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REVIEW

Gastrointestinal bleeding from Dieulafoy's lesion: Clinical presentation, endoscopic findings, and endoscopic therapy

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Abstract

Although relatively uncommon, Dieulafoy's lesion is an important cause of acute gastrointestinal bleeding due to the frequent difficulty in its diagnosis; its tendency to cause severe, life-threatening, recurrent gastrointestinal bleeding; and its amenability to life-saving endoscopic therapy. Unlike normal vessels of the gastrointestinal tract which become progressively smaller in caliber peripherally, Dieulafoy's lesions maintain a large caliber despite their peripheral, submucosal, location within gastrointestinal wall. Dieulafoy's lesions typically present with severe, active, gastrointestinal bleeding, without prior symptoms; often cause hemodynamic instability and often require transfusion of multiple units of packed erythrocytes. About 75% of lesions are located in the stomach, with a marked proclivity of lesions within 6 cm of the gastroesophageal junction along the gastric lesser curve, but lesions can also occur in the duodenum and esophagus. Lesions in the jejunoileum or colorectum have been increasingly reported. Endoscopy is the first diagnostic test, but has only a 70% diagnostic yield because the lesions are frequently small and inconspicuous. Lesions typically appear at endoscopy as pigmented protuberances from exposed vessel stumps, with minimal surrounding erosion and no ulceration (visible vessel sans ulcer). Endoscopic therapy, including clips, sclerotherapy, argon plasma coagulation, thermocoagulation, or electrocoagulation, is the recommended initial therapy, with primary hemostasis achieved in nearly 90% of cases. Dual endoscopic therapy of epinephrine injection followed by ablative or mechanical therapy appears to be effective. Although banding is reportedly highly successful, it entails a small risk of gastrointestinal perforation from banding deep mural tissue. Therapeutic alternatives after failed endoscopic therapy include repeat endoscopic therapy, angiography, or surgical wedge resection. The mortality has declined from about 30% during the 1970's to 9%-13% currently with the advent of aggressive endoscopic therapy.

Key words: Dieulafoy's lesion; Gastrointestinal bleeding

Core tip: Dieulafoy's lesion is an important cause of acute gastrointestinal bleeding. Dieulafoy's lesions maintain an abnormally large caliber despite their

peripheral, submucosal, location. Dieulafoy's lesions typically present with severe, active, gastrointestinal bleeding. About 75% of lesions are located in the stomach, most commonly close to the gastroesophageal junction, but lesions can occur in duodenum and esophagus. Endoscopy is the first diagnostic test (70% diagnostic yield). Lesions typically appear at endoscopy as pigmented protuberances from exposed vessel stumps, with minimal surrounding erosions. Endoscopic therapy, including clips, sclerotherapy, argon plasma coagulation, thermocoagulation, or electrocoagulation, is the recommended initial therapy, with primary hemostasis achieved in nearly 90% of cases. Mortality of bleeding from this lesion is 9%-13%.

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INTRODUCTION

Although relatively uncommon, Dieulafoy's lesion represents an important etiology of acute gastrointestinal (GI) bleeding because of its propensity to cause massive, life-threatening, and recurrent bleeding; and its amenability to life-saving endoscopic therapy. It most commonly causes upper GI bleeding[1], but can also cause middle GI bleeding (defined as bleeding localized between the ampulla of Vater and the cecum[2])[3], and rarely cause lower GI bleeding[4], depending upon the location of the lesion. Numerous, recent, small, retrospective studies have analyzed the efficacy and safety of individual endoscopic therapies for this lesion, but these studies generally lack a comprehensive review of the literature. This work comprehensively reviews the pathophysiology, epidemiology, clinical presentation, endoscopic diagnosis, and endoscopic therapy of Dieulafoy's lesions, with an emphasis on recent studies of endoscopic therapy.

BRIEF HISTORY

Although first reported by Gallard[5] in 1884, Dieulafoy's lesion was more precisely described 14 years later by the French surgeon, Georges Dieulafoy[6]. He reported fatal GI hemorrhage in three, asymptomatic, young, male patients caused by large, actively bleeding, blood vessels within the stomach associated with small ulcers, which he called "exulceratio simplex", as he erroneously believed these lesions were early peptic ulcers. Since then, a multitude of cases of Dieulafoy's lesions have been reported throughout the world[7,8]. The lesion nomenclature has been variable, including the following alternative names: caliber-persistent artery, gastric arteriosclerosis, cirsoid aneurysm, and submucosal arterial malformation[9]. However, the most commonly accepted name is Dieulafoy's lesion, even though the term caliber-persistent artery has the virtue of aptly summarizing its pathophysiology. The term gastric arteriosclerosis is to be avoided because the pathophysiology does not involve arteriosclerosis or atherosclerosis. Likewise, the term cirsoid aneurysm should be avoided because the pathophysiology does not involve an aneurysm.

PATHOPHYSIOLOGY

The lesion is defined anatomically as a dilated, aberrant, submucosal artery that erodes overlying GI mucosa in the absence of an underlying ulcer, aneurysm, or intrinsic mural abnormality[10]. Unlike the normal arterial tree, which like branches of a tree, progressively narrows when approaching distal branches, Dieulafoy's lesion maintains constant arterial caliber, of approximately 1-3 mm, despite its very distal, submucosal location within the GI wall[7]. This caliber is up to ten-fold larger than the normal maximal caliber of such submucosal vessels. The aberrant artery can protrude through a small mucosal defect, become susceptible to even minor mechanical trauma (*e.g.*, passage of food bolus in stomach or solid stool in colon), and eventually erode into the lumen to cause severe acute GI bleeding. Each arterial pulsation transmits mechanical pressure that may traumatize the fragile, thin layer of mucosa overlying the vessel. Alternatively, enhanced blood flow through the enlarged artery may cause hypoperfusion, ischemia, and erosion of overlying mucosa from shunting and redistribution of blood perfusion[11]. This hypothesized "vascular steal" phenomenon resembles that which produces a pale mucosal halo that sometimes surrounds angiodysplasia[12]. Chronic age-related mucosal wear and tear and atrophy may explain the tendency for this bleeding to generally present in older age[8].

About 70% of lesions occur in the stomach[8,9]. The proximal stomach, in particular within 6 cm from the gastroesophageal junction and along the lesser gastric curve, is the most common gastric location, accounting for about 75% of all gastric lesions (Table 1)[13,14]. This proclivity is attributed to the blood supply to this area coming directly from the arterial chain running along the lesser gastric curve because the usual submucosal, arterial anastomotic gastric plexus is absent in this area[15]. Other common lesion locations include duodenum (15% prevalence)[7,9], distal stomach (12% prevalence)[8], and esophagus (8% prevalence)[16]. However, recent publications, consisting mostly of case reports or limited case series, also report Dieulafoy's lesions of the jejunum[3,17], ileum[17-21], cecum[22], appendix[23], colon[24,25], rectum[26], and anal canal[27] which present with lower GI bleeding. Figure 1 summarizes the approximate distribution of bleeding Dieulafoy's lesions within the GI tract. Also,

Table 1 Clinico-epidemiologic characteristics of Dieulafoy lesion

Anatomy
Dilated, aberrant, submucosal artery eroding overlying gastrointestinal mucosa in absence of either underlying ulcer or local aneurysm
Location
70% of ulcers in stomach
In stomach most commonly located within 6 cm of gastroesophageal junction along lesser curve
Can occur moderately commonly in esophagus or duodenum, occasionally in jejunum or ileum, and rarely in colon
Epidemiology
Generally presents clinically in older age, but can occur at any age
Male:female ratio = 2:1
No known epidemiologic risk factors or clinically associated diseases
Clinical presentation
Typically presents with overt GI bleeding, often with hematemesis or melena, or both
Bleeding typically severe
No prodromal symptoms
Typically bleeding is painless
Frequent presentation with signs or laboratory tests of hemodynamic instability, including: tachycardia, hypotension, orthostasis, and acute prerenal azotemia
Frequently requires transfusion of multiple units of packed erythrocytes
Frequent recurrent bleeding if undetected or not treated at initial endoscopy

GI: Gastrointestinal.

extra-gastrointestinal locations of Dieulafoy-like lesions can present with acute non-gastrointestinal bleeding, such as bronchial Dieulafoy's lesion presenting with hemoptysis[28].

It is unknown if this lesion is inherited or acquired[29]. It has not been associated with genetic mutations. The generally older age of patients with Dieulafoy's lesion might suggest an acquired defect. Contrariwise, the propensity of these lesions to be located within 6 cm of the gastroesophageal junction might reflect a congenital defect. While the pediatric literature suggests that the tortuous, dilated artery with a variable course length may represent a congenital anomaly[30], scant data supports familial predisposition in adults[7].

EPIDEMIOLOGY

Dieulafoy's lesion is responsible for approximately 1.5% of acute upper GI bleeding[14,31], and is responsible for approximately 3.5% of jejunoileal GI bleeding[17]. For example, in a recent, retrospective, multicenter, study of 284 patients with suspected overt or occult small intestinal bleeding who underwent 317 double-balloon and 78 single-balloon enteroscopies, 10 patients (3.5%) had Dieulafoy's lesion in the jejunum or ileum as the bleeding etiology[17]. Most of the small bowel lesions were located in the jejunum. Colonic Dieulafoy's lesion is presumably rare; less than 30 cases have been reported since three patients with colonic Dieulafoy's lesion were first reported in 1985[24,32,33].

Epidemiologic characteristics of patients with Dieulafoy's lesions have been described. The lesion

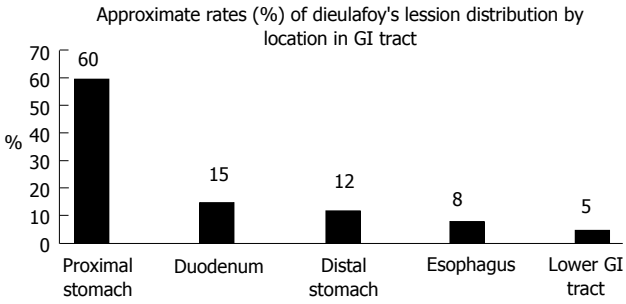

Figure 1 Segmental distribution of Dieulafoy's lesion within the gastrointestinal tract in patients presenting with acute gastrointestinal bleeding. GI: Gastrointestinal.

is reportedly more common in males than females, with a sex ratio of 2:1[8,20,34]. It can occur at any age[7,8], although older series reported a predisposition towards advanced age, with most cases presenting in the sixth or seventh decades[14,35]. Affected patients often have non-gastrointestinal comorbidities such as cardiovascular disease, hypertension, diabetes, and chronic renal insufficiency. Also, affected patients are often administered non-steroidal anti-inflammatory drugs (NSAIDs) or anticoagulants most likely because these drugs promote bleeding from underlying Dieulafoy's lesions which results in clinical detection[10,36]. No causal link has, however, been found between Dieulafoy's lesions and use of NSAIDs, alcohol or tobacco; or the presence of peptic ulcer disease or *Helicobacter pylori* infection[10,15,36-38].

CLINICAL PRESENTATION

Patients are typically asymptomatic before presenting with acute, profuse GI bleeding, which can manifest as hematemesis, melena, or hematochezia[39,40]. Approximately half of patients present with both hematemesis and melena[9]. For example, in a review of 177 cases, 51% presented with hematemesis and melena, 28% of patients presented with hematemesis, and 18% presented with melena alone[40]. Patients with colonic Dieulafoy's lesions typically present with profuse bright red blood per rectum. The bleeding is typically severe, attributed to the arterial nature of the bleeding and the enlarged arterial vessel (Table 1). Patients rarely present with chronic, occult, GI bleeding. Signs of hemodynamic instability such as tachycardia, hypotension, and orthostasis, or laboratory abnormalities of acute prerenal azotemia frequently occur because of the severity and acuity of the GI bleeding[41,42]. For example, 10 (50%) of 20 Mexican patients presented with signs of hemodynamic instability[40]. The mean hemoglobin on admission for bleeding is about 9 g/dL[43]. The bleeding is frequently recurrent, with recurrence < 72 h after initial presentation if it is left untreated at the initial endoscopy[7]. Recurrent bleeding is often extremely severe, which emphasizes the importance of accurate diagnosis and appropriate therapy at the initial

Table 2 Diagnosis of Dieulafoy's lesion

EGD
Small, relatively inconspicuous pigmented protuberance with minimal surrounding erosion and no ulceration
Lesion often actively bleeding or oozing at EGD
Gastric lesions most commonly within 6 cm of GE junction along lesser curve
Initial EGD may be nondiagnostic in up to 30% of cases due to relatively small lesion size
Avoid endoscopic biopsies of lesion
Colonoscopy or enteroscopy
May be useful to diagnose colonic or jejunoileal lesions, respectively, if EGD was negative in setting of severe, acute GI bleeding
Angiography
May be helpful in setting of rectal bleeding after negative EGD and colonoscopy

EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal.

endoscopy. Other GI symptoms, especially abdominal pain, are uncommon and their presence suggests alternative diagnoses such as peptic ulcer disease or complications from the bleeding such as mesenteric ischemia from hemorrhagic shock[14].

The clinical presentation of patients with jejunoileal lesions is similar to that of patients with upper GI Dieulafoy's lesions[17]. Among 10 patients diagnosed with small-intestinal Dieulafoy's lesions, all presented with overt bleeding and all had severe, transfusion-dependent, anemia[17]. Eight of the ten Dieulafoy's lesions were actively bleeding at enteroscopy. Most patients were elderly (mean age = 69.7 years), but the disease occurred at younger ages as well (youngest patient = 35 years old).

Dieulafoy's lesion is also an important cause of obscure GI bleeding because it frequently bleeds intermittently, it occasionally involves unusual GI bleeding sites that are relatively inaccessible to conventional endoscopy, such as the jejunum or ileum; and the lesions are frequently relatively small, subtle, and inconspicuous despite repetitive use of standard diagnostic techniques[44]. Conversely, alternative diseases can sometimes mimic a Dieulafoy's lesion in the setting of acute GI bleeding. For example, two recent reports from Japan describe patients whose initial clinical presentation and endoscopic findings suggested gastric Dieulafoy's lesions, but who were subsequently diagnosed with GI stromal tumors[45,46].

Dieulafoy's lesions are apparently not associated with other GI vascular lesions, such as angiodysplasia or hemangiomas. Although syndromes with multiple vascular lesions occur with angiodysplasia (in hereditary hemorrhagic telangiectasia), syndromes with multiple or disseminated Dieulafoy's lesions have not been reported, One patient, however, had two GI Dieulafoy's lesions[47]. Unlike the genetic mutations associated with hereditary hemorrhagic telangiectasia[48], no genetic mutations have been associated with Dieulafoy's lesions. Hereditary hemorrhagic telangiectasia is occasionally associated with high-output cardiac failure[49], or individual organ (*e.g.*, liver) failure[50], from extensive shunting of blood. However, Dieulafoy's lesion is not associated with high-output cardiac failure or individual end-organ failure because it produces minimal individual organ or systemic vascular shunting due to its relatively moderate size and single lesion status.

DIAGNOSIS

Esophagogastroduodenoscopy (EGD) is usually the first diagnostic test performed for acute, upper, GI bleeding. Dieulafoy's lesion is, therefore, usually diagnosed by EGD, which reveals a pigmented protuberance from the vessel stump, with minimal surrounding erosion and no ulceration (visible vessel sans ulcer; Figures 2A, 3A and 4A). The pigmented protuberance has a variable color, including reddish, purple, blue, or greyish-white. The protuberance is usually relatively inconspicuous at EGD; it is approximately 10-15 mm wide and about 5-10 mm high (Table 2). Approximately 50%-60% of identified upper GI Dieulafoy's lesion are actively bleeding at the initial EGD, typically with spurting or oozing of blood from a miniscule (1-5 mm in diameter) point source on the GI mucosa[40,42]. For example, in a study of 29 patients, 66% had oozing, and 28% had spurting bleeding at endoscopy[51]. Spurting bleeding is often micro-pulsatile reflecting the underlying arterial breach. Other patients typically have a fresh adherent clot or visible (non-actively bleeding) Dieulafoy's lesion at the initial endoscopy. Dieulafoy's lesion should be strongly considered, when a lesion is located in proximal stomach and/or has a small mucosal defect connected by a narrow attachment point to an adherent clot[9]. Dieulafoy's lesion may not be detected when covered by an adherent clot, and the lesion may be exposed by washing away an adherent clot with moderate endoscopic perfusion. The authors do not recommend guillotining an adherent clot covering a Dieulafoy's lesion because of the risk of inducing severe hemorrhage.

Dieulafoy's lesion should be endoscopically distinguished from other clinical entities with a similar clinical presentation and endoscopic appearance, including: arteriovenous malformations, hereditary hemorrhagic teleangiectasia (Osler-Weber-Rendu syndrome), or vascular neoplasms. Additionally, when located close to the gastroesophageal junction, the lesion has to be distinguished from a Mallory-Weiss tear, in which the bleeding originates from a superficial mucosal tear instead of a superficial protruding blood vessel. A history of vomiting before hematemesis may suggest a Mallory-Weiss tear. However, given their frequently similar anatomical location, endoscopic misdiagnoses of Dieulafoy's lesions as Mallory-Weiss tears have been reported[7]. It is important to differentiate a colonic Dieulafoy's lesion from an adenomatous colonic polyp to prevent massive hemorrhage from performing "polypectomy" of a Dieulafoy's lesion[52].

Initial EGD is diagnostic in only about 70% of cases

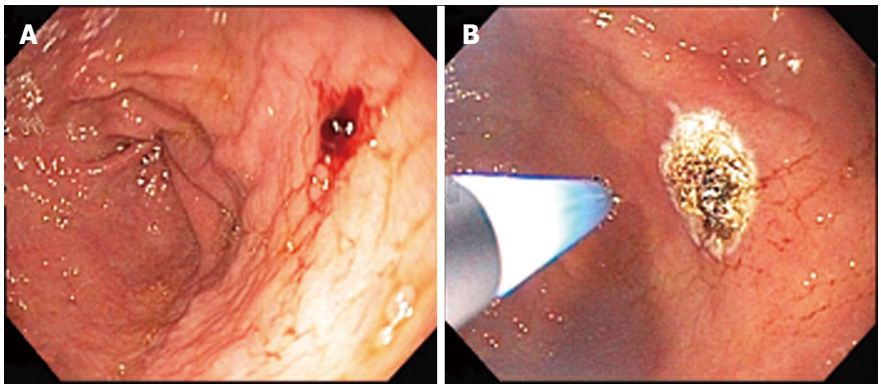

Figure 2 An 86-year-old woman who had undergone two esophagogastroduodenoscopies in the prior 2 years for 2 episodes of acute upper gastrointestinal bleeding that had not revealed any upper gastrointestinal lesions, presented with acute onset of melena and an acute hemoglobin level decline from 11.0 g/dL to 8.6 g/dL. Esophagogastroduodenoscopy revealed an actively oozing, darkly red, 6-8 mm wide, raised, lesion without surrounding erosions or ulceration that was actively oozing along the greater curvature of the gastric body (A), findings characteristic of a Dieulafoy lesion. The lesion was successfully cauterized using 50 watts of argon plasma coagulation at 1 L/min (note probe hovering over cauterized lesion in (B) with cessation of active oozing. The patient was discharged four days later with no evidence of recurrent bleeding during the hospitalization and no further gastrointestinal bleeding during 4 mo of follow-up.

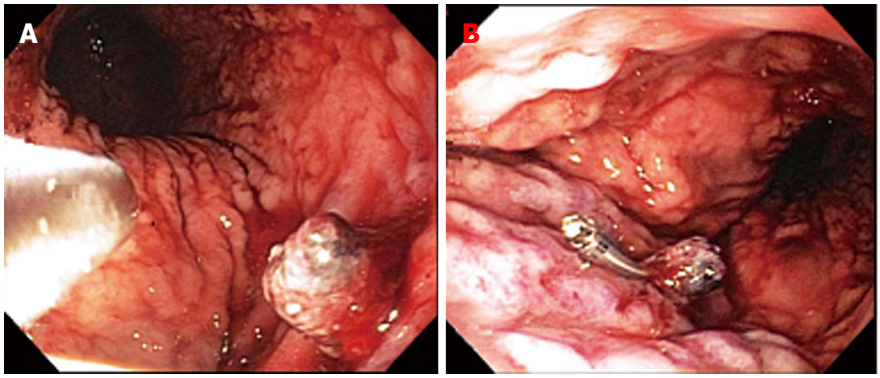

Figure 3 An 88-year-old woman with prior bleeding duodenal ulcer 40 years earlier, and actively administered aspirin, presented with acute onset of hematemesis and melena, with an acute decline in the hemoglobin level from 11.2 g/dL to 9.2 g/dL. Esophagogastroduodenoscopy revealed an actively oozing, darkly red, 8-10 mm wide, raised, lesion without surrounding erosions or ulceration that was actively oozing in the gastric cardia (A), findings characteristic of a Dieulafoy lesion. The lesion was first injected with 7 mL of epinephrine (1:10000 solution), followed by successful placement of a single hemoclip around the protruding vessel (B), with cessation of active oozing. The patient was discharged three days later with no evidence of recurrent bleeding during the hospitalization.

