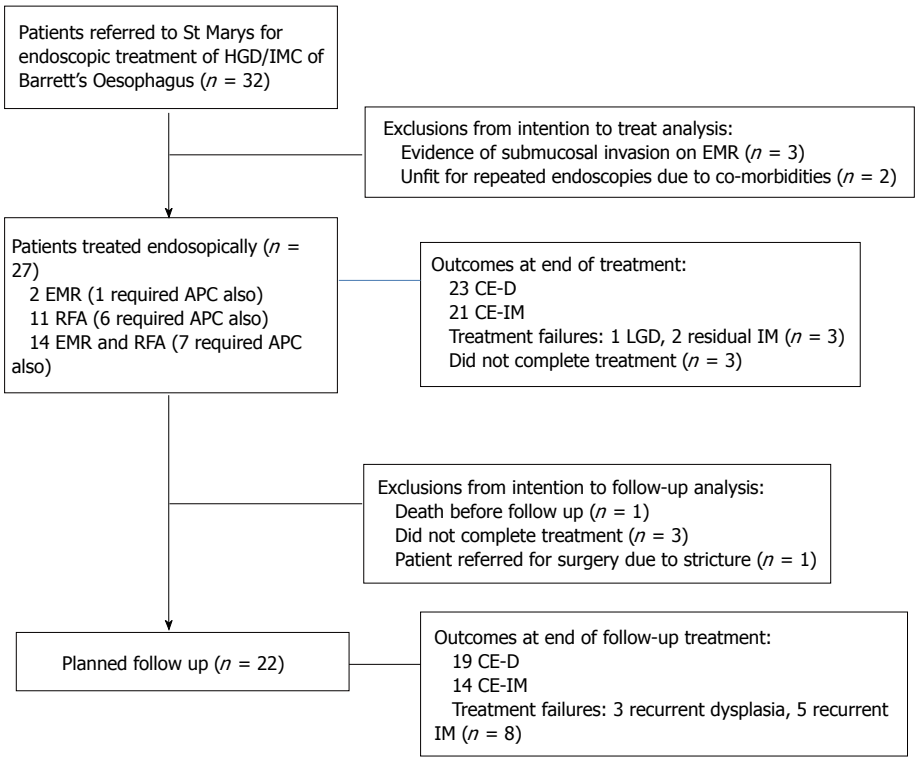

Figure 1 Selection of analysis cohort and outcomes. HGD: High grade dysplasia; LGD: Low grade dysplasia; IMC: Intramucosal cancer; APC: Argon plasma coagulation; EMR: Endoscopic mucosal resection; CE-D: Complete eradication of dysplasia; CE-IM: Intestinal metaplasia.

endoscopically at referral. Of these, 3 patients were found to have lesions extending deep into the submucosa, and an additional 2 patients were considered unfit for repeated endoscopic therapy due to severe co-morbidities. As a result these 5 patients were excluded from analysis.

This left 27 patients who met the inclusion criteria, and were considered for this study (Figure 1). Patient demographics are summarised in Table 1.

Treatment received

Patients received treatment over a median of 5 mo. During this time the median number of treatment sessions required was 3 (range 1-9). Where RFA was used, patients required a median of 1 focal and 1 circumferential ablation.

Sixteen patients (59%), including all those with a known diagnosis of IMC, had a nodule visible at initial endoscopy which was resected. Four of these patients required a further endoscopic resection, during the treatment period. Following successful endoscopic resection, 14 patients received additional treatment with RFA to treat the remaining Barrett's Oesophagus.

While 11 patients were found to have evidence of dysplasia within a flat segment Barrett's Oesophagus, they were treated with RFA alone as the primary therapy.

Following EMR and RFA, additional treatment with APC was needed in 14 patients, to treat small areas of residual Barrett's Oesophagus.

Primary outcomes

On an ITT basis CE-D at the end of treatment was achieved in 85% (23/27) CE-D, while 78% (21/27) achieved CE-IM. But 3 patients did not complete treatment as planned, so for the 24 patients who completed treatment as planned CE-D was achieved in 96% (23/24), with only 1 patient having evidence of residual low grade dysplasia (LGD). A further 2 patients who completed their planned treatment had evidence of visible non-dysplastic Barrett's Oesophagus after completing treatment, so CE-IM was achieved in 88% (21/24) of the cohort on PP analysis.