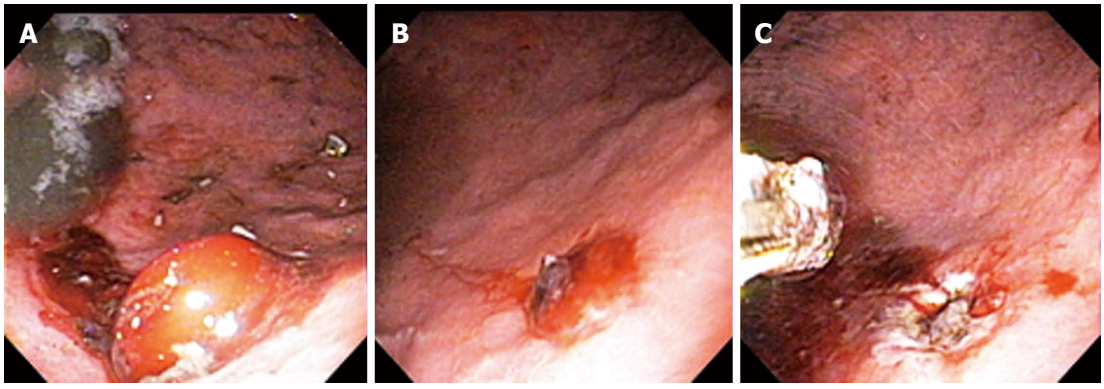

Figure 4 An 81-year-old woman presented with nausea, coffee-ground emesis, and dizziness. She underwent urgent esophagogastroduodenoscopy (EGD), despite a normal initial hemoglobin level of 13.0 g/dL, because of the hematemesis. EGD revealed a small blood clot, overlying a lesion without surrounding ulceration, located in proximal gastric body, which was slowly oozing red blood (A). After detachment of the blood clot with irrigation, a raised, darkly red, blood vessel was visualized consistent with a Dieulafoy lesion (B). The lesion was treated with 4 mL of 1:10000 solution of epinephrine and thermocoagulated *via* heater probe 5 pulses of 30 Joules/pulse without post-procedural bleeding (C). Patient remained stable after the EGD with no further bleeding and she was discharged 3 d later.

due to relatively small lesion size; intermittently active bleeding; lesion location between folds; or lesion location underneath gastric contents, an adherent blood clot, or a pool of blood from massive bleeding[53]. For

example, in a retrospective study of 177 patients with Dieulafoy's lesions causing acute GI bleeding, repeat endoscopic evaluation was needed in 33% of cases, due to nondiagnostic initial examinations[37]. Indeed, about 6% of patients require three or more endoscopies to establish the diagnosis[8]. This diagnostic yield at EGD is significantly lower than that of about 95% for other lesions causing upper GI bleeding[54]. Gastric insufflation may expose a Dieulafoy's lesion previously buried between gastric rugae. Careful aspiration of the gastric lake may demonstrate an underlying Dieulafoy's lesion. Cautious removal of an adherent clot may reveal an underlying Dieulafoy's lesion. Lesion identification may require careful gastric retroflexion due to its predilection to be near the gastroesophageal junction. As with EGD, repeat enteroscopic examinations, after initially nondiagnostic enteroscopy, are frequently required to diagnose jejunoileal lesions. In one study 40% of cases required a second or even a third enteroscopy to establish the diagnosis[17].

Several small reports suggest that, supplemental methods such as endoscopic ultrasound or bleeding provocation with intravenous heparin, may help increase the diagnostic yield of Dieulafoy's lesions at endoscopy[55,56]. Typical endosonographic features include an abnormally large (2-3 mm wide) caliber, pulsatile, high-flow, submucosal artery, usually located along the lesser gastric curve near the gastroesophageal junction. Endosonography has been used to confirm endoscopic hemostasis of a bleeding Dieulafoy's lesion by demonstrating absent blood flow after therapy[55]. However, combining endoscopy with such costly, advanced technology is currently not recommended for routine clinical practice due to insufficient data concerning efficacy. Endoscopic biopsies of suspected Dieulafoy's lesion are generally contraindicated because of the risk of inducing severe bleeding by biopsying the exposed artery and the lack of pathologic diagnosis from endoscopic biopsies.

Colonoscopy is usually indicated following a negative EGD for acute GI bleeding. Multiple individual cases of bleeding Dieulafoy's lesion diagnosed at colonoscopy have been reported during the past 30 years. However, the diagnostic yield of colonoscopy for this entity is unknown[24-27,56-61].

Enteroscopy is often indicated for acute GI bleeding after nondiagnostic EGD and colonoscopy. It enables viewing of the small bowel up to about 150 cm beyond the pylorus, to identify distal duodenal or proximal jejunal lesions. There is limited data on the diagnostic yield of enteroscopy for acute bleeding from small bowel Dieulafoy's lesions[3,17-21]. Single-balloon and double-balloon enteroscopies permit intubation of more distal small intestine, thereby permitting detection of more distal Dieulafoy's lesions.

Several Dieulafoy's lesions have been diagnosed by capsule endoscopy[34,62]. While noninvasive, capsule endoscopy lacks therapeutic capabilities, and a positive test still requires a subsequent invasive therapeutic modality. Still, capsule endoscopy may be diagnostically helpful for Dieulafoy's lesion causing obscure GI bleeding, especially from the distal small intestine[62].

If endoscopy is nondiagnostic, angiography may help establish the diagnosis in the setting of acute bleeding, especially for lower GI Dieulafoy's lesions, because detailed colonoscopic examination of mucosa may be difficult to achieve due to overlying blood or the performance of colonoscopy on an unprepared colon because of severe, acute bleeding (Table 2)[10,35,37]. No angiographic pattern is specific for Dieulafoy's lesions, but features such as visualization of a non-tapering (caliber-persisting), ectatic (tortuous), artery at the bleeding site may suggest this entity[7,63,64]. Often, however, only extravasation is visualized at an eroded site of an otherwise normal appearing artery[65]. Angiography may also suggest an underlying Dieulafoy's lesion when extravasation of contrast is visualized from a point source in the proximal stomach. Angiodysplasia, another point source of bleeding, may be distinguished from Dieulafoy's lesion by its characteristic angiographic features, such as an early filling vein, that are inconsistent with Dieulafoy's lesion[8,66]. In one study, angiography was diagnostic in 11 of 14 patients with Dieulafoy's lesions who underwent nondiagnostic endoscopic examinations[37].

Technetium 99-m-labeled erythrocytes scanning is reportedly useful to locate a bleeding Dieulafoy's lesion after nondiagnostic endoscopies[67,68]. This test may permit diagnosis at lower rates of active GI bleeding, because the threshold to detect blood extravasation is less than half that required for angiography[69].

TREATMENT

As for any severe, acute, GI bleeding, pre-endoscopic therapy for a recently bleeding Dieulafoy's lesion focuses on volume resuscitation to prevent systemic hypotension and consequent end-organ damage to heart, brain, or kidneys from hypoperfusion. Multiple, reliable, large-bore, intravenous lines are inserted. Volume resuscitation is initially performed with crystalline solution, with normal saline or Ringer's lactate, but transfusion of packed erythrocytes is often required, after typing and crossing of blood, as guided by the tempo of the GI bleeding and serial hematocrit determinations. Patients with Dieulafoy's lesions often require transfusion of three or more units of packed erythrocytes due to the severity of the bleeding[9]. Electrolyte abnormalities are assessed and appropriately corrected. Treatment to reverse a severe coagulopathy is important before endoscopy, particularly when endoscopic therapy is contemplated.

Hemostatic therapy is important because of the bleeding severity from Dieulafoy's lesion, the propensity for bleeding to recur without therapy, especially within 72 h after an initial bleed, and the high mortality if it is left untreated. Minimally invasive therapies are derived from their respective diagnostic tests, including

Table 3 Therapy for Dieulafoy's lesion

Pre-endoscopic therapy
Secure IV access using multiple, large bore catheters
Volume resuscitation initially using crystalloid followed by transfusions of packed erythrocytes as dictated by serial hematocrit determinations and tempo of bleeding
Endoscopic therapies
Mechanical therapies
Hemoclips
Band ligation
Injection therapies
Epinephrine injection
Absolute alcohol
Ablative therapies
Heater probe
Electrocoagulation: Bicap, gold probe, *etc.*,
APC (argon plasma coagulation)
Combination therapies
Usually epinephrine injection therapy followed by:
Heater probe
Hemoclip
Or APC
Interventional angiography
Embolization
Pledgelets
Metal coils
Balloon occlusion
Surgery
Mostly salvage therapy after failure of other interventional therapies

APC: Argon plasma coagulation.

therapeutic endoscopy immediately after diagnostic endoscopy, and therapeutic angiography immediately after diagnostic angiography (Table 3). While no consensus recommendations on treatment exist, there has been increased use of endoscopic therapy and therapeutic angiography, with decreasing use of surgery during the last few decades[10,70]. As Dieulafoy's lesions are relatively uncommon, most data on treatment modalities consist of small, retrospective, case-series, or individual case-reports[7,8,10].

Therapeutic endoscopy is the primary treatment modality for acute GI bleeding. It can achieve initial hemostasis in about 90% of accessible lesions with a < 10% rate of rebleeding during the next 7 d[36,71-73]. Therapeutic endoscopy for recently bleeding peptic ulcers depends upon the Forrest criteria, with endoscopic therapy recommended only for lesions that are actively bleeding or oozing, that have a visible vessel, or perhaps have an adherent clot[74]. Endoscopic therapy is not recommended for peptic ulcers that have a flat, pigmented spot or have a clean, homogeneous, flat base. Contrariwise, therapeutic endoscopy is recommended for virtually all Dieulafoy's lesions, whether actively bleeding, oozing, or without any stigmata of recent bleeding. The difference in therapeutic strategies reflects the natural history of Dieulafoy's lesion as compared to peptic ulcers. Peptic ulcers with a flat pigmented spot have a low risk of rebleeding of about 8%-10% without endoscopic therapy and peptic ulcers with a clean, homogeneous, flat, base have only about a 3% risk of rebleeding without endoscopy therapy[74]. This low risk of rebleeding with these two types of peptic ulcers does not justify incurring the approximately 1% or more risk of major, life-threatening, complications from endoscopic therapy including, gastrointestinal perforation, massive bleeding, pulmonary aspiration, and cardiovascular complications[74]. In contrast, the risk of continued bleeding or rebleeding within 72 h from an untreated Dieulafoy's lesion is very high. This high risk of rebleeding justifies undertaking the risks of therapeutic endoscopy to prevent further bleeding from Dieulafoy's lesion.

Although initially developed for EGD for upper GI Dieulafoy's lesions, endoscopic therapy is now performed using the same techniques and devices during colonoscopy for colonic Dieulafoy's lesions[22-25], and during single or double balloon enteroscopy for jejunoileal lesions[17]. The current modalities of endoscopic therapies include injection, ablation, and mechanical therapy. Injection therapy most commonly involves local injection of epinephrine, sclerosing agents (sclerotherapy), or cyanoacrylate. Epinephrine therapy promotes hemostasis *via* vasospasm and tamponade/mechanical pressure from interstitial injection that leads to stasis of blood and thrombus formation. Relative contraindications to epinephrine therapy may include severe tachycardia, cardiac arrhythmias such as atrial flutter, unstable vital signs from severe, uncorrected hypovolemia, and recent myocardial infarction or unstable angina. Sclerotherapy promotes vascular inflammation and thrombosis from local irritation, whereas cyanoacrylate promotes gluing to plug a bleeding artery. Ablation modalities include thermocoagulation, electrocoagulation, and argon plasma coagulation (APC). Photocoagulation using the yittrium aluminum garnet laser to ablate tissue has been discontinued due to an unacceptably high risk of gastrointestinal perforation. Ablation modalities can stem bleeding by destroying and devitalizing tissue. Thermocoagulation and electrocoagulation involve point contact with the lesion with apposition of the probe against the bleeding vessel. Contrariwise, APC involves hovering the probe over the lesion without lesion contact[74]. Mechanical therapy, including band ligation or endoscopic clips, can arrest bleeding by mechanically closing off the bleeding vessel. Mechanical therapy likely requires greater endoscopic skill and experience than injection or ablative therapies because correct placement of the band or clip directly around the lesion is critical for successfully strangulating the vessel within Dieulafoy's lesion.

These therapies are generally effective for most Dieulafoy's lesions, when used individually or in combination[17,35,38,71-75]. Successful cases of hemostasis of bleeding Dieulafoy lesions using various modalities of endoscopic therapy are illustrated in Figures 2-4. Available data suggest that mechanical hemostasis may be more effective than other endoscopic modalities in

Table 4 Efficacy of endoscopic mechanical monotherapies for bleeding Dieulafoy's lesions

Endoscopic procedure (No. of patients)	Lesion location	Type of study	Follow-up	Outcome	Ref.
Hemoclips					
EGD (34)	Stomach/duodenum	Prospective	54 mo	initial hemostasis 32/34 pts (94%), 3 pts (9%) rebled	[75]
EGD (18)	Stomach	Retrospective	36 mo	1 (5%) rebled	[77]
EGD (16)	Stomach/duodenum	Prospective, randomized	1 wk	1 (6%) rebled	[78]
Mostly EGD (14)	Mostly stomach/duodenum	Retrospective	Hospitalization	No rebleeding	[36]
EGD (8)	Stomach	Retrospective	19 mo	1 (12%) rebled	[73]
Colonoscopy (1)	Rectum				
EGD (6)	Stomach/duodenum	Retrospective	47 mo	1 (17%) rebled, unclear if single/combination therapy	[79]
Colonoscopy (3)	Rectum	Retrospective	5 mo	No rebleeding	[80]
Double balloon enteroscopy (3)	Jejunum	Retrospective, multicenter	14.5 mo	1 (33%) rebled 69 d after hemoclip	[17]
Single balloon enteroscopy (2)	Ileum	Retrospective	2 mo	No rebleeding	[18]
Colonoscopy (1)	Colon	Case report	6 mo	No rebleeding	[33]
Band ligation					
EGD (24)	Stomach 23 Jejunum 1	Retrospective	18 mo	1 (4%) hemostasis failure, 1 (4%) rebled (jejunum)	[81]
EGD (13)	Stomach Esophagus	Prospective	24 wk	No rebleeding	[82]
EGD (13)	Stomach/duodenum	Retrospective	30 d	No rebleeding	[83]
EGD (10)	Stomach	Prospective	30 d	No rebleeding	[76]
EGD (7)	Stomach	Retrospective	8 mo	No rebleeding	[84]
EGD (3)	Upper GI	Retrospective	19 mo	No rebleeding	[73]
"Mostly" EGD (2)	Stomach	Retrospective	Hospitalization	No rebleeding	[75]
EGD (1)	Stomach	Retrospective	2 d	No rebleeding	[35]
Colonoscopy (4)	Rectum	Retrospective	2-5 d	2 (50%) rebled	[85]
Colonoscopy (3)	Rectum	Retrospective	5 mo	No rebleeding	[80]

Pts: Patients; EGD: Esophagogastroduodenoscopy; GI: Gastrointestinal.

patients with GI bleeding from Dieulafoy's lesion[73,76]. A review of the published literature on application of endoscopic hemoclips in 106 patients and on application of band ligation in 80 patients as monotherapies for bleeding Dieulafoy lesions reveals that both techniques are almost uniformly effective to achieve initial hemostasis and both techniques have low re-bleeding rates, generally $\leqslant$ 10% (Table 4)[17,18,33,36,73,75-85]. They are particularly effective in the hands of expert endoscopists with extensive experience with these techniques. However, endoscopic band ligation may be less desirable than clips because it can cause perforation from banding too deep tissue. This is a particular concern in GI segments with thin walls such as gastric fundus, small bowel, or right colon. Also bleeding may occur from an ulcer after the band falls off[86,87].

A literature review of endoscopic injection encompassing 68 cases of epinephrine injection and 13 cases of sclerotherapy (12 with injection of absolute ethanol and 1 with injection of ethanolamine) appears to show a somewhat lower rate of achieving hemostasis for injection therapy than mechanical therapy (Table 5)[35,36,40,72,73,78,88,89]. However, this therapy may be particularly useful for initially treating massive bleeding. This therapy is technically easier than mechanical therapy and can be performed rather quickly. Also, injection therapy, especially with epinephrine, may slow down massive bleeding so that the lesion can be more readily visualized to apply mechanical therapy.

A literature review of endoscopic ablation therapies for Dieulafoy's lesion encompassing 40 cases, including 18 cases with thermocoagulation, 7 cases of APC, and 15 cases of electrocoagulation shows a high rate of initial hemostasis (Table 6)[17,35,36,40,72,77,82]. However, the data on efficacy for this therapy is less reliable than that for the mechanical or injection therapies because the individual studies on ablative therapies are all retrospective and relatively small and the total number of studied patients is only 40.

Combined endoscopic mechanical hemostasis with injection or ablation therapeutic endoscopy are highly effective therapeutic modalities (Table 7)[17,35,36,40,59,71,72,79,88-90]. Although combined endoscopic treatment modalities are recommended as more effective in the setting of non-variceal acute upper GI bleeding, there is contradictory evidence on such practice when it comes to Dieulafoy's lesions; some studies found no added benefit from endoscopic dual therapy *vs* monotherapy[10,36]. The overall risk of short-term (< 72 h) recurrent bleeding after endoscopically-achieved initial hemostasis is about 10%[10,37,61]. Dieulafoy's lesions treated with single-modality endoscopic therapy may be more likely to rebleed compared to lesions treated with dual endoscopic therapy[51,72].

Other potential risk factors for rebleeding after endoscopic therapy include administration of NSAIDs, administration of anticoagulants, and Dieulafoy's lesions with actively spurting blood at the time of initial

Table 5 Efficacy of endoscopic injection monotherapy for bleeding Dieulafoy's lesions

Endoscopic procedure (No. of patients)	Lesion location	Type of study	Follow-up	Outcome	Ref.
Epinephrine injection					
EGD (16)	Stomach/duodenum	Prospective	1 wk	2 (12%) hemostasis failure, 5 (31%) rebled	[78]
EGD (11)	Stomach	Retrospective	22 mo	3 (27%) hemostasis failure, 4 (36%) rebled	[73]
Colonoscopy (1)	Rectum				
EGD (11)	Stomach/duodenum	Retrospective	18 mo	3 (27%) hemostasis failure, 2 (18%) rebled	[88]
"Mostly" EGD (8)	Mostly stomach/duodenum	Retrospective	Hospitalization	No rebleeding	[36]
EGD (8)	Stomach	Prospective	30 d	6 (75%) rebled	[76]
EGD (6)	Stomach	Retrospective	60 d	2 (33%) hemostasis failure	[40]
EGD (3)	Stomach/duodenum	Retrospective	14 mo	No rebleeding	[35]
Colonoscopy (1)	cecum (1)				
EGD (3)	Stomach	Retrospective	32 mo	2 (66%) rebled	[72]
Absolute ethanol injection					
EGD (12)	Stomach/duodenum	Retrospective	69 mo	1 (8%) hemostasis failure, no rebleeding	[89]
Ethanolamine injection					
EGD (1)	Stomach	Retrospective	8 mo	Rebled	[72]

EGD: Esophagogastroduodenoscopy.

Table 6 Effectiveness of endoscopic ablation monotherapies for bleeding Dieulafoy's lesions

Endoscopic procedure (No. of patients)	Lesion location	Type of study	Follow-up	Outcome	Ref.
Heater probe coagulation					
EGD (6)	Stomach/duodenum	Retrospective	14 mo (2/3 of pts)	No rebleeding	[35]
EGD (6)	Stomach	Retrospective	36 mo	2 (33%) rebled	[77]
Mostly EGD (5)	Mostly stomach/duodenum	Retrospective	Hospitalization	No rebleeding	[36]
EGD (1)	Stomach	Retrospective	40 mo	No rebleeding	[72]
Argon plasma coagulation					
Double balloon enteroscopy (3)	Jejunum-2, Ileum-1	Retrospective /multicenter	14 mo	1 (33%) rebled	[17]
EGD (3)	Stomach	Retrospective	2 mo	No rebleeding	[40]
EGD (1)	Likely upper GI	Retrospective	Hospitalization	No rebleeding	[36]
Multipolar electrocoagulation					
EGD (14)	Stomach	Retrospective	24 mo	1 (7%) hemostasis failure, 1 rebled	[82]
EGD (1)	Likely upper GI	Retrospective	Hospitalization	Rebled	[36]

EGD: Esophagogastroduodenoscopy.

endoscopy[42,51]. The data in Tables 4-7[17,18,33,35,36,40,59,71-73,75-85,88-90] on initial hemostasis and re-bleeding rates with single-modality and combination-modalities endoscopic therapy for both upper and lower Dieulafoy's lesions should be interpreted cautiously; most reported studies are retrospective, have relatively small sample-size, and generally lack controls to exclude potential confounding variables.

Recurrent bleeding after attempted endoscopic hemostasis can be treated by repeat endoscopic hemostasis, angiographic embolization, or surgical wedge resection. Subtotal gastrectomy is unnecessary if the lesion has been properly localized preoperatively or intraoperatively. Successful hemostasis with angiographic embolization has been reported in scattered case reports[65,91], but requires specialized angiographic expertise. Embolization of a too large and too central vessel feeding the Dieulafoy lesion can occasionally cause GI ischemia leading to GI perforation[92].

The mortality of GI bleeding from Dieulafoy's lesions prior to the era of flexible diagnostic endoscopy was up to 80%, due to the frequent need for emergency surgery for severe, refractory GI bleeding, but declined to about 30% with the advent of flexible diagnostic endoscopy in the 1970's, and has declined to about 9%-13% currently with the advent of therapeutic endoscopy[93].

FUTURE TRENDS

Although the anatomic basis of Dieulafoy's lesion and the pathophysiology of bleeding from this lesion is fairly well understood, the etiology of lesion formation is poorly understood. Why does the lesion most commonly occur within 6 cm below the gastroesophageal junction along the lesser curve? Is this a developmental defect during organogenesis? Do genetic mutations play any role? Is there a familial predisposition to this lesion? Hopefully, the molecular mechanisms and developmental origin of this lesion will be elucidated. Such an understanding might provide a mechanism to

Table 7 Effectiveness of various combination endoscopic therapies for bleeding Dieulafoy's lesions

Endoscopic therapies (No. of patients)	Endoscopy: lesion location	Type of study	Mean length of follow-up	Study outcome	Ref.
Epinephrine and polidocanol (27)	EGD: stomach/duodenum	Retrospective	28 mo	5 (18%) rebled	[71]
Epi and heater probe (28)	EGD: stomach/duodenum	Retrospective	14 mo (2/3 of patients)	2 (7%) rebled	[35]
Epi and heater probe (10)	EGD: stomach/duodenum	Retrospective	18 mo	No rebleeding	[88]
Epi and heater probe (9)	"Mostly" EGD; Mostly stomach/duodenum	Retrospective	Hospitalization	1 (11%) rebled	[36]
Epi and heater probe (8)	EGD: stomach/duodenum	Retrospective	32 mo	No rebleeding	[72]
Epi and heater probe (6)	EGD	Retrospective	2 mo	No rebleeding	[40]
Epi and heater probe (2)	Colonoscopy	Retrospective	1 and 7 mo	No rebleeding	[59]
Epi and hemoclip and ethanol injection (21)	EGD: stomach/duodenum	Retrospective	47 mo	1 (4%) rebled	[79]
Epi and hemoclip (19)	EGD: Stomach	Retrospective	47 mo	1 (5%) rebled	[79]
Epi and hemoclip (16)	"Mostly" EGD: mostly stomach/duodenum	Retrospective	During hospitalization	1 (6%) rebled	[36]
Epi and hemoclip (3)	EGD: Stomach	Retrospective	2 mo	No rebleeding	[40]
Epi and multipolar electrocoagulation (5)	"Mostly" EGD: Mostly stomach/duodenum	Retrospective	During hospitalization	1 (20%) rebled	[36]
Epi and banding (1)	EGD: stomach	Retrospective	During hospitalization	No rebleeding	[36]
Epi and ethanol (52)	EGD: Stomach/ duodenum	Retrospective	69 mo	Approximately 9% hemostasis failure, 10 (20%) rebled	[89]
Epi and ethanol (11)	EGD: stomach duodenum	Retrospective	47 mo	1 rebled	[79]
Epi and ethanolamine (5)	EGD: stomach/duodenum	Retrospective	32 mo	2 (40%) rebled	[72]
Injection therapy and clip (2)	Double balloon enteroscopy: jejunum	Retrospective, multicenter	14 mo	No rebleeding	[17]
Injection therapy and APC (1)	Double balloon enteroscopy: jejunum	Retrospective, multicenter	14 mo	Rebled after 9 d	[17]
Injection and heater probe and clips (1)	Colonoscopy: colon	Case report	NA	No rebleeding	[90]

Epi: Epinephrine; APC: Argon plasma coagulation; NA: Not available.

prevent lesion formation.

Currently the ideal endoscopic therapy for recently bleeding Dieulafoy's lesion is uncertain. Large, prospective, head-to-head clinical trials are needed of different endoscopic modalities are needed but these are difficult to perform and complete due to the relative rarity of this lesion. It is reasonable, therefore for gastroenterologists to adopt particular techniques based on personal and local experience and technologies available within their endoscopy suite. Use of a spray to stem bleeding is an exciting technology because of ease of use but is experimental and unproven[94].

Therapeutic angiography is likely to become a more viable alternative to endoscopic therapy, with greater experience with this technology for this indication, but it is likely to remain a second option after failed endoscopic therapy due to the easy availability of therapeutic endoscopy at the same session when performing the initial diagnostic endoscopy and the very high success rate of therapeutic endoscopy. It is expected that endoscopic therapy will evolve with even better techniques for lesion ablation or mechanical occlusion of vascular lesions, such as the development of clinically applicable endoscopic micro-suturing devices[95].

Although endoscopic ultrasound may potentially prove very useful in identifying whether a vessel in a Dieulafoy's lesion has active flow through it, widespread adoption of this technique awaits lowering the cost of this technology, greater availability of endosonographers, and demonstration of its clinical benefits through clinical trials. CT angiography may assume a greater diagnostic role after nondiagnostic endoscopy in the face of severe, active bleeding, but its role is likely to remain limited due to a lack of therapeutic capabilities.

Currently, single-balloon and double-balloon enteroscopy are generally limited to tertiary hospitals, but should become more available in the future with lowering of costs. This may offer a new technology for diagnosing and treating small bowel Dieulafoy's lesions that are otherwise difficult to reach and treat. Capsule endoscopy may become more helpful in diagnosing jejunoileal lesions with development of capsules with active propulsion, better camera resolution, and longer-lasting and more powerful batteries, but its role will likely remain limited for bleeding from jejunoileal Dieulafoy's lesions because of a lack of therapeutic capabilities[96].

REFERENCES

1 **Longstreth GF**. Epidemiology of hospitalization for acute upper gastrointestinal hemorrhage: a population-based study. *Am J Gastroenterol* 1995; **90**: 206-210 [PMID: 7847286]

2 **Raju GS**, Gerson L, Das A, Lewis B. American Gastroenterological Association (AGA) Institute medical position statement on obscure gastrointestinal bleeding. *Gastroenterology* 2007; **133**: 1694-1696 [PMID: 17983811]

3 **Han MS**, Park BK, Lee SH, Yang HC, Hong YK, Choi YJ. A

case of Dieulafoy lesion of the jejunum presented with massive hemorrhage. *Korean J Gastroenterol* 2013; **61**: 279-281 [PMID: 23756670]
4 **Barnert J**, Messmann H. Diagnosis and management of lower gastrointestinal bleeding. *Nat Rev Gastroenterol Hepatol* 2009; **6**: 637-646 [PMID: 19881516 DOI: 10.1038/nrgastro.2009.167]
5 **Gallard MT**. Aneurysme miliaires de l'estomach, donnant lieu a des hematemese mortelles. *Bull Soc Med Hop Paris* 1884; **1**: 84-91
6 **Dieulafoy G**. Exulceratio simplex. L'intervention chirurgicale dans les hematemeses foudroyantes consecutives a l'exulceration simple de l'estomac. *Bull Acad Med* 1898; **49**: 49-84
7 **Chaer RA**, Helton WS. Dieulafoy's disease. *J Am Coll Surg* 2003; **196**: 290-296 [PMID: 12595057]
8 **Baxter M**, Aly EH. Dieulafoy's lesion: current trends in diagnosis and management. *Ann R Coll Surg Engl* 2010; **92**: 548-554 [PMID: 20883603 DOI: 10.1308/003588410X12699663905311.]
9 Cappell MS. Gastrointestinal vascular malformations or neoplasms: Arterial, venous, arteriovenous and capillary. In: Yamada T, Alpers D, Kalloo AN, et al., eds. Textbook of Gastroenterology. 5th ed. Chichester (West Sussex), United Kingdom: Wiley-Blackwell, 2009: 2785-2810
10 **Lee YT**, Walmsley RS, Leong RW, Sung JJ. Dieulafoy's lesion. *Gastrointest Endosc* 2003; **58**: 236-243 [PMID: 12872092]
11 **Juler GL**, Labitzke HG, Lamb R, Allen R. The pathogenesis of Dieulafoy's gastric erosion. *Am J Gastroenterol* 1984; **79**: 195-200 [PMID: 6199971]
12 **Marwick T**, Kerlin P. Angiodysplasia of the upper gastrointestinal tract. Clinical spectrum in 41 cases. *J Clin Gastroenterol* 1986; **8**: 404-407 [PMID: 3489750]
13 **Fockens P**, Tytgat GN. Dieulafoy's disease. *Gastrointest Endosc Clin N Am* 1996; **6**: 739-752 [PMID: 8899405]
14 **Veldhuyzen van Zanten SJ**, Bartelsman JF, Schipper ME, Tytgat GN. Recurrent massive haematemesis from Dieulafoy vascular malformations--a review of 101 cases. *Gut* 1986; **27**: 213-222 [PMID: 3485070]
15 **Barlow TE**, Bentley FH, Walder DN. Arteries, veins, and arteriovenous anastomoses in the human stomach. *Surg Gynecol Obstet* 1951; **93**: 657-671 [PMID: 14893072]
16 **Scheider DM**, Barthel JS, King PD, Beale GD. Dieulafoy-like lesion of the distal esophagus. *Am J Gastroenterol* 1994; **89**: 2080-2081 [PMID: 7942743]
17 **Dulic-Lakovic E**, Dulic M, Hubner D, Fuchssteiner H, Pachofszky T, Stadler B, Maieron A, Schwaighofer H, Püspök A, Haas T, Gahbauer G, Datz C, Ordubadi P, Holzäpfel A, Gschwantler M. Bleeding Dieulafoy lesions of the small bowel: a systematic study on the epidemiology and efficacy of enteroscopic treatment. *Gastrointest Endosc* 2011; **74**: 573-580 [PMID: 21802676 DOI: 10.1016/j.gie.2011.05.027]
18 **Choi YC**, Park SH, Bang BW, Kwon KS, Kim HG, Shin YW. Two cases of ileal dieulafoy lesion with massive hematochezia treated by single balloon enteroscopy. *Clin Endosc* 2012; **45**: 440-443 [PMID: 23251897 DOI: 10.5946/ce.2012.45.4.440]
19 **Fox A**, Ravi K, Leeder PC, Britton BJ, Warren BF. Adult small bowel Dieulafoy lesion. *Postgrad Med J* 2001; **77**: 783-784 [PMID: 11723319]
20 **Morowitz MJ**, Markowitz R, Kamath BM, von Allmen D. Dieulafoy's lesion and segmental dilatation of the small bowel: an uncommon cause of gastrointestinal bleeding. *J Pediatr Surg* 2004; **39**: 1726-1728 [PMID: 15547843]
21 **Wegdam JA**, Hofker HS, Dijkstra G, Stolk MF, Jacobs MA, Suurmeijer AJ. [Occult gastrointestinal bleeding due to a Dieulafoy lesion in the terminal ileum]. *Ned Tijdschr Geneeskd* 2006; **150**: 1776-1779 [PMID: 16948240]
22 **Sone Y**, Nakano S, Takeda I, Kumada T, Kiriyama S, Hisanaga Y. Massive hemorrhage from a Dieulafoy lesion in the cecum: successful endoscopic management. *Gastrointest Endosc* 2000; **51**: 510-512 [PMID: 10744841]
23 **Johnson A**, Oger M, Capovilla M. Dieulafoy lesion of the appendix. *Dig Liver Dis* 2014; **46**: e11 [PMID: 24791666 DOI: 10.1016/j.dld.2014.04.001]
24 **Jain R**, Chetty R. Dieulafoy disease of the colon. *Arch Pathol Lab Med* 2009; **133**: 1865-1867 [PMID: 19886725 DOI: 10.1043/1543-2165-133.11.1865]
25 **Vogel C**, Thomschke D, Stolte M. Dieulafoy's lesion of the right hemicolon. *Z Gastroenterol* 2006; **44**: 661-665 [PMID: 16902897]
26 **Baccaro L**, Ogu S, Sakharpe A, Ibrahim G, Boonswang P. Rectal dieulafoy lesions: a rare etiology of chronic lower gastrointestinal bleeding. *Am Surg* 2012; **78**: E246-E248 [PMID: 22691315]
27 **Firat O**, Karaköse Y, Calişkan C, Makay O, Ozütemiz O, Korkut MA. Dieulafoy's lesion of the anal canal: report of a case. *Turk J Gastroenterol* 2007; **18**: 265-267 [PMID: 18080926]
28 **Parrot A**, Antoine M, Khalil A, Théodore J, Mangiapan G, Bazelly B, Fartoukh M. Approach to diagnosis and pathological examination in bronchial Dieulafoy disease: a case series. *Respir Res* 2008; **9**: 58 [PMID: 18681960 DOI: 10.1186/1465-9921-9-58]
29 **Mikó TL**, Thomázy VA. The caliber persistent artery of the stomach: a unifying approach to gastric aneurysm, Dieulafoy's lesion, and submucosal arterial malformation. *Hum Pathol* 1988; **19**: 914-921 [PMID: 3042598]
30 **Linhares MM**, Filho BH, Schraibman V, Goitia-Durán MB, Grande JC, Sato NY, Lourenço LG, Lopes-Filho GD. Dieulafoy lesion: endoscopic and surgical management. *Surg Laparosc Endosc Percutan Tech* 2006; **16**: 1-3 [PMID: 16552369]
31 **Stark ME**, Gostud CJ, Balm RK. Clinical features and endoscopic management of Dieulafoy's disease. *Gastrointest Endosc* 1992; **38**: 545-550
32 **Barbier P**, Luder P, Triller J, Ruchti C, Hassler H, Stafford A. Colonic hemorrhage from a solitary minute ulcer. Report of three cases. *Gastroenterology* 1985; **88**: 1065-1068 [PMID: 3871715]
33 **Fukita Y**. Treatment of a colonic Dieulafoy lesion with endoscopic hemoclipping. *BMJ Case Rep* 2013; **2013**: pii: bcr2013009734 [PMID: 23608878 DOI: 10.1136/bcr-2013-009734]
34 **Sai Prasad TR**, Lim KH, Lim KH, Yap TL. Bleeding jejunal Dieulafoy pseudopolyp: capsule endoscopic detection and laparoscopic-assisted resection. *J Laparoendosc Adv Surg Tech A* 2007; **17**: 509-512 [PMID: 17705738]
35 **Schmulewitz N**, Baillie J. Dieulafoy lesions: a review of 6 years of experience at a tertiary referral center. *Am J Gastroenterol* 2001; **96**: 1688-1694 [PMID: 11419815]
36 **Lara LF**, Sreenarasimhaiah J, Tang SJ, Afonso BB, Rockey DC. Dieulafoy lesions of the GI tract: localization and therapeutic outcomes. *Dig Dis Sci* 2010; **55**: 3436-3441 [PMID: 20848205 DOI: 10.1007/s10620-010-1385-0]
37 **Reilly HF 3rd**, al-Kawas FH. Dieulafoy's lesion. Diagnosis and management. *Dig Dis Sci* 1991; **36**: 1702-1707 [PMID: 1748038]
38 **Meister TE**, Varilek GW, Marsano LS, Gates LK, Al-Tawil Y, de Villiers WJ. Endoscopic management of rectal Dieulafoy-like lesions: a case series and review of literature. *Gastrointest Endosc* 1998; **48**: 302-305 [PMID: 9744611]
39 **Luis LF**, Sreenarasimhaiah J, Jiang Tang S. Localization, efficacy of therapy, and outcomes of Dieulafoy lesions of the GI tract – The UT Southwestern GI Bleed Team experience. *Gastrointest Endosc* 2008; **67**: AB 87
40 **López-Arce G**, Zepeda-Gómez S, Chávez-Tapia NC, Garcia-Osogobio S, Franco-Guzmán AM, Ramirez-Luna MA, Téllez-Ávila FI. Upper gastrointestinal dieulafoy's lesions and endoscopie treatment: first report from a Mexican centre. *Therap Adv Gastroenterol* 2008; **1**: 97-101 [PMID: 21180518 DOI: 10.1177/1756283X08096285]
41 **Iacopini F**, Petruzziello L, Marchese M, Larghi A, Spada C, Familiari P, Tringali A, Riccioni ME, Gabbrielli A, Costamagna G. Hemostasis of Dieulafoy's lesions by argon plasma coagulation (with video). *Gastrointest Endosc* 2007; **66**: 20-26 [PMID: 17591469]
42 **Lim W**, Kim TO, Park SB, Rhee HR, Park JH, Bae JH. Endoscopic treatment of Dieulafoy lesions and risk factors for bleeding. *Korean J Intern Med* 2009; **24**: 318-322 [PMID: 19949729 DOI: 10.3904/kjim.2009.24.4318]
43 **al-Mishlab T**, Amin AM, Ellul JP. Dieulafoy's lesion: an obscure cause of GI bleeding. *J R Coll Surg Edinb* 1999; **44**: 222-225 [PMID:

10453143]
44 **Monsanto P**, Almeida N, Lérias C, Figueiredo P, Gouveia H, Sofia C. Is there still a role for intraoperative enteroscopy in patients with obscure gastrointestinal bleeding? *Rev Esp Enferm Dig* 2012; **104**: 190-196 [PMID: 22537367]
45 **Aomatsu N**, Nakamura M, Takeuchi K, Nishii T, Kosaka K, Uchima Y, Nakajima H, Hanno H, Takeda O, Kawamura M, Takayanagi S, Hirooka T, Dozaiku T, Hirooka T, Aomatsu K. [A case of emergency resection of a giant gastrointestinal stromal tumor of the stomach associated with hemorrhagic shock]. *Gan To Kagaku Ryoho* 2013; **40**: 2185-2187 [PMID: 24394054]
46 **Seya T**, Tanaka N, Yokoi K, Shinji S, Oaki Y, Tajiri T. Life-threatening bleeding from gastrointestinal stromal tumor of the stomach. *J Nippon Med Sch* 2008; **75**: 306-311 [PMID: 19023173]
47 **Marangoni G**, Cresswell AB, Faraj W, Shaikh H, Bowles MJ. An uncommon cause of life-threatening gastrointestinal bleeding: 2 synchronous Dieulafoy lesions. *J Pediatr Surg* 2009; **44**: 441-443 [PMID: 19231553]
48 **Abdalla SA**, Letarte M. Hereditary haemorrhagic telangiectasia: current views on genetics and mechanisms of disease. *J Med Genet* 2006; **43**: 97-110 [PMID: 15879500]
49 **Thevenot T**, Vanlemmens C, Di Martino V, Becker MC, Denue PO, Kantelip B, Bresson-Hadni S, Heyd B, Mantion G, Miguet JP. Liver transplantation for cardiac failure in patients with hereditary hemorrhagic telangiectasia. *Liver Transpl* 2005; **11**: 834-838 [PMID: 15973723]
50 **Mavrakis A**, Demetris A, Ochoa ER, Rabinovitz M. Hereditary hemorrhagic telangiectasia of the liver complicated by ischemic bile duct necrosis and sepsis: case report and review of the literature. *Dig Dis Sci* 2010; **55**: 2113-2117 [PMID: 19757046 DOI: 10.1007/s10620-009-0968-0]
51 **Jamanca-Poma Y**, Velasco-Guardado A, Piñero-Pérez C, Calderón-Begazo R, Umaña-Mejía J, Geijo-Martínez F, Rodríguez-Pérez A. Prognostic factors for recurrence of gastrointestinal bleeding due to Dieulafoy's lesion. *World J Gastroenterol* 2012; **18**: 5734-5738 [PMID: 23155314]
52 **Schwab G**, Pointner R, Feichtinger J, Schmidt KW. Exulceratio simplex Dieulafoy of the colon--a case report. *Endoscopy* 1988; **20**: 88-89 [PMID: 3260175]
53 **Chung YF**, Wong WK, Soo KC. Diagnostic failures in endoscopy for acute upper gastrointestinal haemorrhage. *Br J Surg* 2000; **87**: 614-617 [PMID: 10792319]
54 **Chak A**, Cooper GS, Lloyd LE, Kolz CS, Barnhart BA, Wong RC. Effectiveness of endoscopy in patients admitted to the intensive care unit with upper GI hemorrhage. *Gastrointest Endosc* 2001; **53**: 6-13 [PMID: 11154481]
55 **Jaspersen D**. Dieulafoy's disease controlled by Doppler ultrasound endoscopic treatment. *Gut* 1993; **34**: 857-858 [PMID: 8314523]
56 **Wright CA**, Petersen BT, Bridges CM, Alexander JA. Heparin provocation for identification and treatment of a gastric Dieulafoy's lesion. *Gastrointest Endosc* 2004; **59**: 728-730 [PMID: 15114325]
57 **Dharia T**, Tang SJ, Lara L. Bleeding sigmoid colonic Dieulafoy lesion (with video). *Gastrointest Endosc* 2009; **70**: 1028; discussion 1028-1029 [PMID: 19703690]
58 **Souza JL**. Treatment of Dieulafoy's lesion of the right colon with epinephrine injection and argon plasma coagulation. *Endoscopy* 2009; **41**(suppl 2): E192
59 **Gimeno-García AZ**, Parra-Blanco A, Nicolás-Pérez D, Ortega Sánchez JA, Medina C, Quintero E. Management of colonic Dieulafoy lesions with endoscopic mechanical techniques: report of two cases. *Dis Colon Rectum* 2004; **47**: 1539-1543 [PMID: 15486754]
60 **Katsinelos P**, Pilpilidis I, Paroutoglou G, Galanis I, Tsolkas P, Fotiadis G, Kapelidis P, Georgiadou E, Baltagiannis S, Dimiropoulos S, Kamperis E, Koutras C. Dieulafoy-like lesion of the colon presenting with massive lower gastrointestinal bleeding. *Surg Endosc* 2004; **18**: 346 [PMID: 15106623]
61 **Dy NM**, Gostout CJ, Balm RK. Bleeding from the endoscopically-identified Dieulafoy lesion of the proximal small intestine and colon. *Am J Gastroenterol* 1995; **90**: 108-111 [PMID: 7801908]
62 De Franchis R, Rondonotti E, Abbiati C. Successful identification of a jejunal Dieulafoy lesion by wireless capsule enteroscopy: a case report. *Dig Liver Dis* 2002; **34**: A118
63 **Eidus LB**, Rasuli P, Manion D, Heringer R. Caliber-persistent artery of the stomach (Dieulafoy's vascular malformation). *Gastroenterology* 1990; **99**: 1507-1510 [PMID: 2210260]
64 **Durham JD**, Kumpe DA, Rothbarth LJ, Van Stiegmann G. Dieulafoy disease: arteriographic findings and treatment. *Radiology* 1990; **174**: 937-941 [PMID: 2305095]
65 **Alomari AI**, Fox V, Kamin D, Afzal A, Arnold R, Chaudry G. Embolization of a bleeding Dieulafoy lesion of the duodenum in a child. Case report and review of the literature. *J Pediatr Surg* 2013; **48**: e39-e41 [PMID: 23331838 DOI: 10.1016/j.jpedsurg.2012.10.055]
66 **Nga ME**, Buhari SA, Iau PT, Raju GC. Jejunal Dieulafoy lesion with massive lower intestinal bleeding. *Int J Colorectal Dis* 2007; **22**: 1417-1418 [PMID: 17086394]
67 **Lee KS**, Moon YJ, Lee SI, Park IS, Sohn SK, Yu JS, Kie JH. A case of bleeding from the Dieulafoy lesion of the jejunum. *Yonsei Med J* 1997; **38**: 240-244 [PMID: 9339133]
68 **Eguchi S**, Maeda J, Taguchi H, Kanematsu T. Massive gastrointestinal bleeding from a Dieulafoy-like lesion of the rectum. *J Clin Gastroenterol* 1997; **24**: 262-263 [PMID: 9252855]
69 **Jensen DM**. Endoscopic diagnosis and treatment of severe haematochezia. *Tech Gastrointest Endosc* 2001; **3**: 178-184
70 **Alshumrani G**, Almuaikeel M. Angiographic findings and endovascular embolization in Dieulafoy disease: a case report and literature review. *Diagn Interv Radiol* 2006; **12**: 151-154 [PMID: 16972222]
71 **Baettig B**, Haecki W, Lammer F, Jost R. Dieulafoy's disease: endoscopic treatment and follow up. *Gut* 1993; **34**: 1418-1421 [PMID: 8244112]
72 **Kasapidis P**, Georgopoulos P, Delis V, Balatsos V, Konstantinidis A, Skandalis N. Endoscopic management and long-term follow-up of Dieulafoy's lesions in the upper GI tract. *Gastrointest Endosc* 2002; **55**: 527-531 [PMID: 11923766]
73 **Chung IK**, Kim EJ, Lee MS, Kim HS, Park SH, Lee MH, Kim SJ, Cho MS. Bleeding Dieulafoy's lesions and the choice of endoscopic method: comparing the hemostatic efficacy of mechanical and injection methods. *Gastrointest Endosc* 2000; **52**: 721-724 [PMID: 11115902]
74 **Cappell MS**. Therapeutic endoscopy for acute upper gastrointestinal bleeding. *Nat Rev Gastroenterol Hepatol* 2010; **7**: 214-229 [PMID: 20212504]
75 **Yamaguchi Y**, Yamato T, Katsumi N, Imao Y, Aoki K, Morita Y, Miura M, Morozumi K, Ishida H, Takahashi S. Short-term and long-term benefits of endoscopic hemoclip application for Dieulafoy's lesion in the upper GI tract. *Gastrointest Endosc* 2003; **57**: 653-656 [PMID: 12709692]
76 **Alis H**, Oner OZ, Kalayci MU, Dolay K, Kapan S, Soylu A, Aygun E. Is endoscopic band ligation superior to injection therapy for Dieulafoy lesion? *Surg Endosc* 2009; **23**: 1465-1469 [PMID: 19125307]
77 **Parra-Blanco A**, Takahashi H, Méndez Jerez PV, Kojima T, Aksoz K, Kirihara K, Palmerín J, Takekuma Y, Fuijta R. Endoscopic management of Dieulafoy lesions of the stomach: a case study of 26 patients. *Endoscopy* 1997; **29**: 834-839 [PMID: 9476766]
78 **Park CH**, Sohn YH, Lee WS, Joo YE, Choi SK, Rew JS, Kim SJ. The usefulness of endoscopic hemoclipping for bleeding Dieulafoy lesions. *Endoscopy* 2003; **35**: 388-392 [PMID: 12701008]
79 **Sone Y**, Kumada T, Toyoda H, Hisanaga Y, Kiriyama S, Tanikawa M. Endoscopic management and follow up of Dieulafoy lesion in the upper gastrointestinal tract. *Endoscopy* 2005; **37**: 449-453 [PMID: 15844024]
80 **Park JG**, Park JC, Kwon YH, Ahn SY, Jeon SW. Endoscopic management of rectal Dieulafoy's lesion: A case series and optimal treatment. *Clin Endosc* 2014; **47**: 362-366 [PMID: 25133127 DOI: 10.5946/ce.2014.47.4.362]
81 **Nikolaidis N**, Zezos P, Giouleme O, Budas K, Marakis G, Paroutoglou G, Eugenidis N. Endoscopic band ligation of Dieulafoy-like lesions in the upper gastrointestinal tract. *Endoscopy* 2001; **33**: 754-760 [PMID: 11558028]
82 **Matsui S**, Kamisako T, Kudo M, Inoue R. Endoscopic band ligation