One patient who did not complete planned treatment was lost to follow up, after failing to attend several appointments. He represented 2 years later with a T2 oesophageal cancer, this was treated with an oesophagectomy but he subsequently died. The other two patients were lost to follow up, despite multiple attempts to re-engage them.

Secondary outcomes

Follow up results: 22 patients were considered for analysis in the follow up cohort. The 5 patients who were dropped from this cohort included the 3 patients who had failed to complete treatment, 1 who died from pancreatic cancer before starting follow up and 1 patient was referred for surgery after endoscopic treatment failed and resulted in a severe stricture refractory to endoscopic dilatation. The median follow up duration was 18 mo (range 7-34 mo).

During follow up 3 patients had recurrence of dysplasia. One patient had recurrent IMC, this has been retreated endoscopically and the patient is awaiting follow up. One patient who had LGD at the end of treatment

Table 1 Patient demographics

Male: female	25:2
Median age (yr) (range)	66 (53-89)
Median length Barrett's (cm) (range)	5 (1-10)
Worst diagnosis on biopsy or ER specimen	9 IMC/18 HGD

HGD: High grade dysplasia; LGD: Low grade dysplasia; IMC: Intramucosal cancer.

progressed to HGD during follow up. This patient is now undergoing regular surveillance instead of further treatment, on account of their co-morbidities and wishes. The final patient who developed LGD during follow up is undergoing more intense surveillance, but has not received further treatment. So overall 19/22 (86%) patients achieved CE-D at the most recent follow up.

A further 5 patients had recurrence of visible non-dysplastic Barrett's Oesophagus during follow up, so CE-IM was maintained in 14/22 (64%).

Complication rates

Overall 6 patients suffered from complications related to the procedure (22%). Two patients suffered acute bleeding post EMR, both were successfully treated endoscopically.

A further four (14.8%) patients developed oesophageal stenosis during follow up, all had had a prior EMR. This was treated successfully with endoscopic dilatation in three patients (two patients required a single dilatation, but one patient required three dilatations). The final patient, treated midway through the study, had five attempts at dilatation but the stricture was refractory to treatment, this patient was referred for an oesophagectomy which confirmed there was no evidence of residual disease.

There were no fatalities or oesophageal perforations related to treatment.

DISCUSSION

Given the high morbidity and mortality associated with oesophagectomy, endoscopic treatment for Barrett's Oesophagus with HGD or IMC is now considered the treatment of choice in most patients[5,16]. To date these treatments have been provided predominantly by high volume research centres. However, with the increasing prevalence of oesophageal cancer and Barrett's Oesophagus in Europe[12], an increasing number of lower volume treatment centres are being established. As a result the AMC in Amsterdam developed a specialised training program aimed at optimising the recognition and treatment of dysplastic Barrett's Oesophagus in these centres. It is therefore important to establish whether similar outcomes, in terms of both treatment efficacy and complication rates, can be achieved in lower volume centres after attending such a program.

This retrospective case series started with the first case of dysplastic Barrett's Oesophagus treated at our institution after attending the course, and demonstrates that EMR and RFA for dysplastic Barrett's Oesophagus can be safely performed in lower volume institutions outside of a research setting.

Analysis of outcomes focused on the rates of eradication of dysplasia and intestinal metaplasia at the end of treatment and at follow up. For this analysis we considered presence of dysplasia on biopsies taken below the neo-squamocolumnar junction as evidence of treatment failure, because studies have suggested the risk of recurrence of dysplasia is highest in this area and may predict development of neoplasia[17,18]. But presence of intestinal metaplasia alone below the NSCJ was not considered significant, as the relevance of this finding is debatable. Morales *et al*[19] demonstrated the presence of intestinal metaplasia in routine biopsies taken from the cardia in 25% of a healthy population, suggesting the finding is not clinically relevant[19].

Overall treatment was very successful in patients who completed treatment as planned, with 100% success in eradication of HGD and IMC, 96% success in eradication of any dysplasia and 88% success in eradicating visible Barrett's Oesophagus. These results are comparable to previous studies, with prospective studies from large volume tertiary referral centres reporting between 81%-100% CE-D and 74%-100% CE-IM at the end of treatment[20-24].