for control of nonvariceal upper GI hemorrhage: comparison with bipolar electrocoagulation. *Gastrointest Endosc* 2002; **55**: 214-218 [PMID: 11818925]

83 **Mumtaz R**, Shaukat M, Ramirez FC. Outcomes of endoscopic treatment of gastroduodenal Dieulafoy's lesion with rubber band ligation and thermal/injection therapy. *J Clin Gastroenterol* 2003; **36**: 310-314 [PMID: 12642736]

84 **Xavier S**. Band ligation of Dieulafoy lesions. *Indian J Gastroenterol* 2005; **24**: 114-115 [PMID: 16041104]

85 **Kim HK**, Kim JS, Son HS, Park YW, Chae HS, Cho YS. Endoscopic band ligation for the treatment of rectal Dieulafoy lesions: risks and disadvantages. *Endoscopy* 2007; **39**: 924-925 [PMID: 17701855]

86 **Chen YY**, Su WW, Soon MS, Yen HH. Delayed fatal hemorrhage after endoscopic band ligation for gastric Dieulafoy's lesion. *Gastrointest Endosc* 2005; **62**: 630-632 [PMID: 16185987]

87 **Barker KB**, Arnold HL, Fillman EP, Palekar NA, Gering SA, Parker AL. Safety of band ligator use in the small bowel and the colon. *Gastrointest Endosc* 2005; **62**: 224-227 [PMID: 16046983]

88 **Cheng CL**, Liu NJ, Lee CS, Chen PC, Ho YP, Tang JH, Yang C, Sung KF, Lin CH, Chiu CT. Endoscopic management of Dieulafoy lesions in acute nonvariceal upper gastrointestinal bleeding. *Dig Dis Sci* 2004; **49**: 1139-1144 [PMID: 15387335]

89 **Romãozinho JM**, Pontes JM, Lérias C, Ferreira M, Freitas D. Dieulafoy's lesion: management and long-term outcome. *Endoscopy* 2004; **36**: 416-420 [PMID: 15100950]

90 **Tan FL**, Tan YM, Chung YF. Images of interest. Gastrointestinal: colonic Dieulafoy lesion. *J Gastroenterol Hepatol* 2005; **20**: 483 [PMID: 15740496]

91 **Mohd Rizal MY**, Kosai NR, Sutton PA, Rozman Z, Razman J, Harunarashid H, Das S. Arterial embolization of a bleeding gastric Dieulafoy lesion: a case report. *Clin Ter* 2013; **164**: 25-27 [PMID: 23455738]

92 **Loffroy R**, Rao P, Ota S, De Lin M, Kwak BK, Geschwind JF. Embolization of acute nonvariceal upper gastrointestinal hemorrhage resistant to endoscopic treatment: results and predictors of recurrent bleeding. *Cardiovasc Intervent Radiol* 2010; **33**: 1088-1100 [PMID: 20232200]

93 **Joarder AI**, Faruque MS, Nur-E-Elahi M, Jahan I, Siddiqui O, Imdad S, Islam MS, Ahmed HS, Haque MA. Dieulafoy's lesion: an overview. *Mymensingh Med J* 2014; **23**: 186-194 [PMID: 24584397]

94 **Yau AH**, Ou G, Galorport C, Amar J, Bressler B, Donnellan F, Ko HH, Lam E, Enns RA. Safety and efficacy of Hemospray® in upper gastrointestinal bleeding. *Can J Gastroenterol Hepatol* 2014; **28**: 72-76 [PMID: 24501723]

95 **Henderson JB**, Sorser SA, Atia AN, Catalano MF. Repair of esophageal perforations using a novel endoscopic suturing system. *Gastrointest Endosc* 2014; **80**: 535-537 [PMID: 25127954 DOI: 10.1016/j.gie.2014.03.032]

96 **Hall B**, Holleran G, McNamara D. Current applications and potential future role of wireless capsule technology in Crohn's disease. *Scand J Gastroenterol* 2014; **49**: 1275-1284 [PMID: 25260016 DOI: 10.3109/00365521.2014.962606]

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REVIEW

Biomarkers in bile-complementing advanced endoscopic imaging in the diagnosis of indeterminate biliary strictures

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Abstract

Biliary strictures present a diagnostic challenge and a conundrum, particularly when an initial work up including abdominal imaging and endoscopic retrograde cholangiopancreatography based sampling are non-diagnostic. Advances in endoscopic imaging have helped us diagnose these strictures better. However, even with modern technology, some strictures remain a diagnostic challenge. The proximity of bile fluid to the bile duct epithelia makes it an attractive option to investigate for bio-markers, which might be representative of the functions/abnormal changes taking place in the biliary system. A number of biomarkers in bile have been discovered recently in approaching biliary strictures with their potential future diagnostic utility, further supported by the immunohistochemical analysis of the resected tissue specimens. Novel biliary biomarkers especially carcinoembryonic cell adhesion molecule 6 and neutrophil gelatinase-associated lipocalin seem promising in differentiating malignant from benign biliary strictures. Recent developments in lipidomic profiling of bile are also very promising. Biliary biomarkers appear to complement endoscopic imaging in diagnosing malignant etiologies of biliary stricture. Future studies addressing these biomarkers need to be incorporated to the current endoscopic techniques to determine the best approach in determining the etiology of biliary strictures.

Key words: Bile; Pancreato-biliary malignancies; Biomarkers; Cholangiocarcinoma; Pancreatic cancers; Biliary strictures

Core tip: Pancreato-biliary malignancies remain a diagnostic challenge despite advances in endoscopy and imaging. Serum carbohydrate antigen 19-9 which is the most commonly used tumor marker has not been able to complement the endoscopic techniques effectively. Bile fluid is a better representative of the pancreato-biliary malignancies and various tumor markers in bile have been described recently with advances in proteomics. Carcinoembryonic cell adhesion molecule 6, neutrophil gelatinase-associated lipocalin and other novel biliary markers seem promising with high sensitivities and specificities, little affected by the presence of inflammation or the degree of biliary obstruction. These are potential future tumor markers

that can complement endoscopic techniques in diagnosing malignant biliary strictures.

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INTRODUCTION

Pancreato-biliary malignancies are often difficult to diagnose with the current diagnostics, and many are detected in their advanced stages with poor prognosis[1,2]. Endoscopic retrograde cholangiopancreatography (ERCP) with brushings is often the routine choice for the endoscopists to diagnose these malignancies, but is limited by its low to moderate sensitivities[3,4]. Also, the desmoplastic nature of cholangiocarcinoma (CCA) can make the histological diagnosis more complicated[5]. Fluoroscence *in situ* hybridization polysomy to increase the sensitivity of diagnosis has also not yielded very significant differences[6,7]. Imaging techniques like endoscopic ultrasound with needle aspirations have certain limitations. Though they offer better sensitivities for pancreatic malignancies[8], they have been found to increase the risk of peritoneal metastasis in hilar CCA and cannot be justified for routine use, particularly in hilar CCA[9]. Advanced endoscopic-imaging options such as use of cholangioscopes require expertise in the field and not much data is available on their use[10]. Peroral cholangioscopy can provide direct visualization of the bile ducts, and targeted biopsies obtained through spyglass cholangioscopy (single operator cholangioscopy) might help diagnose malignant lesions especially cholangiocarcinoma better than the conventional ERCP brushing/biopsy techniques[11,12]. But they are available only in a few centers, and more randomised trials comparing the effectiveness of spyglass biopsies with the routine ERCP brush cytology or forceps biopsies are necessary to justify their advantages in routine use. Clinical and/or radiological methods thus have not been successful in the early detection of the biliary tract malignancies. Surgery is the only cure for pancreato-biliary malignancies, and early detection of these lesions is necessary. With the limitations of the above diagnostics, several tumor markers have been analyzed to complement the endoscopic techniques. The relative rarity of these biliary tract neoplasms has been a hindrance for the progression in biomarker detection, though there have been recent advances in the techniques of biomarker analysis, especially the proteomics.

One of the most commonly employed diagnostic/prognostic markers in pancreato-biliary malignancies is serum carbohydrate antigen 19-9 (CA 19-9), which is also not without limitations. Firstly, in about 10% of the patients with a negative Lewis antigen, the test would prove futile[13]. Also there have been reports on the limitation of serum CA 19-9 with its values getting affected by the presence of biliary obstruction, which can be a confounding factor in differentiation of benign and malignant lesions[14,15]. Though it can be a reasonably good prognostic marker, its diagnostic utility is not very convincing. Hence the search for new markers continues.

Biliary biomarkers

Serum has been more easily the choice for many studies in identifying biomarkers, as it is easier to obtain unlike bile which requires ERCP. The proximity of bile to the bile duct epithelia makes it a harbor of various substances, which might be representative of the functions/abnormal changes taking place in the biliary system. Bile can be obtained during the routine diagnostic or therapeutic ERCPs performed in patients with indeterminate biliary strictures without imparting any additional risks apart from the baseline risks of the procedure. Novel methods have also been used for obtaining bile (BIDA-Bile Intraductal Aspiration)[16]. Here, the biliary catheter is connected to a central suction line through a specimen trap, and obtaining bile can be quick and simple. In one of the recent studies, it was found that a large proportion of the proteins detected in bile were cellular ("secreted'" from the surrounding biliary system), stressing the importance of bile fluid analysis[17]. The fact that after bile centrifugation, the supernatant analysis and not the cell debris (sediments) reveals the presence of these tumor markers could explain that it is mostly the secreted substances in bile that are analyzed[17]. Hence, paucity of shed cells in bile should not affect the bile analysis. The results of many of the recent studies identifying novel bile biomarkers have been encouraging with their potential future diagnostic utility, further supported by the immunohistochemical analysis of the resected tissue specimens. Table 1 summarizes the various bile bio-markers that have been studied in biliary strictures.

Is there a new role for the traditional tumor markers?

Serum CA 19-9 and carcinoembryonic antigen (CEA) are the tumor markers routinely used in the diagnosis and prognosis of pancreato-biliary malignancies[18-20]. The utility of these glycoprotein tumor markers in bile has been studied too, and their diagnostic performance has not been consistent. In a large study involving 100 patients, reasonably high sensitivity of 84% and a specificity of 64% was obtained with biliary CEA (levels > 20 ng/mL), but there was a considerable overlap between the malignant and benign lesions. Moreover, in the multivariate analysis biliary CEA levels were not predictive of malignancy[21]. The low to moderate specificities for these markers suggest that

they are increased in benign/inflammatory conditions too. Multiple studies have shown that biliary CA 19-9 and CEA did not add much to the diagnostic accuracy when compared to the serum levels, as they had high false positive results[22-25]. Further supporting this view, in an older study[26], a reasonably high specificity of 84% with CEA was obtained, when benign biliary diseases due to stones were excluded from the study. In another recent study of biliary strictures[27], CA19-9 levels in bile had a sensitivity of 74%, but a poor specificity of 34%, even after eliminating patients with cholangitis.

CA 125, a marker for ovarian cancer was found to be the most specific marker in bile for CCA (specificity-76%, sensitivity-59%) in a study, which could complement endoscopic methods either alone or in combination with CEA (specificity-88%) for diagnosing malignancy[22]. Summarizing, the available studies of these tumor markers in bile are limited. However these appear to have limited diagnostic utility.

Proteomics

The changes that occur at protein level when a normal cell undergoes malignant transformation form the basis of proteomics[28]. The analytical techniques in proteomics, which are used in quantifying the proteins, are the liquid chromatography-mass spectrometry and nuclear magnetic resonance spectroscopy, apart from Western blot (Immuno blot) and ELISA. Bile serves as the direct media, which carries proteins from the local environment (liver, biliary tract and pancreas). This makes it a very valuable source of novel proteins for identifying biomarkers suggestive of biliary tract malignancy. But, one of the limitations of bile is its complex constitution with various components, and proteins accounting for a mere 7% of the total dry weight; and differential fractionation (centrifugation) could be used to reduce the complexity, concentrating the protein component as a preparatory for mass spectrometry[17]. Delipidation and desalination of bile to remove the abundant phospholipids and bile salts have also been proposed[29]. Protein biomarkers might be suggestive of the possible mechanisms of carcinogenesis, as they are reflective of the changes taking place in DNA, but more importantly in clinical context, might play a major role in improving the prognosis through early detection. Alterations of tissue proteins can occur during the early stages of carcinogenesis, and hence proteomics could detect cancers early[30].

Bile can be a host of various proteins, especially those secreted from the hepatocytes/biliary epithelia and the enzymes from the distally located pancreas. Presence of various classes of proteins such as the transport proteins (haptoglobulin, ceruloplasmin, albumin, and globulin), immune proteins (complements, immunoglobulins), and other liver and pancreatic

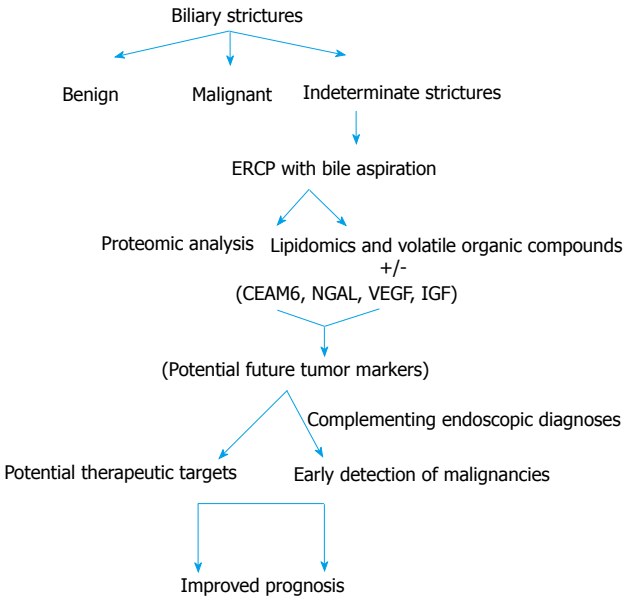

Figure 1 Approach to biliary strictures through bile biomarkers. ERCP: Endoscopic retrograde cholangiopancreatography; CEAM6: Carcinoembryonic cell adhesion molecule 6; NGAL: Neutrophil gelatinase-associated lipocalin; VEGF: Vascular endothelial growth factor; IGF: Insulin like growth factor.

enzymes (GGT, Adenosine deaminase, pancreatic lipase, carboxypeptidase) are expected to contribute to a large proportion of the proteins in bile[31]. Hence to identify the low abundance proteins that might play a role in tumorigenesis, albumin and immunoglobulins, were removed prior to separating the peptides with electrophoresis and subsequent analysis by mass spectrometry in a study[32]. Also, the presence of normally occurring proteins in elevated levels could be pathologic, suggestive of increased apoptosis/protein catabolism occurring in malignant conditions[33]. In this study, a model for identification of CCA was based on the differential levels of normally occurring proteins in bile. Hence it is not always the tumor-associated proteins that give clue regarding the possibility of malignancies.

Potential bio-markers

Novel biliary proteins that appear promising with supporting evidences from tissue immunochemistry are carcinoembryonic cell adhesion molecule 6 (CEAM6) and Neutrophil gelatinase-associated lipocalin (NGAL), though available literatures on their biliary levels are not many. Lipocalins are glycoproteins found to be associated with various inflammatory conditions and malignancies[34-36]. Table 1 describes the characteristics of the potential tumor markers in bile. Figure 1 shows the approach to the biliary strictures through bile biomarkers.

NGAL: The presence of NGAL in bile was first reported in a patient with CCA[31]. Two recent studies have found significantly elevated biliary levels of NGAL in pancreato-biliary malignancies[37,38]. In the most recent

Table 1 Potential biomarkers in bile

Bile biomarkers	Cut off value	Identification of CCA/pancreatic cancer	Sensitivity	Specificity	Comments
VEGF[57]	0.5 ng/mL	Pancreatic cancer (*vs* benign)	93.3%	72.7%	VEGF level in bile in CCA was not elevated. Another study[58] demonstrated increased serum VEGF in CCA-possible basolateral secretion of VEGF in bile duct epithelia in CCA?
	0.5 ng/mL	Pancreatic cancer (*vs* CCA)	93.3%	88.9%	
IGF[58]	NA	CCA	NA	NA	ROC (area under the curve = 1); Serum IGF levels were similar among CCA, pancreatic cancer and benign groups
CEAM6[50]	67.9 ng/mL	Malignant (CCA + pancreatic cancer)	93%	83%	Biliary levels were not critically affected by bile duct obstruction; Serum CEAM6 levels were not significantly different between the malignant and benign groups
CEAM6 + Serum CA 19-9	67.9 ng/mL, 157 kU/L		97%	83%	
NGAL[37]	459 ng/mL	Malignant (CCA + pancreatic cancer)	77.3%	72.2%	In both the studies, serum NGAL levels were not significantly different between benign and malignant groups; biliary levels were independent of serum bilirubin levels. Especially elevated in early well differentiated carcinomas in tissue immunohistochemistry-possible future application in PSC to R/O early malignant lesions/dysplasias
NGAL + Serum CA 19-9	459 ng/mL, 30.1 U/mL		91%	66.7%	
NGAL[38]	570 ng/mL	Malignant (CCA + Pancreatic cancer + GB carcinoma + metastasis)	94%	55%	
NGAL + Serum CA 19-9	3000 ng /mL, 125 U/L		85%	82%	
HSP[67]					
HSP 27	2.52 ng/mL	CCA	90%	90%	Serum levels of these markers were not significantly different between CCA and benign strictures
HSP 70	5.67 ng/mL		80%	80%	
HSP 27 + HSP 70	10.2 ng/mL		90%	100%	
Galectin Ligands					
Mac 2-BP[76]	853 ng/mL	All malignant strictures	69%	67%	Serum levels were not elevated in malignancies
Fibronectin[77]	40 ng/μmol	CCA	57%	79%	-
MCM 5[82]	1000 (cells)	CCA + Pancreatic cancer	66%	94%	MCM 5 levels in bile were significantly more sensitive than brush cytology (66% *vs* 20%; $P = 0.004$)
Pancreatic Elastase/ Amylase[83]	0.065	CCA	82%	89%	mRNA of PE 3B was also up-regulated in CCA tissues
Lipids[84]					
ON-PC	6020.1 nmol/L	CCA	85.7%	80.3%	-
S-PC	12 nmol/L	CCA	83.3%	77.8%	
ON-PC + S-PC	6032.2 nmol/L	CCA	100%	83.3%	
VOCs					
(TMA, acetone, isoprene, dimethyl sulfide, and acetaldehyde)[86]	Logarithmic model	Pancreatic cancer	83.3%	81.9%	-
(Acrylonitrile, methyl hexane and benzene)[87]	Logarithmic model	CCA in the setting of PSC	90.5%	72.7%	Biliary levels of VOCs in CCA (in the setting of PSC) were significantly lower than (benign) PSC

CCA: Cholangiocarcinoma; VEGF: Vascular endothelial growth factor; IGF: Insulin like growth factor; CEAM6: Carcinoembryonic cell adhesion molecule 6; NGAL: Neutrophil gelatinase-associated lipocalin; HSP: Heat shock proteins; PSC: Primary sclerosing cholangitis; MCM: Minichromosome maintenance proteins; VOC: Volatile organic compounds.

study, the sensitivities and specificities of NGAL in diagnosing malignant biliary strictures were 77% and 72% respectively when the cut off was taken as 459 ng/mL[37]. A higher sensitivity of 94% was achieved in the other study with the cutoff of 570 ng/mL, albeit with decreased specificity (55%)[38]. Addition of serum CA 19-9 to biliary NGAL had varying impacts on the sensitivities and specificities in both studies, but led to better results than obtained with biliary NGAL levels alone. Further encouraging was biliary NGAL's low correlation to serum bilirubin levels in both the studies, indicating that NGAL's elevation might be independent of the level of biliary obstruction. Significant NGAL elevation (tissue immunohistochemistry) in early dysplastic pancreatic lesions (including pancreatic intraepithelial neoplasia-1) in addition to well-differentiated adenocarcinoma was observed in a study[39]. Most studies report biliary/tissue NGAL rather than serum NGAL to be more representative of pancreato-biliary malignancies[37-40]. Prospective studies comparing both serum and biliary NGAL levels are much needed.