One of the major drawbacks of studies to date has been the short follow up periods reported, between 14 and 22 mo[20-24]. This study provides a median follow up of 18 mo. Overall durability of eradication of dysplasia was good, with 86% of patients maintaining complete eradication of dysplasia at the end of treatment. Previous studies had reported 79%-100% CE-D at follow up[20-22,25,26].

Currently St Marys is a relatively low volume centre, with only 32 new patients considered for treatment during the 4 year study period (equating to less than 1 new patient per month). So our patient volumes are likely to be similar to those reported by centres involved in the United Kingdom HALO registry. This registry collected data from 216 patients recruited from 14 United Kingdom centres, and reported the following outcomes at the end of treatment: 83% CE-HGD, 76% CE-D and 50% CE-IM[27]. It is uncertain what initial training endoscopists had at each centre involved in this study. But our comparatively favourable results suggest that access to a specialised training program may have a beneficial impact on treatment outcomes, and allow lower volume centres to provide access to high quality endoscopic treatment for dysplastic Barrett's Oesophagus.

Throughout this series there were no reported deaths or perforations, but two patients required endoscopic treatment for bleeding post EMR. A further four patients (14.8%) suffered late complications, due to oesophageal stenosis. Our overall rates of oesophageal stenosis was slightly higher than rates reported in previous studies (0%-14%)[20-23,26,28,29]. This can be explained by two factors,

firstly the relatively high proportion of patients (59%) who required EMR prior to use of RFA (it should be noted that all strictures in this study occurred in patients who had had a previous EMR) and secondly this series started with the first case treated by our endoscopists. Van Vilsteren *et al*[9] previously demonstrated that there is a significant learning curve associated with learning to perform oesophageal EMR, and noted that complication rates were highest for the first few therapeutic endoscopies performed[9].

In conclusion, this study demonstrates that following structured training good outcomes can be achieved in the endoscopic treatment of dysplastic Barrett's Oesophagus in lower volume centres. While our rate of oesophageal stenosis was slightly higher than previously reported, it must be noted that these results represent the start of our learning curve. We therefore expect this rate to fall as the endoscopist's experience increases.

COMMENTS

Background

Barrett's Oesophagus is a pre-malignant condition which progresses through a dysplasia-carcinoma sequence. As it does the risk of progression to cancer increases rapidly. It is therefore important to treat patients with evidence of high grade dysplasia as they are at higher risk of developing oesophageal cancer. Until recently oesophagectomy has been the mainstay of treatment this is associated with significant risk, and therefore used predominantly in younger fitter patients. But recently newer endoscopic techniques have been developed with proven safety and efficacy in treating dysplastic Barrett's Oesophagus.

Research frontiers

With the increasing incidence of Barrett's Oesophagus in the United Kingdom it is important to assess whether these endoscopic techniques can be used safely and effectively outside of research centres, where the majority of the current literature is derived.

Innovations and breakthroughs

Several large studies have already demonstrated the safety and efficacy of endoscopic resection and radiofrequency ablation in dysplastic Barrett's Oesophagus (as summarised in a review by Chadwick *et al*). But these studies have come from high volume research centres. This is the first study to demonstrate that with structured training clinicians can achieve good outcomes in the endoscopic treatment of dysplastic Barrett's Oesophagus in low volume centres.

Applications

The results of this study suggest that with structured training, endoscopic treatment of dysplastic Barrett's can be used safely and effectively in lower volume hospitals.

Terminology

Barrett's Oesophagus: This is the replacement of the normal stratified epithelium lining of the lower oesophagus with columnar cells. This is important because it puts the person at increased risk of development of oesophageal cancer; Dysplasia: Refers to the development of abnormal epithelium, which in the case of Barrett's Oesophagus is at risk of progression to cancer; Intramucosal oesophageal cancer: Cancer affecting the very superficial layer of the oesophagus. This stage of cancer is at low risk of spreading to the regional lymph nodes and distant organs; Endoscopic Mucosal Resection: A procedure to remove cancerous or other abnormal tissues (lesions) using an endoscope which is passed down the oesophagus. Radiofrequency ablation is the use of high frequency current to destroy areas of abnormal tissue.