The role of NGAL in cancer progression, metastasis and potential therapy deserves mention[41,42]. Targeted silencing of *NGAL* gene in human CCA cell lines significantly decreased the *in vitro* cellular migration and invasion, suggestive of its role in cancer metastasis, and its potential for targeted anti-cancer therapy[41]. On the contrary, another study reported that NGAL as a potential suppressor of invasion and angiogenesis by suppressing vascular endothelial growth factor (VEGF) production in pancreatic cells[42]. Also in this study, tissue NGAL was expressed only by the well-

differentiated cells and not by the poorly differentiated pancreatic adenocarcinoma cells. This suggests the possible diagnostic role of NGAL in early pancreato-biliary malignancies, such as in the setting of primary sclerosing cholangitis which is a risk factor for the development of CCA[43-45]. Also as most of these patients undergo repeated ERCP stenting for biliary drainage, obtaining bile would not be a major issue too. Future studies on bile levels of NGAL in primary sclerosing cholangitis (PSC) patients with suspicious strictures would be valuable and interesting.

CEAM6: Other biliary biomarker, which seems very promising with high diagnostic sensitivities and specificities, is CEAM6. It is a cell adhesion molecule belonging to the immunoglobulin super family, which plays an important role in cell adhesion, invasion and metastasis[46]. Increased tissue expression of CEAM6 on immunohistochemical analysis of tissues in 82/89 patients with pancreatic adenocarcinoma was reported initially[47]. In this study, it was also found that negative expression of CEAM6 was significantly associated with absent lymph node metastasis and increased postoperative survival. The same group had earlier demonstrated an increase in caspase mediated apoptotic response and inhibited *in vivo* metastatic potential of pancreatic adenocarcinoma cells with *CEAM6* gene silencing. Thus this could be a possible therapeutic target for pancreatic adenocarcinoma[48]. Infact in a preclinical animal study, Strickland *et al*[49] targeted CEAM6 expressing pancreatic tumor cells using anti-CEAM6 monoclonal antibody, and observed marked inhibition of tumor growth. Its role in cancer progression, invasion and metastasis remains obvious.

Biliary CEAM6 levels were found to be elevated in malignant biliary lesions from a recent proteomic analysis of bile involving 41 patients, and the results appear promising[50]. With a cut off value of 67.9 ng/mL, the sensitivity and specificity of CEAM6 in diagnosing malignant strictures was 93% and 83% respectively, with area under the curve (AUC) of 0.92. The results were also not critically affected by biliary obstruction according to the authors when the correlation between the markers and bilirubin levels was analyzed. Addition of serum CA 19-9 further improved the diagnostic sensitivity, specificity and accuracy (sensitivity-97%, specificity-83%, AUC-0.96). The same group showed that CEAM6 was rather secreted into bile directly as it was found in the soluble form (supernatant) and not as a sediment along with the cellular debris, proving the role of bile analysis in identifying the marker.

VEGF: VEGF plays an important role in angiogenesis in cancer by stimulating the vascular endothelial proliferation, increasing vascular permeability and vasodilatation[51]. Expression of VEGF in pancreatic and cholangiocarcinoma has been described[52-54]. The role of VEGF in pancreatic cancers is especially significant as they are being used in clinical trials as therapeutic targets[55,56]. We recently analyzed the VEGF levels in bile from patients with biliary strictures; and with a cut off value of 0.5 ng/mL, we distinguished pancreatic cancer from CCA with a sensitivity of 93.3% and a specificity of 88.9%[57]. Using the same cut off value, pancreatic cancer could be differentiated from benign lesions with a sensitivity of 93.3% and a specificity of 72.7%. We also confirmed the pancreatic specificity of biliary VEGF through immunohistochemical analysis of the resected pancreatic specimens. An earlier study found increased levels of VEGF in serum of patients with CCA when compared to other groups, but the levels in bile did not differ significantly among the benign and malignant groups[58]. The insignificant levels of VEGF in bile in CCA patients could be linked to the baso-lateral secretion of VEGF from the bile duct epithelium, and not into the lumen. But in the Italian study, the levels of biliary VEGF were normal in the patients with pancreatic cancer, which contrasts with our observations. When compared to 84%, only 30% in the Italian study had histological confirmation. Future studies need to target the above mentioned issues.

Insulin like growth factor: In the same study as above, they also found biliary insulin like growth factor (IGF) to be diagnostic of extra-hepatic CCA, with the AUC = 1, when benign conditions or pancreatic cancer were taken as the control[58]. The levels of biliary IGF were also not correlating with the degree of cholestasis. IGF has been found to be associated with many cancers such as endometrial and other gynecological malignancies, lung cancers, and various other cancers including pancreatic cancers[59-62]. In a recently published study, silencing IGF 1 receptors in human pancreatic ductal adenocarcinoma cell lines inhibited pancreatic cell growth and metastasis by blocking many key signaling pathways[63]. IGF-1R antagonists have already entered clinical trials in patients with metastatic pancreatic cancer[64,65]. More studies on biliary levels of IGF to enhance its diagnostic significance in pancreato biliary malignancies are needed.

Heat shock proteins: Heat shock proteins (HSP) play an important role in protein folding and are anti-apoptotic and favors tumorigenesis[66]. A recent study showed that by combining the biliary values of HSP27 and HSP70, the sensitivity and specificity of diagnosing CCA was 90% and 100%, respectively[67]. However there was no significant increase of these proteins in serum of the patients with CCA when compared to benign lesions, though immunohistochemistry showed increased expression of these proteins in CCA and biliary intraepithelial neoplastic cells[67]. Plasma antibodies against HSP 70 were very recently described as one of the potential markers of CCA[68]. Expression of HSP 27 and HSP 70 has been found to modulate the

response of pancreatic cells to chemotherapy and hence might be potential prognostic markers as well[69,70]. In a very recent study where CCA cell lines from 78 patients with intrahepatic CCA were treated with a combination of HSP 90 inhibitor and a PTEN related pathway inhibitor *in vitro*, antiproliferative and proapoptotic effects were observed in the cell lines, demonstrating their potential therapeutic use[71]. In another study HSPD1, a heat shock protein was overexpressed in bile in patients with CCA[72]. Here in this study, other markers such as SSP411 (spermatogenesis associated protein) and PGAM-1 (phosphoglycerate mutase) in bile were also significantly elevated in CCA. Its sensitivity and specificity for detecting CCA were 90% and 83% respectively in that study. The role of these proteins, although studied remains unclear because of low specificity.

Galectin ligands: Galectins mediate cell to cell, cell to matrix interactions, apoptosis and angiogenesis; Fibronectin, Mac 2-binding protein (Mac 2-BP) and laminin are some of the ligands[73-75]. Koopmann *et al*[76] found that biliary Mac 2-BP could differentiate benign and malignant biliary tract lesions with a sensitivity and specificity of 69% and 67% respectively, that was comparable to serum CA 19-9. Similarly fibronectin, another ligand for galectin, was found to be a biliary diagnostic marker for CCA with a sensitivity of 57% and a specificity of 79%, but it was also elevated in biliary inflammation[77]. Future studies to validate these observations are necessary.

Minichromosome maintenance proteins: These are involved in DNA replication and have been found to be associated with the carcinogenesis[78-81]. The role of minichromosome maintenance proteins (MCM) 2 and MCM 5 proteins was studied through immunohistochemistry prospectively on 102 consecutive patients undergoing ERCP for biliary strictures[82]. In this study, the levels of MCM 5 in bile were also determined by automated immunoflurometric assay and compared with brush cytology. An additional 45% of cases of pancreato-biliary malignancies were detected through MCM 5 analysis in bile. With a cutoff greater than 1000, the sensitivity and specificity were 66% and 94% respectively, with a good accuracy (AUC 0.8).

Elastase/amylase: Increased levels of pancreatic elastase and decreased amylase levels in bile were detected in patients with CCA compared to benign strictures in a study[83]. The elastase-amylase ratio could detect CCA with a sensitivity and specificity of 82% and 89% respectively, with AUC-0.877. They also detected increased pancreatic elastase 3B mRNA in the CCA tissues.

Lipidomic profiling: In a pilot study, we showed that lipidomic profiling of bile could help differentiating benign and malignant biliary strictures[84]. Oxidative stress in the setting of malignancy results in the expression of oxidized phospholipids on the cancer cells, which are recognized by the host defenses leading to apoptosis of cancer cells[85]. The oxidized phospholipids were analyzed using a specialized liquid chromatography electrospray ionization tandem mass spectrometry (LC-ESI-MS/MS) assay. Two phosphatidylcholines {ON-PC [1-palmitoyl-2-(9-oxononanoyl)-sn -glycero-3-phosphatidylcholine], S-PC (1-palmitoyl-2-succinoyl-sn -glycero-3-phosphatidylcholine)} were elevated in CCA, with ON-PC being the most diagnostic with a sensitivity and specificity of 86% and 80% respectively (AUC-0.86). The combination of the two yielded even better results with a sensitivity of 100%, specificity of 83% and area under the curve of 0.91. The development of global lipidomics of bile could make this more interesting in the development of specific biomarkers for the diagnosis of CCA.

Volatile organic compounds: Our group has also shown, from our preliminary observation, that volatile organic compounds in bile in the headspaces (gas above the sample) may be useful for early diagnosis of CCA in the setting of PSC and in distinguishing malignant from benign strictures[86,87].

About 5 mL of bile collected at the time of ERCP is centrifuged for 8 min at 150 g and 4 ℃ and the sample heated to 40 ℃ to allow the volatile organic compounds (VOCs) in the headspace to equilibrate with the samples. Twenty milliliters of headspace gas was removed and analyzed with a selected ion flow tube mass spectrometry instrument. In a prospective cross sectional study, we showed that the concentrations of 6 compounds (acetaldehyde, acetone, benzene, carbon disulfide, pentane, and trimethylamine) were increased in patients with pancreatic cancer compared with controls ($P < 0.05$)[86]. In another study, we demonstrated that out of 22 analytes tested, a VOC signature consisting of acrylonitrile, methyl hexane and benzene, had a sensitivity and specificity of 90.5% and 72.7% respectively, with a significantly lower level in CCA in the setting of PSC, after accounting for all confounding variables[87]. By using receiver-operating characteristic curve analysis, we developed a model for the prediction and diagnosis of cholangio-pancreatic cancer based on the levels of signature VOC's in these two settings[86,87]. This might need validation from our ongoing prospective study and results reproducible from other centers. The extension of this to develop biomarkers based on the concept of exhaled breath VOC print, which could be detected by a simple test, is intriguing as a potential non-invasive diagnostic marker for pancreato-biliary cancer.

To compare the biomarkers in bile and to identify the differentially expressed proteins between intra and extra hepatic CCA would be valuable, and might provide insight on their origin and pathogenesis. In a recent meta analysis, Wiggers and coworkers identified certain markers including VEGF-A, epidermal growth

factor receptor, c-erbB-2 (HER-2/neu) through tissue immunohistochemistry that were significantly differing between the intra and extra hepatic CCA[88]. Based on the tumor markers, treatment strategies might also differ between the two. Future comparative studies on bile markers (Intrahepatic *vs* Extrahepatic CCA) would be worthful.

CONCLUSION

Novel biliary biomarkers especially CEAM6 and NGAL seem promising in differentiating malignant from benign biliary strictures. Also in malignant strictures, they appear to be elevated in bile rather than serum, which is interesting and must be, evaluated in future studies. Biliary VEGF, IGF, MCM's, lipidomic profiles and VOC's are new biomarkers in bile that might become available to clinicians in the near future when facing a challenging patient with biliary strictures. Analyses of biomarkers in bile have yielded encouraging results with supporting evidences from tissue immunohistochemistry in most of the studies. In addition, with their potential therapeutic implications, targeting the malignant cells/receptors with the antibodies/inhibitors remains plausible, and more future studies on establishing their therapeutic role are also necessary. Thus, biliary biomarkers complement endoscopic imaging in diagnosing malignant etiologies of biliary stricture. Future studies addressing these biomarkers need to incorporate endoscopic techniques to determine the best approach in determining the etiology of biliary strictures.

REFERENCES

1 **Friman S**. Cholangiocarcinoma--current treatment options. *Scand J Surg* 2011; **100**: 30-34 [PMID: 21491796]
2 **Saif MW**. Pancreatic neoplasm in 2011: an update. *JOP* 2011; **12**: 316-321 [PMID: 21737886]
3 **Burnett AS**, Calvert TJ, Chokshi RJ. Sensitivity of endoscopic retrograde cholangiopancreatography standard cytology: 10-y review of the literature. *J Surg Res* 2013; **184**: 304-311 [PMID: 23866788 DOI: 10.1016/j.jss.2013.06.028]
4 **Trikudanathan G**, Navaneethan U, Njei B, Vargo JJ, Parsi MA. Diagnostic yield of bile duct brushings for cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2014; **79**: 783-789 [PMID: 24140129 DOI: 10.1016/j.gie.2013.09.015]
5 **Patel T**. Cholangiocarcinoma--controversies and challenges. *Nat Rev Gastroenterol Hepatol* 2011; **8**: 189-200 [PMID: 21460876 DOI: 10.1038/nrgastro.2011.20]
6 **Smoczynski M**, Jablonska A, Matyskiel A, Lakomy J, Dubowik M, Marek I, Biernat W, Limon J. Routine brush cytology and fluorescence in situ hybridization for assessment of pancreatobiliary strictures. *Gastrointest Endosc* 2012; **75**: 65-73 [PMID: 22078103 DOI: 10.1016/j.gie.2011.08.040]
7 **Navaneethan U**, Njei B, Venkatesh PG, Vargo JJ, Parsi MA. Fluorescence in situ hybridization for diagnosis of cholangiocarcinoma in primary sclerosing cholangitis: a systematic review and meta-analysis. *Gastrointest Endosc* 2014; **79**: 943-950.e3 [PMID: 24360654 DOI: 10.1016/j.gie.2013.11.001]
8 **Weilert F**, Bhat YM, Binmoeller KF, Kane S, Jaffee IM, Shaw RE, Cameron R, Hashimoto Y, Shah JN. EUS-FNA is superior to ERCP-based tissue sampling in suspected malignant biliary obstruction: results of a prospective, single-blind, comparative study. *Gastrointest Endosc* 2014; **80**: 97-104 [PMID: 24559784 DOI: 10.1016/j.gie.2013.12.031]
9 **Heimbach JK**, Sanchez W, Rosen CB, Gores GJ. Trans-peritoneal fine needle aspiration biopsy of hilar cholangiocarcinoma is associated with disease dissemination. *HPB* (Oxford) 2011; **13**: 356-360 [PMID: 21492336 DOI: 10.1111/j.1477-2574.2011.00298.x]
10 **Chin MW**, Byrne MF. Update of cholangioscopy and biliary strictures. *World J Gastroenterol* 2011; **17**: 3864-3869 [PMID: 22025874 DOI: 10.3748/wjg.v17.i34.3864]
11 **Kalaitzakis E**, Webster GJ. Endoscopic diagnosis of biliary tract disease. *Curr Opin Gastroenterol* 2012; **28**: 273-279 [PMID: 22343346 DOI: 10.1097/MOG.0b013e328351436e]
12 **Draganov PV**, Chauhan S, Wagh MS, Gupte AR, Lin T, Hou W, Forsmark CE. Diagnostic accuracy of conventional and cholangioscopy-guided sampling of indeterminate biliary lesions at the time of ERCP: a prospective, long-term follow-up study. *Gastrointest Endosc* 2012; **75**: 347-353 [PMID: 22248602 DOI: 10.1016/j.gie.2011.09.020]
13 **Lamerz R**. Role of tumour markers, cytogenetics. *Ann Oncol* 1999; **10** Suppl 4: 145-149 [PMID: 10436809 DOI: 10.1093/annonc/10.suppl_4.S145]
14 **Lin MS**, Huang JX, Yu H. Elevated serum level of carbohydrate antigen 19-9 in benign biliary stricture diseases can reduce its value as a tumor marker. *Int J Clin Exp Med* 2014; **7**: 744-750 [PMID: 24753772]
15 **Ong SL**, Sachdeva A, Garcea G, Gravante G, Metcalfe MS, Lloyd DM, Berry DP, Dennison AR. Elevation of carbohydrate antigen 19.9 in benign hepatobiliary conditions and its correlation with serum bilirubin concentration. *Dig Dis Sci* 2008; **53**: 3213-3217 [PMID: 18465243 DOI: 10.1007/s10620-008-0289-8]
16 **Curcio G**, Granata A, Barresi L, Tarantino I, Mocciaro F, Traina M. Bile intraductal aspiration (BIDA): a fast method for bile collection. *Endoscopy* 2012; **44** Suppl 2 UCTN: E230-E231 [PMID: 22715008 DOI: 10.1055/s-0031-1291644]
17 **Farina A**, Dumonceau JM, Delhaye M, Frossard JL, Hadengue A, Hochstrasser DF, Lescuyer P. A step further in the analysis of human bile proteome. *J Proteome Res* 2011; **10**: 2047-2063 [PMID: 21314112 DOI: 10.1021/pr200011b]
18 **Lee KJ**, Yi SW, Chung MJ, Park SW, Song SY, Chung JB, Park JY. Serum CA 19-9 and CEA levels as a prognostic factor in pancreatic adenocarcinoma. *Yonsei Med J* 2013; **54**: 643-649 [PMID: 23549809 DOI: 10.3349/ymj.2013.54.3.643]
19 **Poruk KE**, Gay DZ, Brown K, Mulvihill JD, Boucher KM, Scaife CL, Firpo MA, Mulvihill SJ. The clinical utility of CA 19-9 in pancreatic adenocarcinoma: diagnostic and prognostic updates. *Curr Mol Med* 2013; **13**: 340-351 [PMID: 23331006]
20 **Malaguarnera G**, Paladina I, Giordano M, Malaguarnera M, Bertino G, Berretta M. Serum markers of intrahepatic cholangiocarcinoma. *Dis Markers* 2013; **34**: 219-228 [PMID: 23396291 DOI: 10.3233/DMA-130964]
21 **Buffet C**, Fourré C, Altman C, Prat F, Fritsch J, Choury A, Briantais MJ, Desgrez A, Etienne JP. Bile levels of carcino-embryonic antigen in patients with hepatopancreatobiliary disease. *Eur J Gastroenterol Hepatol* 1996; **8**: 131-134 [PMID: 8723416 DOI: 10.1097/00042737-199602000-00007]
22 **Chen CY**, Shiesh SC, Tsao HC, Lin XZ. The assessment of biliary CA 125, CA 19-9 and CEA in diagnosing cholangiocarcinoma--the influence of sampling time and hepatolithiasis. *Hepatogastroenterology* 2002; **49**: 616-620 [PMID: 12063953]
23 **Lindberg B**, Arnelo U, Bergquist A, Thörne A, Hjerpe A, Granqvist S, Hansson LO, Tribukait B, Persson B, Broomé U. Diagnosis of biliary strictures in conjunction with endoscopic retrograde cholangiopancreaticography, with special reference to patients with primary sclerosing cholangitis. *Endoscopy* 2002; **34**: 909-916 [PMID: 12430077 DOI: 10.1055/s-2002-35298]
24 **Ker CG**, Chen JS, Lee KT, Sheen PC, Wu CC. Assessment of serum and bile levels of CA19-9 and CA125 in cholangitis and bile duct carcinoma. *J Gastroenterol Hepatol* 1991; **6**: 505-508 [PMID: 1657243 DOI: 10.1111/j.1440-1746.1991.tb00896.x]

25 **Ohshio G**, Manabe T, Watanabe Y, Endo K, Kudo H, Suzuki T, Tobe T. Comparative studies of DU-PAN-2, carcinoembryonic antigen, and CA19-9 in the serum and bile of patients with pancreatic and biliary tract diseases: evaluation of the influence of obstructive jaundice. *Am J Gastroenterol* 1990; **85**: 1370-1376 [PMID: 2220731]

26 **Nakeeb A**, Lipsett PA, Lillemoe KD, Fox-Talbot MK, Coleman J, Cameron JL, Pitt HA. Biliary carcinoembryonic antigen levels are a marker for cholangiocarcinoma. *Am J Surg* 1996; **171**: 147-152; discussion 152-153 [PMID: 8554130 DOI: 10.1016/S0002-9610(99)80090-7]

27 **Ince AT**, Yıldız K, Baysal B, Danalıoğlu A, Kocaman O, Tozlu M, Gangarapu V, Sarbay Kemik A, Uysal Ö, Şentürk H. Roles of serum and biliary CEA, CA19-9, VEGFR3, and TAC in differentiating between malignant and benign biliary obstructions. *Turk J Gastroenterol* 2014; **25**: 162-169 [PMID: 25003676 DOI: 10.5152/tjg.2014.6056]

28 **Srinivas PR**, Srivastava S, Hanash S, Wright GL. Proteomics in early detection of cancer. *Clin Chem* 2001; **47**: 1901-1911 [PMID: 11568117]

29 **Bonney GK**, Craven RA, Prasad R, Melcher AF, Selby PJ, Banks RE. Circulating markers of biliary malignancy: opportunities in proteomics? *Lancet Oncol* 2008; **9**: 149-158 [PMID: 18237849 DOI: 10.1016/S1470-2045(08)70027-5]

30 **Wulfkuhle JD**, Liotta LA, Petricoin EF. Proteomic applications for the early detection of cancer. *Nat Rev Cancer* 2003; **3**: 267-275 [PMID: 12671665]

31 **Kristiansen TZ**, Bunkenborg J, Gronborg M, Molina H, Thuluvath PJ, Argani P, Goggins MG, Maitra A, Pandey A. A proteomic analysis of human bile. *Mol Cell Proteomics* 2004; **3**: 715-728 [PMID: 15084671 DOI: 10.1074/mcp.M400015-MCP200]

32 **Farid SG**, Craven RA, Peng J, Bonney GK, Perkins DN, Selby PJ, Rajendra Prasad K, Banks RE. Shotgun proteomics of human bile in hilar cholangiocarcinoma. *Proteomics* 2011; **11**: 2134-2138 [PMID: 21500345 DOI: 10.1002/pmic.201000653]

33 **Lankisch TO**, Metzger J, Negm AA, Vosskuhl K, Schiffer E, Siwy J, Weismüller TJ, Schneider AS, Thedieck K, Baumeister R, Zürbig P, Weissinger EM, Manns MP, Mischak H, Wedemeyer J. Bile proteomic profiles differentiate cholangiocarcinoma from primary sclerosing cholangitis and choledocholithiasis. *Hepatology* 2011; **53**: 875-884 [PMID: 21374660 DOI: 10.1002/hep.24103]

34 **Bolignano D**, Donato V, Lacquaniti A, Fazio MR, Bono C, Coppolino G, Buemi M. Neutrophil gelatinase-associated lipocalin (NGAL) in human neoplasias: a new protein enters the scene. *Cancer Lett* 2010; **288**: 10-16 [PMID: 19540040 DOI: 10.1016/j.canlet.2009.05.027]

35 **Chakraborty S**, Kaur S, Guha S, Batra SK. The multifaceted roles of neutrophil gelatinase associated lipocalin (NGAL) in inflammation and cancer. *Biochim Biophys Acta* 2012; **1826**: 129-169 [PMID: 22513004 DOI: 10.1016/j.bbcan.2012.03.008]

36 **McLean MH**, Thomson AJ, Murray GI, Fyfe N, Hold GL, El-Omar EM. Expression of neutrophil gelatinase-associated lipocalin in colorectal neoplastic progression: a marker of malignant potential? *Br J Cancer* 2013; **108**: 2537-2541 [PMID: 23736029 DOI: 10.1038/bjc.2013.264]

37 **Budzynska A**, Nowakowska-Dulawa E, Marek T, Boldys H, Nowak A, Hartleb M. Differentiation of pancreatobiliary cancer from benign biliary strictures using neutrophil gelatinase-associated lipocalin. *J Physiol Pharmacol* 2013; **64**: 109-114 [PMID: 23568978]

38 **Zabron AA**, Horneffer-van der Sluis VM, Wadsworth CA, Laird F, Gierula M, Thillainayagam AV, Vlavianos P, Westaby D, Taylor-Robinson SD, Edwards RJ, Khan SA. Elevated levels of neutrophil gelatinase-associated lipocalin in bile from patients with malignant pancreatobiliary disease. *Am J Gastroenterol* 2011; **106**: 1711-1717 [PMID: 21670771 DOI: 10.1038/ajg.2011.187]

39 **Moniaux N**, Chakraborty S, Yalniz M, Gonzalez J, Shostrom VK, Standop J, Lele SM, Ouellette M, Pour PM, Sasson AR, Brand RE, Hollingsworth MA, Jain M, Batra SK. Early diagnosis of pancreatic cancer: neutrophil gelatinase-associated lipocalin as a marker of pancreatic intraepithelial neoplasia. *Br J Cancer* 2008; **98**: 1540-1547 [PMID: 18392050 DOI: 10.1038/sj.bjc.6604329]

40 **Leelawat K**, Narong S, Wannaprasert J, Leelawat S. Serum NGAL to Clinically Distinguish Cholangiocarcinoma from Benign Biliary Tract Diseases. *Int J Hepatol* 2011; **2011**: 873548 [PMID: 21994874 DOI: 10.4061/2011/873548]

41 **Nuntagowat C**, Leelawat K, Tohtong R. NGAL knockdown by siRNA in human cholangiocarcinoma cells suppressed invasion by reducing NGAL/MMP-9 complex formation. *Clin Exp Metastasis* 2010; **27**: 295-305 [PMID: 20373132 DOI: 10.1007/s10585-010-9327-y]

42 **Tong Z**, Kunnumakkara AB, Wang H, Matsuo Y, Diagaradjane P, Harikumar KB, Ramachandran V, Sung B, Chakraborty A, Bresalier RS, Logsdon C, Aggarwal BB, Krishnan S, Guha S. Neutrophil gelatinase-associated lipocalin: a novel suppressor of invasion and angiogenesis in pancreatic cancer. *Cancer Res* 2008; **68**: 6100-6108 [PMID: 18676832 DOI: 10.1158/0008-5472.CAN-08-0540]

43 **Tyson GL**, El-Serag HB. Risk factors for cholangiocarcinoma. *Hepatology* 2011; **54**: 173-184 [PMID: 21488076 DOI: 10.1002/hep.24351]

44 **Liu R**, Cox K, Guthery SL, Book L, Witt B, Chadwick B, Adler DG. Cholangiocarcinoma and high-grade dysplasia in young patients with primary sclerosing cholangitis. *Dig Dis Sci* 2014; **59**: 2320-2324 [PMID: 24748183 DOI: 10.1007/s10620-014-3152-0]

45 **Burak K**, Angulo P, Pasha TM, Egan K, Petz J, Lindor KD. Incidence and risk factors for cholangiocarcinoma in primary sclerosing cholangitis. *Am J Gastroenterol* 2004; **99**: 523-526 [PMID: 15056096 DOI: 10.1111/j.1572-0241.2004.04067.x]

46 **Blumenthal RD**, Leon E, Hansen HJ, Goldenberg DM. Expression patterns of CEACAM5 and CEACAM6 in primary and metastatic cancers. *BMC Cancer* 2007; **7**: 2 [PMID: 17201906]

47 **Duxbury MS**, Matros E, Clancy T, Bailey G, Doff M, Zinner MJ, Ashley SW, Maitra A, Redston M, Whang EE. CEACAM6 is a novel biomarker in pancreatic adenocarcinoma and PanIN lesions. *Ann Surg* 2005; **241**: 491-496 [PMID: 15729073 DOI: 10.1097/01.sla.0000154455.86404.e9]

48 **Duxbury MS**, Ito H, Zinner MJ, Ashley SW, Whang EE. CEACAM6 gene silencing impairs anoikis resistance and in vivo metastatic ability of pancreatic adenocarcinoma cells. *Oncogene* 2004; **23**: 465-473 [PMID: 14724575 DOI: 10.1038/sj.onc.1207036]

49 **Strickland LA**, Ross J, Williams S, Ross S, Romero M, Spencer S, Erickson R, Sutcliffe J, Verbeke C, Polakis P, van Bruggen N, Koeppen H. Preclinical evaluation of carcinoembryonic cell adhesion molecule (CEACAM) 6 as potential therapy target for pancreatic adenocarcinoma. *J Pathol* 2009; **218**: 380-390 [PMID: 19334050 DOI: 10.1002/path.2545]

50 **Farina A**, Dumonceau JM, Antinori P, Annessi-Ramseyer I, Frossard JL, Hochstrasser DF, Delhaye M, Lescuyer P. Bile carcinoembryonic cell adhesion molecule 6 (CEAM6) as a biomarker of malignant biliary stenoses. *Biochim Biophys Acta* 2014; **1844**: 1018-1025 [PMID: 23806607 DOI: 10.1016/j.bbapap.2013.06.010]

51 **Dimova I**, Popivanov G, Djonov V. Angiogenesis in cancer - general pathways and their therapeutic implications. *J BUON* 2014; **19**: 15-21 [PMID: 24659637]

52 **Ikeda N**, Adachi M, Taki T, Huang C, Hashida H, Takabayashi A, Sho M, Nakajima Y, Kanehiro H, Hisanaga M, Nakano H, Miyake M. Prognostic significance of angiogenesis in human pancreatic cancer. *Br J Cancer* 1999; **79**: 1553-1563 [PMID: 10188906 DOI: 10.1038/sj.bjc.6690248]

53 **Niedergethmann M**, Hildenbrand R, Wostbrock B, Hartel M, Sturm JW, Richter A, Post S. High expression of vascular endothelial growth factor predicts early recurrence and poor prognosis after curative resection for ductal adenocarcinoma of the pancreas. *Pancreas* 2002; **25**: 122-129 [PMID: 12142733 DOI: 10.1097/00006676-200208000-00002]

54 **Park BK**, Paik YH, Park JY, Park KH, Bang S, Park SW, Chung JB, Park YN, Song SY. The clinicopathologic significance of the expression of vascular endothelial growth factor-C in intrahepatic cholangiocarcinoma. *Am J Clin Oncol* 2006; **29**: 138-142 [PMID: 16601431 DOI: 10.1097/01.coc.0000204402.29830.08]

55 **Sahora K**, Schindl M, Kuehrer I, Eisenhut A, Werba G, Brostjan C,

Telek B, Ba'ssalamah A, Stift J, Schoppmann SF, Gnant M. A phase II trial of two durations of Bevacizumab added to neoadjuvant gemcitabine for borderline and locally advanced pancreatic cancer. *Anticancer Res* 2014; **34**: 2377-2384 [PMID: 24778046]

56 **Watkins DJ**, Starling N, Cunningham D, Thomas J, Webb J, Brown G, Barbachano Y, Oates J, Chau I. The combination of a chemotherapy doublet (gemcitabine and capecitabine) with a biological doublet (bevacizumab and erlotinib) in patients with advanced pancreatic adenocarcinoma. The results of a phase I/II study. *Eur J Cancer* 2014; **50**: 1422-1429 [PMID: 24613126 DOI: 10.1016/j.ejca.2014.02.003]

57 **Navaneethan U**, Gutierrez NG, Jegadeesan R, Venkatesh PG, Poptic E, Liu X, Sanaka MR, Jang S, Vargo JJ, Parsi MA. Vascular endothelial growth factor levels in bile distinguishes pancreatic cancer from other etiologies of biliary stricture: a pilot study. *Dig Dis Sci* 2013; **58**: 2986-2992 [PMID: 23828141 DOI: 10.1007/s10620-013-2764-0]

58 **Alvaro D**, Macarri G, Mancino MG, Marzioni M, Bragazzi M, Onori P, Corradini SG, Invernizzi P, Franchitto A, Attili AF, Gaudio E, Benedetti A. Serum and biliary insulin-like growth factor I and vascular endothelial growth factor in determining the cause of obstructive cholestasis. *Ann Intern Med* 2007; **147**: 451-459 [PMID: 17909206 DOI: 10.7326/0003-4819-147-7-200710020-00003]

59 **Bruchim I**, Sarfstein R, Werner H. The IGF Hormonal Network in Endometrial Cancer: Functions, Regulation, and Targeting Approaches. *Front Endocrinol* (Lausanne) 2014; **5**: 76 [PMID: 24904527 DOI: 10.3389/fendo.2014.00076]

60 **Zhang M**, Li X, Zhang X, Yang Y, Feng Z, Liu X. Association of serum hemoglobin A1c, C-peptide and insulin-like growth factor-1 levels with the occurrence and development of lung cancer. *Mol Clin Oncol* 2014; **2**: 506-508 [PMID: 24940485 DOI: 10.3892/mco.2014.289]

61 **Cao Y**, Lindström S, Schumacher F, Stevens VL, Albanes D, Berndt S, Boeing H, Bueno-de-Mesquita HB, Canzian F, Chamosa S, Chanock SJ, Diver WR, Gapstur SM, Gaziano JM, Giovannucci EL, Haiman CA, Henderson B, Johansson M, Le Marchand L, Palli D, Rosner B, Siddiq A, Stampfer M, Stram DO, Tamimi R, Travis RC, Trichopoulos D, Willett WC, Yeager M, Kraft P, Hsing AW, Pollak M, Lin X, Ma J. Insulin-like growth factor pathway genetic polymorphisms, circulating IGF1 and IGFBP3, and prostate cancer survival. *J Natl Cancer Inst*2014; **106**: dju085 [PMID: 24824313 DOI: 10.1093/jnci/dju085]

62 **Lin Y**, Tamakoshi A, Kikuchi S, Yagyu K, Obata Y, Ishibashi T, Kawamura T, Inaba Y, Kurosawa M, Motohashi Y, Ohno Y. Serum insulin-like growth factor-I, insulin-like growth factor binding protein-3, and the risk of pancreatic cancer death. *Int J Cancer* 2004; **110**: 584-588 [PMID: 15122592 DOI: 10.1002/ijc.20147]

63 **Subramani R**, Lopez-Valdez R, Arumugam A, Nandy S, Boopalan T, Lakshmanaswamy R. Targeting insulin-like growth factor 1 receptor inhibits pancreatic cancer growth and metastasis. *PLoS One* 2014; **9**: e97016 [PMID: 24809702 DOI: 10.1371/journal.pone.0097016]

64 **McCaffery I**, Tudor Y, Deng H, Tang R, Suzuki S, Badola S, Kindler HL, Fuchs CS, Loh E, Patterson SD, Chen L, Gansert JL. Putative predictive biomarkers of survival in patients with metastatic pancreatic adenocarcinoma treated with gemcitabine and ganitumab, an IGF1R inhibitor. *Clin Cancer Res* 2013; **19**: 4282-4289 [PMID: 23741071 DOI: 10.1158/1078-0432.CCR-12-1840]

65 **Kindler HL**, Richards DA, Garbo LE, Garon EB, Stephenson JJ, Rocha-Lima CM, Safran H, Chan D, Kocs DM, Galimi F, McGreivy J, Bray SL, Hei Y, Feigal EG, Loh E, Fuchs CS. A randomized, placebo-controlled phase 2 study of ganitumab (AMG 479) or conatumumab (AMG 655) in combination with gemcitabine in patients with metastatic pancreatic cancer. *Ann Oncol* 2012; **23**: 2834-2842 [PMID: 22700995 DOI: 10.1093/annonc/mds142]

66 **Garrido C**, Brunet M, Didelot C, Zermati Y, Schmitt E, Kroemer G. Heat shock proteins 27 and 70: anti-apoptotic proteins with tumorigenic properties. *Cell Cycle* 2006; **5**: 2592-2601 [PMID: 17106261 DOI: 10.4161/cc.5.22.3448]

67 **Sato Y**, Harada K, Sasaki M, Yasaka T, Nakanuma Y. Heat shock proteins 27 and 70 are potential biliary markers for the detection of cholangiocarcinoma. *Am J Pathol* 2012; **180**: 123-130 [PMID: 22051775 DOI: 10.1016/j.ajpath.2011.09.010]

68 **Rucksaken R**, Pairojkul C, Pinlaor P, Khuntikeo N, Roytrakul S, Selmi C, Pinlaor S. Plasma autoantibodies against heat shock protein 70, enolase 1 and ribonuclease/angiogenin inhibitor 1 as potential biomarkers for cholangiocarcinoma. *PLoS One* 2014; **9**: e103259 [PMID: 25058392 DOI: 10.1371/journal.pone.0103259]

69 **Tsiaousidou A**, Lambropoulou M, Chatzitheoklitos E, Tripsianis G, Tsompanidou C, Simopoulos C, Tsaroucha AK. B7H4, HSP27 and DJ-1 molecular markers as prognostic factors in pancreatic cancer. *Pancreatology* 2013; **13**: 564-569 [PMID: 24280570 DOI: 10.1016/j.pan.2013.10.005]

70 **Hyun JJ**, Lee HS, Keum B, Seo YS, Jeen YT, Chun HJ, Um SH, Kim CD. Expression of heat shock protein 70 modulates the chemoresponsiveness of pancreatic cancer. *Gut Liver* 2013; **7**: 739-746 [PMID: 24312717 DOI: 10.5009/gnl.2013.7.6.739]

71 **Chen MH**, Chiang KC, Cheng CT, Huang SC, Chen YY, Chen TW, Yeh TS, Jan YY, Wang HM, Weng JJ, Chang PM, Liu CY, Li CP, Chao Y, Chen MH, Huang CY, Yeh CN. Antitumor activity of the combination of an HSP90 inhibitor and a PI3K/mTOR dual inhibitor against cholangiocarcinoma. *Oncotarget* 2014; **5**: 2372-2389 [PMID: 24796583]

72 **Shen J**, Wang W, Wu J, Feng B, Chen W, Wang M, Tang J, Wang F, Cheng F, Pu L, Tang Q, Wang X, Li X. Comparative proteomic profiling of human bile reveals SSP411 as a novel biomarker of cholangiocarcinoma. *PLoS One* 2012; **7**: e47476 [PMID: 23118872 DOI: 10.1371/journal.pone.0047476]

73 **Lee JH**, Zhang X, Shin BK, Lee ES, Kim I. Mac-2 binding protein and galectin-3 expression in mucinous tumours of the ovary: an annealing control primer system and immunohistochemical study. *Pathology* 2009; **41**: 229-233 [PMID: 19291534 DOI: 10.1080/00313020902756279]

74 **Compagno D**, Gentilini LD, Jaworski FM, Pérez IG, Contrufo G, Laderach DJ. Glycans and galectins in prostate cancer biology, angiogenesis and metastasis. *Glycobiology* 2014; **24**: 899-906 [PMID: 24939371 DOI: 10.1093/glycob/cwu055]

75 **Fortuna-Costa A**, Gomes AM, Kozlowski EO, Stelling MP, Pavão MS. Extracellular galectin-3 in tumor progression and metastasis. *Front Oncol* 2014; **4**: 138 [PMID: 24982845 DOI: 10.3389/fonc.2014.00138]

76 **Koopmann J**, Thuluvath PJ, Zahurak ML, Kristiansen TZ, Pandey A, Schulick R, Argani P, Hidalgo M, Iacobelli S, Goggins M, Maitra A. Mac-2-binding protein is a diagnostic marker for biliary tract carcinoma. *Cancer* 2004; **101**: 1609-1615 [PMID: 15378479 DOI: 10.1002/cncr.20469]

77 **Chen CY**, Lin XZ, Tsao HC, Shiesh SC. The value of biliary fibronectin for diagnosis of cholangiocarcinoma. *Hepatogastroenterology* 2003; **50**: 924-927 [PMID: 12845951]

78 **You Z**, De Falco M, Kamada K, Pisani FM, Masai H. The mini-chromosome maintenance (Mcm) complexes interact with DNA polymerase α-primase and stimulate its ability to synthesize RNA primers. *PLoS One* 2013; **8**: e72408 [PMID: 23977294 DOI: 10.1371/journal.pone.0072408]

79 **Das M**, Prasad SB, Yadav SS, Govardhan HB, Pandey LK, Singh S, Pradhan S, Narayan G. Over expression of minichromosome maintenance genes is clinically correlated to cervical carcinogenesis. *PLoS One* 2013; **8**: e69607 [PMID: 23874974 DOI: 10.1371/journal.pone.0069607]

80 **Williams GH**, Swinn R, Prevost AT, De Clive-Lowe P, Halsall I, Going JJ, Hales CN, Stoeber K, Middleton SJ. Diagnosis of oesophageal cancer by detection of minichromosome maintenance 5 protein in gastric aspirates. *Br J Cancer* 2004; **91**: 714-719 [PMID: 15266314 DOI: 10.1038/sj.bjc.6602028]

81 **Stoeber K**, Swinn R, Prevost AT, de Clive-Lowe P, Halsall I, Dilworth SM, Marr J, Turner WH, Bullock N, Doble A, Hales CN, Williams GH. Diagnosis of genito-urinary tract cancer by detection of minichromosome maintenance 5 protein in urine sediments. *J Natl Cancer Inst* 2002; **94**: 1071-1079 [PMID: 12122098 DOI:

10.1093/jnci/94.14.1071]
82 **Ayaru L**, Stoeber K, Webster GJ, Hatfield AR, Wollenschlaeger A, Okoturo O, Rashid M, Williams G, Pereira SP. Diagnosis of pancreaticobiliary malignancy by detection of minichromosome maintenance protein 5 in bile aspirates. *Br J Cancer* 2008; **98**: 1548-1554 [PMID: 18414413 DOI: 10.1038/sj.bjc.6604342]
83 **Chen CY**, Tsai WL, Wu HC, Syu MJ, Wu CC, Shiesh SC. Diagnostic role of biliary pancreatic elastase for cholangiocarcinoma in patients with cholestasis. *Clin Chim Acta* 2008; **390**: 82-89 [PMID: 18252202 DOI: 10.1016/j.cca.2008.01.011]
84 **Navaneethan U**, Gutierrez NG, Venkatesh PG, Jegadeesan R, Zhang R, Jang S, Sanaka MR, Vargo JJ, Parsi MA, Feldstein AE, Stevens T. Lipidomic profiling of bile in distinguishing benign from malignant biliary strictures: a single-blinded pilot study. *Am J Gastroenterol* 2014; **109**: 895-902 [PMID: 24710507 DOI: 10.1038/ajg.2014.60]
85 **Volinsky R**, Kinnunen PK. Oxidized phosphatidylcholines in membrane-level cellular signaling: from biophysics to physiology and molecular pathology. *FEBS J* 2013; **280**: 2806-2816 [PMID: 23506295 DOI: 10.1111/febs.12247]
86 **Navaneethan U**, Parsi MA, Gutierrez NG, Bhatt A, Venkatesh PG, Lourdusamy D, Grove D, Hammel JP, Jang S, Sanaka MR, Stevens T, Vargo JJ, Dweik RA. Volatile organic compounds in bile can diagnose malignant biliary strictures in the setting of pancreatic cancer: a preliminary observation. *Gastrointest Endosc* 2014; **80**: 1038-1045 [PMID: 24929484 DOI: 10.1016/j.gie.2014.04.016]
87 **Navaneethan U**, Parsi, MA, Lourdusamy D, Bhatt A, Gutierrez NG, Grove D, Venkatesh PGK, Sanaka MR, Hammel JP, Stevens T, Vargo JJ, Dweik RA. Volatile organic compounds in Bile for Early Diagnosis of Cholangiocarcinoma in Patients with Primary Sclerosing Cholangitis: A Pilot Study. *Gastrointest Endosc* 2014; In press
88 **Wiggers JK**, Ruys AT, Groot Koerkamp B, Beuers U, ten Kate FJ, van Gulik TM. Differences in immunohistochemical biomarkers between intra- and extrahepatic cholangiocarcinoma: a systematic review and meta-analysis. *J Gastroenterol Hepatol* 2014; **29**: 1582-1594 [PMID: 24787096 DOI: 10.1111/jgh.12620]

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REVIEW

Endoscopic ultrasound in the evaluation of pancreatic neoplasms-solid and cystic: A review

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Abstract

Pancreatic neoplasms have a wide range of pathology, from pancreatic adenocarcinoma to cystic mucinous neoplasms. Endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA) is a helpful diagnostic tool in the work-up of pancreatic neoplasms. Its utility in pancreatic malignancy is well known. Over the last two decades EUS-FNA has become a procedure of choice for diagnosis of pancreatic adenocarcinoma. EUS-FNA is highly sensitive and specific for solid lesions, with sensitivities as high as 80%-95% for pancreatic masses and specificity as high as 75%-100%. Multiple aspects of the procedure have been studied to optimize the rate of diagnosis with EUS-FNA including cytopathologist involvement, needle size, suctioning and experience of endoscopist. Onsite pathology is one of the most important elements in increasing diagnostic yield rate in EUS-FNA. EUS-FNA is valuable in diagnosing rare and atypical pancreatic neoplasms including neuroendocrine, lymphoma and metastatic disease. As more and more patients undergo cross sectional imaging, cystic lesions of the pancreas are becoming a more common occurrence and EUS-FNA of these lesions can be helpful for differentiation. This review covers the technical aspects of optimizing pancreatic neoplasm diagnosis rate, highlight rare pancreatic neoplasms and role of EUS-FNA, and also outline the important factors in diagnosis of cystic lesions by EUS-FNA.