Peer review

This article is really very interesting.

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CASE REPORT

Russell body duodenitis with immunoglobulin kappa light chain restriction

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Abstract

Russell bodies are eosinophilic intracytoplasmic globules which are likely the result of disturbed secretion of immunoglobulins that accumulate within the plasma cell. Russell body collections have been identified within the stomach, known as Russell body gastritis. Similar lesions within the duodenum are referred to as Russell body duodenitis, which is rare. Several Russell body gastritis case reports are associated with *Helicobacter pylori*. However, the etiology of Russell body duodenitis remains unclear. Here we report the first case of Russell body duodenitis with immunoglobulin light chain restriction in a background of peptic duodenitis.

Key words: Russell body duodenitis; Russell bodies; Immunoglobulin

Core tip: Russell body duodenitis is rare and the etiology is unclear. We report a case of Russell body duodenitis with immunoglobulin light chain restriction in a background of peptic duodenitis.

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INTRODUCTION

Russell bodies are eosinophilic intracytoplasmic globules which were first described by Russell *et al*[1] in 1890. These globules are likely the result of disturbed secretion of immunoglobulins that accumulate within the plasma cell. Sixteen case reports have identified abundant collections of Russell bodies in the stomach, known as Russell body gastritis. Similarly, three cases have been reported to occur within the duodenum, with the first in 2011[2]. All three cases presented clinically with upper gastrointestinal symptoms with the subsequent identification of polytypic, Russell body containing plasma cells in the duodenum referred to as Russell body duodenitis[2-4]. Several of the Russell body gastritis case reports are

associated with *Helicobacter pylori* (*H. pylori*). However, the etiology of Russell body duodenitis remains unclear. Here we report the first case of asymptomatic Russell body duodenitis. Additionally, this is the first reported case showing immunoglobulin light chain restriction.

CASE REPORT

Clinical, endoscopic and pathologic findings

A 78-year-old female with a past medical history of congestive heart failure, atrial fibrillation, chronic obstructive pulmonary disease, and chronic renal injury, presented to hospital with shortness of breath and lower extremity edema. Past medical history was also significant for diabetes, and hypertension. Past surgical history included sigmoid resection for diverticulitis, rotator cuff repair, and carpal tunnel release. The patient denied alcohol use, and had a history of smoking over sixty pack-years. Upon admission for shortness of breath, the patient was treated with intravenous diuresis and her symptoms subsequently improved.

Further laboratory investigation revealed concomitant iron deficiency anemia and chart review showed progressive decline in hemoglobin over a nine-month period. There was no clinical or laboratory evidence to suggest monoclonal gammopathy.

Esophagogastroduodenoscopy and colonoscopy were performed to evaluate the source of anemia. The patient had no prior history of upper or lower gastrointestinal symptoms. Upper endoscopy revealed a few scattered gastric fundic sub-centimeter polyps, and prominent gastric antral folds without evidence of inflammation. In the duodenum, clusters of lobulated polyps (Figure 1A) were located in the duodenal bulb, with a normal appearing second portion of the duodenum. No ulceration was present. Colonoscopy revealed a three centimeter ulcerated, sessile mass at the distal ascending colon, concerning for malignancy.

Random stomach biopsies from the body and antrum showed normal morphology and no evidence of *H. pylori*. Duodenal biopsies of the lobulated polyps at the duodenal bulb showed numerous eosinophilic globules, or Russell bodies, as well as gastric surface foveolar metaplasia (Figure 1B). CD138 immunostain was positive in plasma cells containing Russell bodies (Figure 1C). Immunoglobulin kappa light chain immunostain showed a dark peripheral rim with light center staining pattern in the Russell bodies (Figure 1D) while lambda immunostain was negative (not shown). The surrounding plasma cells with mature morphology showed polytypic light chain staining pattern. IgH gene rearrangement was negative. Biopsies of the ulcerated, sessile distal colonic mass revealed invasive adenocarcinoma.

DISCUSSION

Russell bodies are eosinophilic inclusions located in the cytoplasm of plasma cells. While they are typically identified in the setting of several malignancies of hematopoietic origin, they can be seen in some reactive conditions as well. The plasma cells containing Russell bodies, referred to as Mott cells, are often found in the setting of plasma cell myeloma, MALT lymphoma, plasmacytoma, or lymphoplasmacytic lymphoma. Russell body gastritis is a rare reactive condition in which Russell bodies are found within the lamina propria of the gastric mucosa, and so far without a definitive association with *H. pylori* or malignancy.

Of the sixteen reported cases of Russell body gastritis, several identified monoclonality[5-7]. In these cases, there were no clinical and pathologic features of MALT lymphoma or significant plasma cell neoplasia[5]. One case did show lambda restricted Mott cells, positivity for *H. pylori*, and concomitant monoclonal gammopathy of undermined significance (MGUS); however, eradication of *H. pylori* caused the Russell body gastritis to subside while the paraproteinemia remained unaffected[7]. Thus, these cases of monoclonal Mott cell proliferations are either reactive in nature, or possibly, precursor proliferations to more significant conditions, such as MALT lymphoma or plasmacytoma.

Interestingly, the phenomenon of Russell body monoclonality in the presence of mature polytypic plasma cells, as in our case, has been observed before, although outside the gastrointestinal tract. In a biopsy of labial mucosa, Matthews *et al*[8] identified a patient with monoclonal Russell bodies restricted to IgG and kappa chains in a background of mature plasma cells. Of the twelve patients in their study, this was the only patient diagnosed with a significant medical pathology, namely, Sjogren's syndrome. B-cell clonality in Sjogren's syndrome has been hypothesized to alter the salivary or lacrimal gland microenvironment, enabling the progression to lymphoma[9]. Indeed, approximately 5% of patients with Sjogren's syndrome will develop lymphoma, an incidence 40 times that of the general population[10]. It could be postulated that monotypic Mott cells are similar to monoclonal B-cells in this setting, such that the finding indicates a transient or intermediate step between an inflammatory condition, such as Sjogren's syndrome, and the progression to malignancy, such as lymphoma.

Further evidence supporting monoclonal Mott cells as an intermediary between inflammatory conditions and malignancy comes from a rare case of gastric Mott cell tumor associated with *H. pylori*[11]. In this case, abundant monotypic IgG kappa Mott cells were found on gastric biopsy with features suggestive of MALT lymphoma[11]. Furthermore, Mott cells were found in regional lymph nodes[11]. It is possible that *H. pylori* gastritis, a chronic inflammatory condition, over time stimulated an intermediary monoclonal Mott cell proliferation that subsequently developed malignant transformation and lymph node involvement. Whatever the sequence of events, it may be inferred from this example that monotypic Mott cells harbor malignant potential.