Key words: Endoscopic ultrasound-fine needle aspiration; Pancreatic neoplasms; Pancreatic cysts; Review; Pancreatic adenocarcinoma

Core tip: Endoscopic ultrasound-fine needle aspiration (EUS-FNA) is a common, reliable way of obtaining tissue from within the abdominal cavity. This review details the current evidence of optimizing EUS-FNA results for pancreatic lesions, specifically adenocarcinoma. EUS and cytology from rare pancreatic lesions are highlighted to demonstrate the wide variety of pancreatic lesions and the importance of cytopathology. Also covered are cystic lesions and the ability of EUS-FNA to differentiate cysts based on EUS appearance and aspiration analysis

including new DNA analysis and measurement of k-ras mutation.

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INTRODUCTION

Pancreatic neoplasms have a wide range of pathology, from pancreatic adenocarcinoma to cystic mucinous neoplasms. Endoscopic ultrasound (EUS) with or without fine needle aspiration (FNA) is a helpful diagnostic tool in the work-up of pancreatic neoplasms. Its utility in pancreatic malignancy is well known. Over the last two decades it has become the procedure of choice for tissue diagnosis and staging of pancreatic adenocarcinoma. In this review the utility of EUS in the diagnosis of pancreatic adenocarcinoma and technical aspects of the procedure that can increase rates of pathology diagnosis will be discussed. Examples of rare and atypical lesions and the role of EUS-FNA will be highlighted. Also reviewed are the advances in differentiation and diagnosis of pancreatic cysts, including new tests (DNA analysis, k-ras measurement) that may play a role in the future discriminating cystic lesions. The current evidence, limitations, and complications of EUS-FNA in the evaluation of both solid and cystic pancreatic neoplasms will be reviewed.

PANCREATIC ADENOCARCINOMA

Pancreatic adenocarcinoma remains a rising and leading cause of cancer death in the United States. The five year survival is less than 5%[1,2], which stems from the fact that more than 80% of pancreatic adenocarcinomas present as advanced disease at time of diagnosis[2]. Often the diagnosis and stage can be clearly established with cross sectional imaging and patients can be taken for definitive surgical management. However, when there is lack of clarity in the diagnosis or stage of the disease, EUS-FNA can play an important role. Additionally, it is useful when neoadjuvant therapy is planning to be used and tissue diagnosis is needed. EUS alone is a valuable tool for staging pancreatic lesions. Figure 1 demonstrates an endoscopic ultrasound image (Figure 1A) and typical cytology of a pancreatic adenocarcinoma (Figure 1B and C). EUS has been shown to be superior to other imaging [computed tomography (CT) or abdominal US] in pancreatic tumor detection, specifically in tumors < 3 cm[3]. Earlier studies showed that EUS may be superior to CT in staging and determining surgical resectability. However with the advances in CT imaging, whether EUS still holds advantage in this setting appears to be less clear[4]. It is likely that these two modalities are complimentary in the staging of pancreatic adenocarcinoma.

EUS-FNA was first described in the early 1990's and since then it has become the standard of care in diagnosis of pancreatic masses[5]. Much of the data regarding EUS-FNA is in regards to diagnosing pancreatic adenocarcinoma. EUS-FNA is highly sensitive and specific for solid lesions, with sensitivities as high as 80%-95% for pancreatic masses and specificity as high as 75%-100%[6-8]. More recently a meta-analysis of 41 studies of EUS-FNA found a pooled sensitivity of 87%[9]; additionally, a recent systemic review of ten high-quality studies showed a pooled sensitivity and specificity of 94% and 95%, respectively[10]. When compared to CT-guided biopsy and endoscopic retrograde cholangiopancreatography (ERCP) with brush cytology, EUS-FNA has a distinct advantage. ERCP brush cytology sensitivity is quite low ranging from 30% to 85%[11]. CT-guided biopsy is a more invasive procedure than EUS-FNA and has a lower diagnostic yield. CT guided biopsy also carries the risk of peritoneal seeding, with one retrospective study showing rates as high as 16.3% compared to 2.2% with EUS-FNA[12]. Currently more centers are performing EUS-FNA so there may be a wide range of diagnostic yield in pancreatic masses, but the general trend over the last 10 years is towards higher sensitivity and specificity for pancreatic masses[9].

OPTIMIZING EUS-FNA OF PANCREATIC MASSES

Much of the research in EUS-FNA has focused on optimizing diagnostic yield for pancreatic masses. Multiple aspects of the procedure have been studied including cytopathologist involvement, needle size, providing suctioning and experience of endoscopist. The current data regarding optimization of EUS-FNA results will be reviewed below.

Studies have shown that the total number of EUS-FNA performed within a facility have been linked to higher diagnostic yield. Additionally, the availability of rapid on-site cytopathology evaluation (ROSE) evaluation also significantly increased diagnostic yield of EUS-FNA[13,14]. ROSE has become much more common in practice. All studies to date have shown that ROSE improves diagnostic yield for EUS-FNA and reduces the need for more passes and duration of the procedure[15-17]. An EUS-FNA study of 182 patients showed that with ROSE there was a significantly lower number of inadequate samples (1% *vs* 12.6%) and a much higher diagnostic sensitivity (96.2% *vs* 78.2%)[18].

Cytopathologist availability may be difficult and costly; many institutions do not have a cytopathologist readily available to come to endoscopy suites. Two studies have shown that having cytopathologist

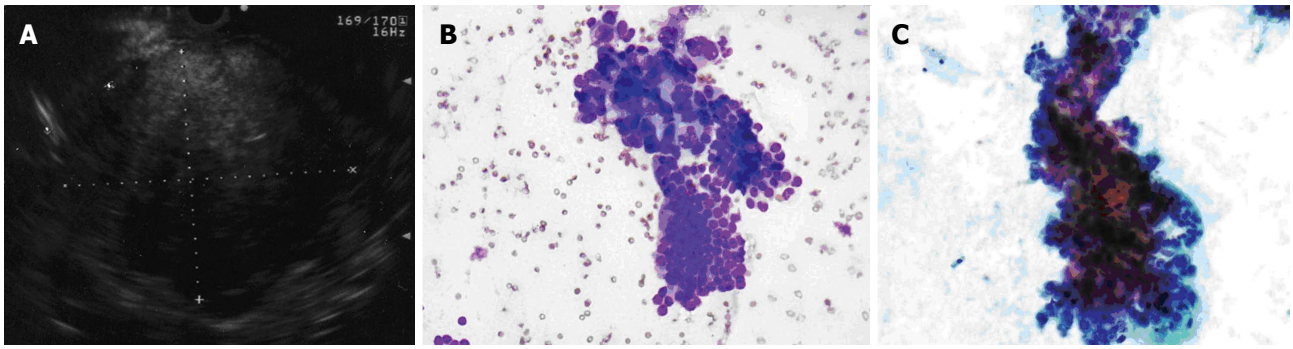

Figure 1 Pancreatic adenocarcinoma. A: Endoscopic ultrasound image demonstrating a large pancreatic adenocarcinoma; B: Pancreatic adenocarcinoma. A crowded group of large, pleomorphic ductal cells with irregular hyperchromatic nuclei and prominent anisocytosis. These contrast well with an orderly sheet of benign ductal epithelial cells with round, uniform nuclei (bottom) (Diff-QuikTM stain, × 100); C: Similar in appearance malignant cells in a Papanicolaou-stained preparation (× 400).

available *via* telepathology for rapid review is as effective as when they are present in the room[19,20]. Further studies are looking at the impact of individual cytopathologists and cytology technicians on diagnostic yield. Recently it was shown that providing specific training to cytology technicians can dramatically impact their personal ability to confirm accuracy and diagnosis[21].

The use of optimal equipment for EUS-FNA, including optimal needle size, has been studied extensively. Most commonly 22 or 25 gauge needles are used in EUS-FNA of pancreatic masses. There have been three randomized control studies looking at 22 gauge *vs* 25 gauge needles. The overall trend of these studies was a slightly more favorable yield with the 25 gauge needle, however none showed a statistically significant difference[22-24].

Beyond choosing the appropriate needle size, different aspects of obtaining cytology including suctioning and stylet use have been studied. The role of suctioning in EUS-FNA has been studied with two randomized control trials showing no difference in diagnostic yield. One study did show higher cellularity with suctioning, however this did not lead to an increase in diagnostic accuracy[25,26]. Most experts agree that suction does not increase diagnostic yield, and in fact likely increases the amount of blood in specimens[27]. Use of stylet has also shown no benefit in improving diagnostic yield, with studies showing that it also increases the amount of blood thus leading to poorer samples[28,29].

There is a definite learning curve in performing EUS-FNA for pancreatic masses. As endoscopists perform more EUS-FNA, sensitivity rises[30]. The current ASGE guidelines recommend 25 supervised EUS-FNA for the diagnosis of pancreatic adenocarcinoma, however literature supports more experience. It has been shown that rates of complications and number of passes needed also decrease with more experience. This study looked specifically at the performance of one endoscopist over the course of the first 300 EUS-FNAs, showing improved performance when comparing the last 100 procedures performed to the first 100[31].

NON-ADENOCARCINOMA MASSES

Pancreatic adenocarcinoma is the most common pancreatic mass lesion, however approximately 10%-15% masses are due to other lesions including cystic neoplasms and neuroendocrine tumors[32]. Thus, getting an accurate diagnosis is important to devise an appropriate management plan. Recently, primary non-adenocarcinoma of the pancreas was found in 25% of EUS-FNA of pancreatic masses[33]. Neuroendocrine tumors comprised 37.5% of the primary non-adenocarcinomas of the pancreas while mucinous neoplasms with mixed cystic/solid components made up 25%. In this study, masses in the tail of the pancreas were more commonly primary non-adenocarcinoma of the pancreas, and these masses were less likely to have vascular invasion or malignant lymphadenopathy when compared to adenocarcinoma[33]. Primary non-adenocarcinoma of the pancreas is often difficult to differentiate from adenocarcinoma with EUS alone. Cytopathology becomes more useful in these cases. The differential diagnosis for pancreatic masses should include not only adenocarcinoma but also neuroendocrine tumors, lymphoma, and metastatic disease.

NEUROENDOCRINE TUMORS

Neuroendocrine tumors of the pancreas are most commonly sporadic but some arise in context of inherited genetic syndromes, including multiple endocrine neoplasia type 1 and 2. Pancreatic neuroendocrine tumors are non-functional 40%-91% of time; the most common functioning tumors are insulinomas followed by glucagonomas, gastrinomas (Zollinger-Ellison syndrome) and somatostatinomas[34]. Some studies have shown that EUS-FNA is effective for obtaining preoperative determination of Ki-67 expression, which is an important prognostic factor for grading pancreatic endocrine tumors[35]. EUS-FNA is highly accurate for neuroendocrine tumors with sensitivity above 90%;

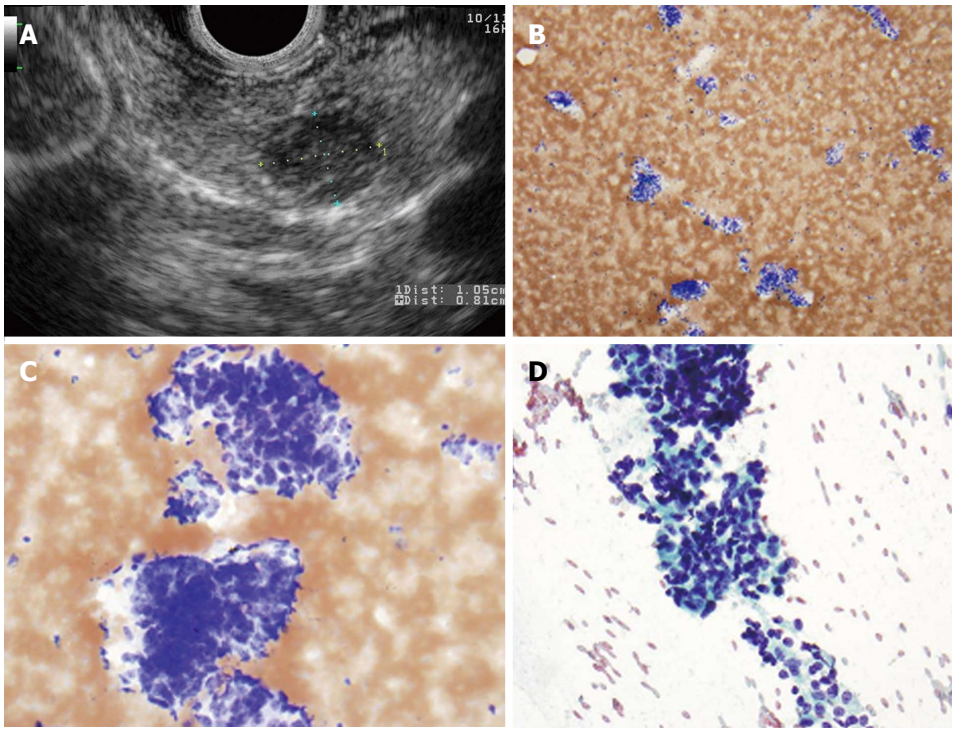

Figure 2 Pancreatic neuroendocrine neoplasm. A: Endoscopic ultrasound image showing a 9 mm × 10 mm neuroendocrine tumor (insulinoma); B: Low-power view shows a cellular aspirate composed of clusters of uniform cells (Diff-QuikTM stain, × 100); C: High power view shows uniform cells with high N:C ratios and coarse chromatin (Diff-QuikTM stain, × 400); D: Papanicolaou stain highlights coarse, evenly distributed chromatin (× 400).

thus it is helpful for making a diagnosis[35,36]. Typical EUS imaging of a neuroendocrine tumor and cytologic appearance of the tumor cells are presented in Figure 2.

LYMPHOMA

Primary pancreatic lymphoma is rare, comprising only 0.5% of all pancreatic masses[37]. In one study of EUS-FNA, lymphoma made up to 8% of the non-adenocarcinoma masses[33]. Most pancreatic lymphomas are non-Hodgkin lymphomas. Making an accurate diagnosis of lymphoma is important as treatment is generally chemotherapy and/or radiation as opposed to adenocarcinoma which is most often managed by surgery[37]. EUS-FNA has become more commonly used in the diagnosis of pancreatic lymphoma. Pancreatic lymphomas are less likely to present with jaundice. The addition of flow cytometry has greatly improved lymphoma diagnosis compared to cytology alone[38]. Figure 3 represents cytology from pancreatic follicular lymphoma showing a cellular aspirate composed of relatively monotonous in appearance lymphocytes with mild atypia.

PANCREATIC GASTROINTESTINAL STROMAL TUMOR

Primary extra-gastrointestinal stromal tumor arising in the pancreas is exceedingly rare. There have been 21 cases reported in the English literature in the last 10 years. The diagnosis of gastrointestinal stromal tumor (GIST) is based on histological, immunohistochemical, and molecular features. Microscopically the tumor usually consists of spindle and/or epithelioid cells typically arranged in fascicles or nests. GIST can often have the appearance of neuroendocrine tumors on EUS (Figure 4) thus an addition of EUS-FNA is highly valuable for differentiating these tumor types[39]. Figure 5 represents cytology from a primary pancreatic GIST tumor. Immunoistochemical positivity of CD117 confirms the diagnosis of GIST (Figure 6).

METASTATIC DISEASE

Metastatic disease to the pancreas is uncommon. The most common metastatic disease found with EUS-FNA includes renal cell carcinoma, melanoma and small cell lung cancer with renal cell carcinoma being the most common[33,40,41]. Other tumors metastatic to pancreas include papillary serous carcinoma (Figure 7), breast cancer, and rarely, sarcoma. EUS-FNA may be helpful in making these rare diagnoses.

NON-DIAGNOSTIC SAMPLES

Despite pancreatic adenocarcinoma being the most common mass of the pancreas, the above examples highlight the broad differential that exists with a pancreatic mass. It also highlights the importance of tissue diagnosis especially when diagnosis is not clear. While EUS-FNA remains the procedure of choice for

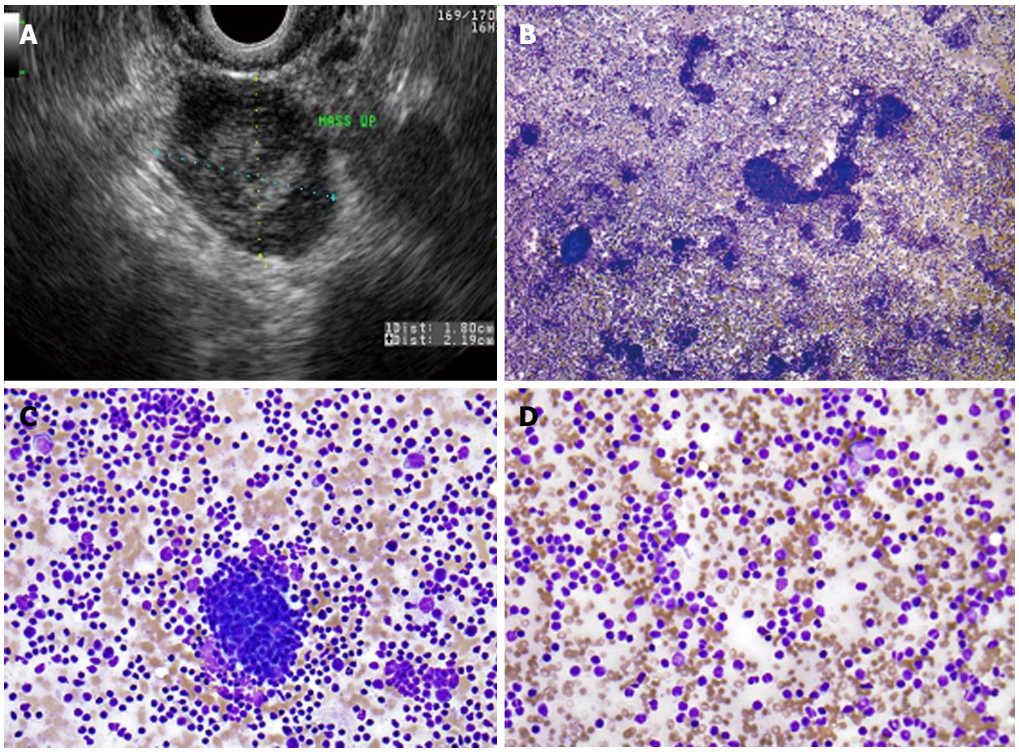

Figure 3 Primary pancreatic lymphoma. A: Endoscopic ultrasound demonstrating a 1.8 cm × 2.2 cm lymphoma in the uncinate process of the pancreas; B: Low-power view showing a very cellular aspirate composed of discohesive lymphoid cells (Diff-QuikTM stain, × 100); C: High-power view showing an admixture of mature lymphocytes of various sizes with no more than a minimal atypia; lymphoid aggregates resembling a germinal center are also present (bottom); D: Small mature lymphocytes with cleaved and irregular nuclei raising suspicion for a mature B-cell lymhoma. (Diff-QuikTM stain, × 400).

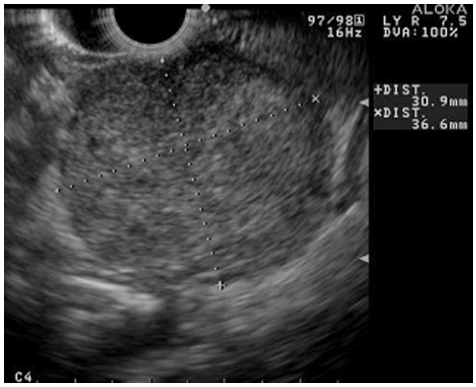

Figure 4 Endoscopic ultrasound image of large, 3.5 cm × 4.4 cm, round, hypoechoic, heterogenous mass lesion arising from the tail of the pancreas.