To summarize, the present case shows a unique

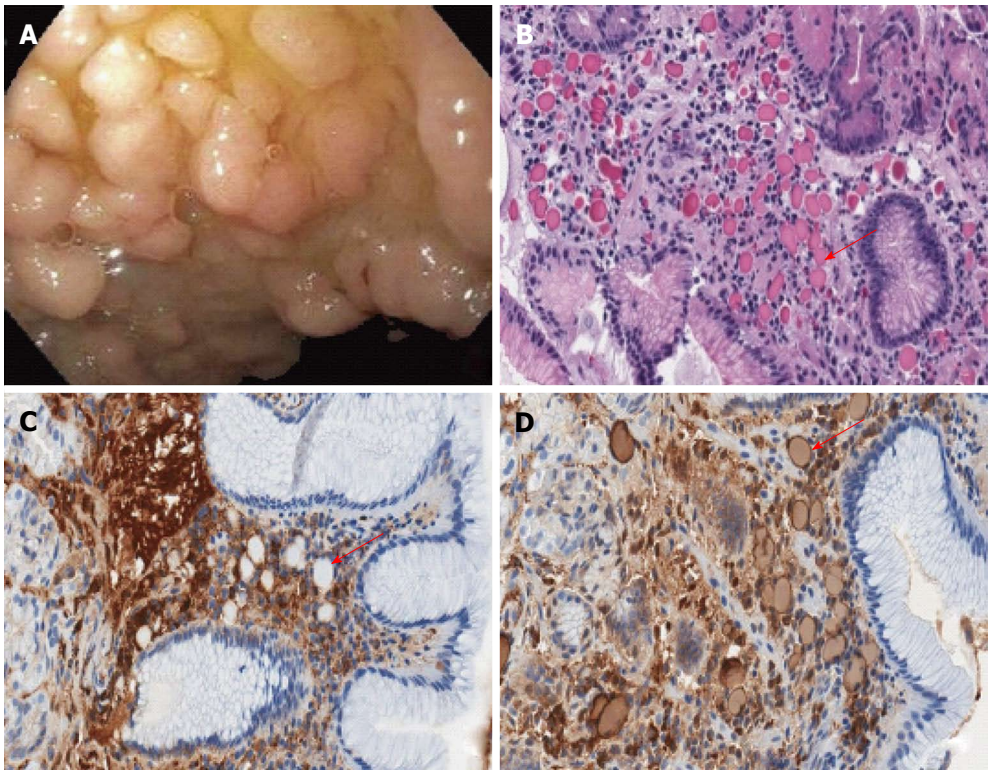

Figure 1 Endoscopic findings of duodenum. A: Endoscopic image shows a cluster of lobulated polyps in duodenal bulb; B: Numerous eosinophilic inclusions (Russell bodies, arrow) in the lamina propria and gastric foveolar metaplasia of the duodenal surface epithelium. H and E, 400 ×; C: CD138 immunohistochemistry highlights numerous mature plasma cells. The Russell bodies are round to ovoid clear spaces (arrow) within the lamina propria. Immunohistochemistry, 400 ×; D: Immunoglobulin kappa light chain immunohistochemistry shows a dark-rim staining and light internal staining pattern of Russell bodies (arrow). Immunohistochemistry, 400 ×.

type of Mott cell monoclonality for several reasons. First, the monoclonal Mott cells were located within the duodenum, of which this is the first reported case at this site. To date, only three cases of Russell body duodenitis have been reported, none of which demonstrate monoclonality[2-4]. Secondly, the monoclonal cells are present in a background of mature, polytypic plasma cells, a finding which is infrequently reported. Lastly, our patient was asymptomatic, the findings of Russell body duodenitis was incidental, and work up for *H. pylori* was negative. In this case, Russell body duodenitis likely originated from peptic duodenitis, indicated by gastric surface foveolar metaplasia of the overlying duodenal epithelium, and independent of *H. pylori*. Over time, chronic inflammation at this site may have caused Mott cells to accumulate, which subsequently progressed to monoclonality. It has been suggested that monoclonality of Mott cells may occur secondary to alternations at the immunoglobulin locus, and may be induced by chronic inflammation[7]. Given the low grade nature of MALT lymphomas in the stomach and duodenum, and the likelihood that monotypic Russell body duodenitis is either reactive or pre-malignant, treatment beyond eradication of *H. pylori* (if present) is likely unnecessary. Further investigation, and the accumulation of additional cases, will be necessary to better understand the clinical significance of monoclonal Russell body duodenitis.

COMMENTS

Case characteristics

The patient presented with shortness of breath and lower extremity edema. Further laboratory investigation revealed concomitant iron deficiency anemia.

Clinical diagnosis

Iron deficiency anemia.

Differential diagnosis

Cause of iron deficiency is unknown. Considering patient's age, the possibility of gastrointestinal blood loss due to ulcer or malignancy should be ruled out. Esophagogastroduodenoscopy and colonoscopy were performed to evaluate the source of anemia.

Endoscopic diagnosis

Gastric fundic polyps, duodenal polyps and a 3 cm ulcerated, sessile mass at the distal ascending colon.

Pathological diagnosis

Russell body duodenitis and colonic invasive adenocarcinoma.

Related reports

Three cases of polytypic Russell body duodenitis have been reported. Here we report the first case of Russell body duodenitis with immunoglobulin light chain restriction in a background of peptic duodenitis.

Experiences and lessons

Russell body duodenitis is uncommon and the etiology remains unclear. The monotypic Russell body duodenitis is either reactive or pre-malignant, treatment beyond eradication of *Helicobacter pylori* (if present) is likely unnecessary. Further investigation, and the accumulation of additional cases, will be necessary to better understand the clinical significance of monoclonal Russell body duodenitis.

Peer review

This is a case report of a rare disease (Russell body duodenitis) described to

occur in the duodenum first in 2011.

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