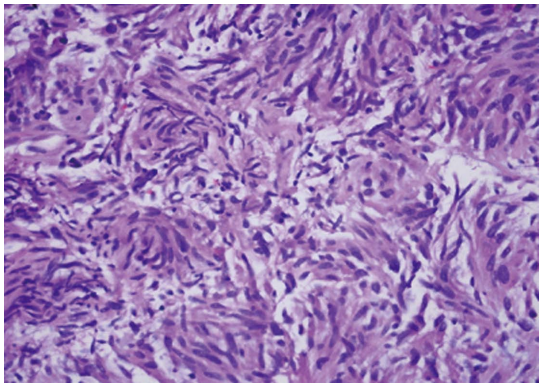

Figure 5 Cytology from a primary pancreatic gastrointestinal stromal tumor.

obtaining tissue from pancreas lesions, non-diagnostic samples are not uncommon. Determining what to do when FNA is non-diagnostic is difficult. Multiple studies have shown the benefit of repeat EUS-FNA with high diagnostic yield rates of 61% to 84%[42-44]. Given this data, many authors recommend repeat EUS-FNA when providers are faced with a non-diagnostic sample.

PANCREATIC NEOPLASMS-CYSTIC LESIONS

EUS-FNA plays a vital role in the examination of pancreatic cystic lesions. Pancreatic cysts are quite common with incidental cysts being reported in range of 2.6%-13.6% depending on imaging modality used[45,46]. In one autopsy study cysts occurred in 24.3% of patients[47]. The true incidence of neoplastic pancreatic cysts is difficult to determine. Deciding which pancreatic cysts require EUS-FNA for evaluation is one of the first steps in management. With advances and ease of EUS-FNA, it would be tempting for endoscopists to perform FNA on all lesions referred to them; however there are certain attributes on imaging which may help to avoid FNA altogether. Magnetic resonance imaging (MRI) and CT are valuable in assessing cystic size and determining if cystic lesions have worrisome findings

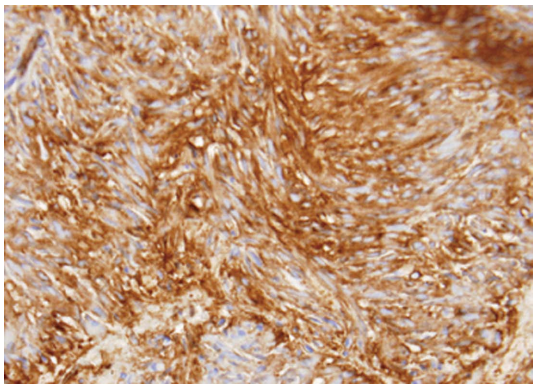

Figure 6 Pancreatic gastrointestinal stromal tumor, cytology demonstrates a spindle cell neoplasm with moderate nuclear pleomorphism which stains strongly positive for CD117 and negative for desmin, consistent with a gastrointestinal stromal tumor arising from the pancreas. (Courtesy of Rashmi Agni, University of Wisconsin Department of Pathology and Laboratory Medicine).

such as connection with the pancreatic main duct. MRI has a distinct advantage over CT in visualizing fluid, particularly in T2 weighted series[46]. EUS alone has a particular advantage over other imaging modalities for evaluation of cysts due to the close proximity of lesions. EUS is particularly good at examining cyst morphology including size location, internal structural features, wall thickness, the presence of calcifications and ductal communication.

Generally cystic lesions are divided into two categories: neoplastic cystic tumors and non-neoplastic cystic tumors. Neoplastic cystic tumors include mucinous cystic neoplasm (MCN), intraductal papillary-mucinous neoplasm (IPMN), and serous cystic neoplasm (SCN). Morphologic features are different for each cyst type.

SCNs, often called microcystic adenoma or glycogen-rich cystadenoma, are generally considered benign lesions as they have been associated with only a few cases of malignant conversion. On imaging, SCNs often have a honeycomb appearance. A central stellate scar is pathognomonic for SCN. There tend to be thin internal septa that are hypervascular on Doppler. Around 10% of SCNs are unilocular without an obvious microcystic component[48,49].

MCNs are found almost exclusively in the distal pancreas. They tend to occur in middle-aged women and generally considered to have a low malignant potential[50]. MCNs are characterized by two distinct histologic components: an inner epithelial layer composed of tall mucin-secreting cells, and a densely cellular ovarian-type stroma[50]. On imaging, MCNs are multiloculated cysts with a visible cystic wall. Peripheral calcification (egg shell calcification) can be seen in 10%-25% of MCNs and help to differentiate them from SCN. It is not always possible to determine lesions to be MCN on imaging alone thus FNA can be helpful. Due to malignant potential, most MCNs are removed surgically. Lesions less than 4 cm have low malignant potential, and in elderly patients who are not strong surgical candidates, these lesions can be observed[50]. Differentiating MCN from mucinous cystadenocarcinoma (Figure 8) by imaging alone is difficult; cytology and fluid analysis are both helpful in differentiating the two.

IPMNs were first recognized in 1982 and since then these cysts are commonly seen incidentally on cross sectional imaging. IPMN can appear as a cyst or a cluster of cysts in the uncinate process (Figure 9). IPMNs are generally defined as intraductal epithelial neoplasms of mucin-producing cells of the main duct or side branches[51]. Main duct IPMNs can cause dilation of the pancreatic duct up often > 5 cm; and have higher malignant potential thus are generally managed surgically[52]. Main duct IPMNs can create the classic "fish mouth papilla" due to the presence of mucin within the main duct (Figure 10).

Despite the advances of EUS in visualizing cystic lesions, EUS alone is often not enough in determining if malignancy is present. The addition of cystic fluid analysis further helps differentiate cysts. Currently, measurement of amylase and carcino-embryonic antigen (CEA) are the most routinely used in clinical practice. Amylase is often used in differentiating cystic neoplasms from pseudocysts, with amylase < 250 U/L being highly specific for SCN and MCNS (98%). In a review of 12 studies, the median values of amylase in pseudocysts, SCN, MCN and mucinous cystadenocarcinoma were 11000, 250, 8000 and 150 IU/L, respectively[53].

Multiple tumor markers have been studied to help differentiate mucinous neoplasms from non-mucinous neoplasms. These markers include CEA, CA 19-9, CA 72-4 and CA-125; ultimately CEA was determined to be the most useful in this setting[53]. A cut off of 192 ng/mL for CEA was first demonstrated by Brugge *et al*[54] as providing the greatest area under the curve (0.79) for differentiating mucinous *vs* nonmucinous cystic lesions. Additionally, a CEA > 800 ng/mL has been shown to be 79% accurate for mucinous lesions (MCN or mucinous cystadenocarcinoma)[53]. Higher CEA levels are more often associated with malignant lesions. Cyst fluid cytology can also be helpful in determining if there is an underlying mucinous cystadenocarcinoma although sensitivity is not high (sensitivity of 48% for malignant cystic lesions)[53]. Brugge *et al*[54] showed the sensitivity of cytology for MCN to be as low as 34.5% with a specificity of 83%. Figure 11A and B represents cytology from a mucinous neoplasm; mucinous cystic neoplasm and intraductal papillary mucinous neoplasm are indistinguishable cytologically. Most centers combine amylase and CEA measurements and fluid cytology to establish the diagnosis of mucinous cystic neoplasm.

Recently DNA analysis and k-ras mutation have also been shown to be useful to determine pancreatic cyst type and the presence of malignancy. In the PANDA

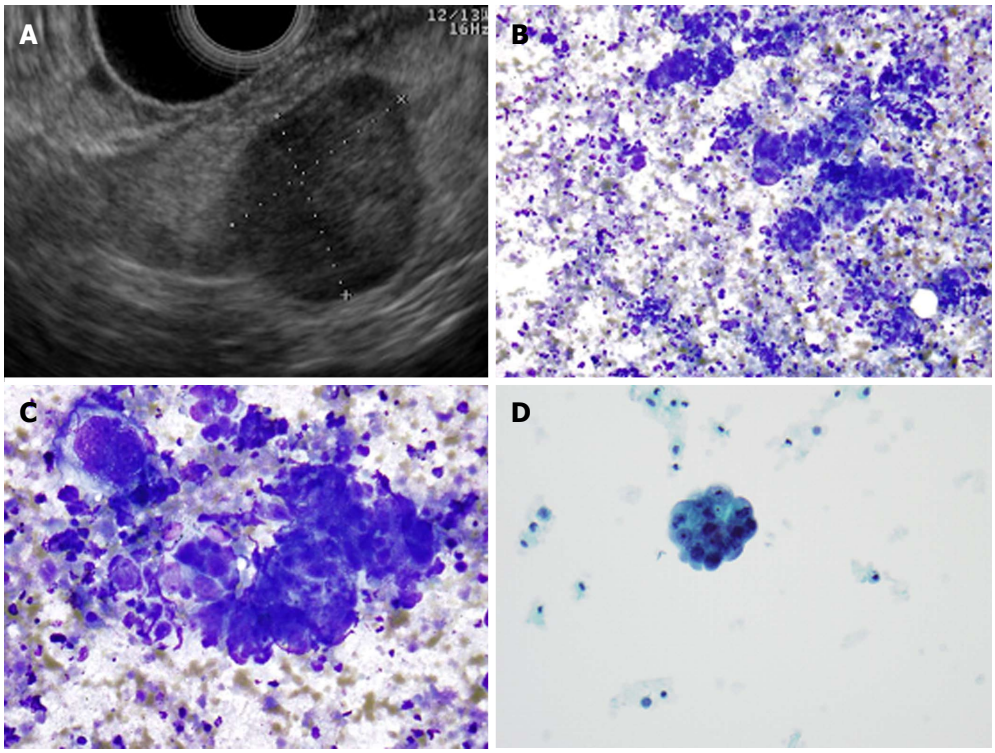

Figure 7 Metastatic high-grade serous carcinoma of the ovary. A: Endoscopic ultrasound image of a metastatic high-grade serous carcinoma of the ovary; B: Low-power view showing a cellular aspirate with a necrotic background (Diff-QuikTM stain, × 100); C: High-power view showing groups of malignant cells with large nuclei and prominent nucleoli. These cells are difficult to distinguish from a primary pancreatic ductal adenocarcinoma; however, necrotic background is not common in a primary tumor (Diff-QuikTM stain, × 400); D: Papanicolaou stain showing a cannon ball shaped group of malignant cells with large, round nuclei and prominent nucleoli, characteristic of serous ovarian carcinoma (× 400).

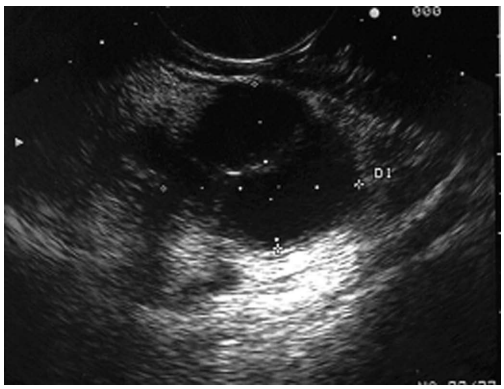

Figure 8 Endoscopic ultrasound image demonstrating a cystadenocarcinoma.

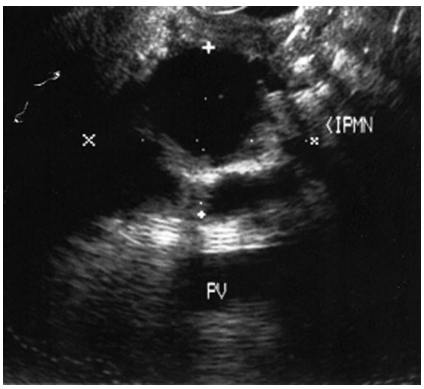

Figure 9 Endoscopic ultrasound image demonstrating an intraductal papillary-mucinous neoplasm.

study, using the criteria of a high amplitude k-ras mutation followed by allelic loss showed a maximum specificity of 96% for malignancy. Additionally, this study was able to demonstrate that all malignant cysts that were negative by conventional cytologic evaluation could be diagnosed as malignant by using DNA analysis[55]. Recently two studies have used microRNAs (miRNA) with good success differentiating pancreatic cysts[56,57] with one study showing a panel of miRNA being able to distinguish MCN from SCN, branch duct-IPMN, main duct-IPMN, and adenocarcinoma with a sensitivity and specificity of 100%.

COMPLICATIONS

One of the biggest concerns when considering aspiration of a cystic lesion is the introduction of infection. Although rare, multiple aspirations increase this risk. The current guidelines recommend one aspiration for cysts to minimize this risk, followed by 48 h of antibiotic therapy[58]. Another complication when aspirating cysts is intracystic hemorrhage, also rare, endoscopists should be aware of this complication. Most patients with intracystic hemorrhage can still be managed on an outpatient basis with antibiotics[59].

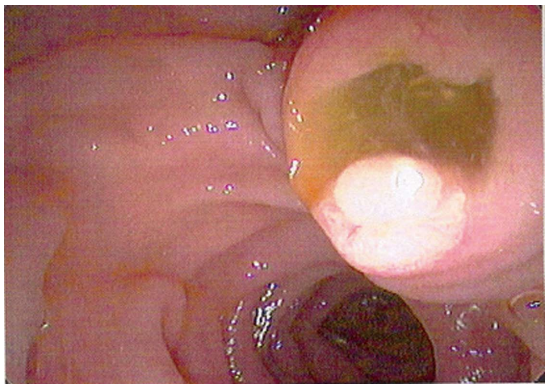

Figure 10 Endoscopic view of "fish mouth papilla" due to the presence of mucin within the main duct.

The overall rate of complication with EUS alone or EUS-FNA is quite low. Complications other than infection and bleeding include perforation and the unique risk of pancreatitis. Perforation with EUS is rather rare. In a survey study, cervical esophageal perforation occurred in only 16 of 43852 reported upper EUS procedures at a frequency of 0.03%. Most of these patients were elderly, and most of the EUS procedures were done by trainees or personal with limited experience (less than 1 year)[60]. Experts agree that EUS is associated with a similar rate of perforations compared with standard endoscopy[58].

Pancreatitis is a unique complication associated with EUS-FNA for aspiration of both masses and cysts. Reported rates of pancreatitis associated with pancreatic EUS-FNA range from 0% to 2%[58]. In one study where two cases of pancreatitis were reported, both were mild and both patients had a recent history of pancreatitis. Authors concluded a history of recent pancreatitis could be potential risk factor for procedure-induced pancreatitis[61].

CONCLUSIONS

EUS-FNA is a safe and effective procedure for the evaluation of solid and cystic lesions of the pancreas. Ways to optimize diagnostic yield for pancreatic masses continue to be investigated; overall the availability of ROSE seems to have the biggest impact on results. Optimal needle size appears to be 22 or 25 gauge, while suctioning and stylet do not have a positive impact on performance. EUS-FNA is helpful in differentiating adenocarcinoma from other more rare lesions including neuroendocrine tumors, lymphoma and metastatic lesions, and whenever diagnostic uncertainty exists; EUS-FNA should be pursued. In the evaluation of cystic lesions, EUS-FNA is a safe and effective way of classifying lesions. Measurement of cystic fluid CEA, amylase and cytology remain valuable in routine aspiration. Studies on DNA markers show promise in optimizing the detection of cystic malignancies, although currently routine use of DNA markers is not recommended. Whether it is evaluating a solid or cystic pancreatic lesion, EUS-FNA plays a pivotal role, as technology improves this role will continue to grow.

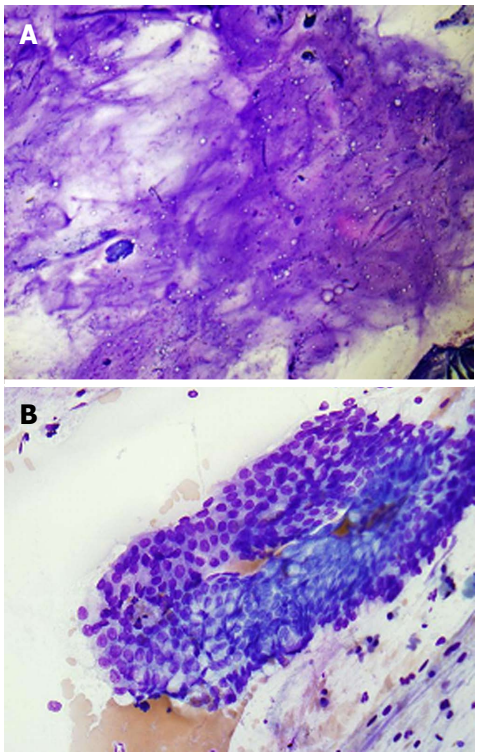

Figure 11 Pancreatic mucinous neoplasm. A: Low-power view of pancreatic mucinous neoplasm showing copious thick, colloid-like mucin (Diff-QuikTM stain, × 100); B: High-power view of pancreatic mucinous neoplasm showing sheets of only mildly atypical columnar cells containing intracytoplasmic mucin; these cells are very difficult to distinguish from benign gastric or duodenal epithelium (Diff-QuikTM stain, × 400).

REFERENCES

1 **Helmstaedter L**, Riemann JF. Pancreatic cancer--EUS and early diagnosis. *Langenbecks Arch Surg* 2008; **393**: 923-927 [PMID: 18247044 DOI: 10.1007/s00423-007-0275-1]
2 **Jemal A**, Siegel R, Ward E, Hao Y, Xu J, Thun MJ. Cancer statistics, 2009. *CA Cancer J Clin* 2009; **59**: 225-249 [PMID: 19474385 DOI: 10.3322/caac.20006]
3 **Volmar KE**, Vollmer RT, Jowell PS, Nelson RC, Xie HB. Pancreatic FNA in 1000 cases: a comparison of imaging modalities. *Gastrointest Endosc* 2005; **61**: 854-861 [PMID: 15933687]
4 **Dewitt J**, Devereaux BM, Lehman GA, Sherman S, Imperiale TF. Comparison of endoscopic ultrasound and computed tomography for the preoperative evaluation of pancreatic cancer: a systematic review. *Clin Gastroenterol Hepatol* 2006; **4**: 717-725; quiz 664 [PMID: 16675307 DOI: 10.1016/j.cgh.2006.02.020]
5 **Vilmann P**, Jacobsen GK, Henriksen FW, Hancke S. Endoscopic ultrasonography with guided fine needle aspiration biopsy in pancreatic disease. *Gastrointest Endosc* 1992; **38**: 172-173 [PMID: 1568614]
6 **Afify AM**, al-Khafaji BM, Kim B, Scheiman JM. Endoscopic ultrasound-guided fine needle aspiration of the pancreas. Diagnostic utility and accuracy. *Acta Cytol* 2003; **47**: 341-348 [PMID: 12789912]
7 **Turner BG**, Cizginer S, Agarwal D, Yang J, Pitman MB, Brugge WR. Diagnosis of pancreatic neoplasia with EUS and FNA: a report of accuracy. *Gastrointest Endosc* 2010; **71**: 91-98 [PMID: 19846087 DOI: 10.1016/j.gie.2009.06.017]
8 **Eloubeidi MA**, Varadarajulu S, Desai S, Shirley R, Heslin MJ, Mehra M, Arnoletti JP, Eltoum I, Wilcox CM, Vickers SM. A

prospective evaluation of an algorithm incorporating routine preoperative endoscopic ultrasound-guided fine needle aspiration in suspected pancreatic cancer. *J Gastrointest Surg* 2007; **11**: 813-819 [PMID: 17440790 DOI: 10.1007/s11605-007-0151-x]

9 **Puli SR**, Bechtold ML, Buxbaum JL, Eloubeidi MA. How good is endoscopic ultrasound-guided fine-needle aspiration in diagnosing the correct etiology for a solid pancreatic mass?: A meta-analysis and systematic review. *Pancreas* 2013; **42**: 20-26 [PMID: 23254913 DOI: 10.1097/MPA.0b013e3182546e79]

10 **Chen J**, Yang R, Lu Y, Xia Y, Zhou H. Diagnostic accuracy of endoscopic ultrasound-guided fine-needle aspiration for solid pancreatic lesion: a systematic review. *J Cancer Res Clin Oncol* 2012; **138**: 1433-1441 [PMID: 22752601 DOI: 10.1007/s00432-012-1268-1]

11 **Athanassiadou P**, Grapsa D. Value of endoscopic retrograde cholangiopancreatography-guided brushings in preoperative assessment of pancreaticobiliary strictures: what's new? *Acta Cytol* 2008; **52**: 24-34 [PMID: 18323272]

12 **Micames C**, Jowell PS, White R, Paulson E, Nelson R, Morse M, Hurwitz H, Pappas T, Tyler D, McGrath K. Lower frequency of peritoneal carcinomatosis in patients with pancreatic cancer diagnosed by EUS-guided FNA vs. percutaneous FNA. *Gastrointest Endosc* 2003; **58**: 690-695 [PMID: 14595302]

13 **Dumonceau JM**, Koessler T, van Hooft JE, Fockens P. Endoscopic ultrasonography-guided fine needle aspiration: Relatively low sensitivity in the endosonographer population. *World J Gastroenterol* 2012; **18**: 2357-2363 [PMID: 22654426 DOI: 10.3748/wjg.v18.i19.2357]

14 **Ecka RS**, Sharma M. Rapid on-site evaluation of EUS-FNA by cytopathologist: an experience of a tertiary hospital. *Diagn Cytopathol* 2013; **41**: 1075-1080 [PMID: 24166808 DOI: 10.1002/dc.23047]

15 **Pellisé Urquiza M**, Fernández-Esparrach G, Solé M, Colomo L, Castells A, Llach J, Mata A, Bordas JM, Piqué JM, Ginès A. Endoscopic ultrasound-guided fine needle aspiration: predictive factors of accurate diagnosis and cost-minimization analysis of on-site pathologist. *Gastroenterol Hepatol* 2007; **30**: 319-324 [PMID: 17662213]

16 **Savoy AD**, Raimondo M, Woodward TA, Noh K, Pungpapong S, Jones AD, Crook J, Wallace MB. Can endosonographers evaluate on-site cytologic adequacy? A comparison with cytotechnologists. *Gastrointest Endosc* 2007; **65**: 953-957 [PMID: 17531627 DOI: 10.1016/j.gie.2006.11.014]

17 **Klapman JB**, Logrono R, Dye CE, Waxman I. Clinical impact of on-site cytopathology interpretation on endoscopic ultrasound-guided fine needle aspiration. *Am J Gastroenterol* 2003; **98**: 1289-1294 [PMID: 12818271 DOI: 10.1111/j.1572-0241.2003.07472.x]

18 **Iglesias-Garcia J**, Dominguez-Munoz JE, Abdulkader I, Larino-Noia J, Eugenyeva E, Lozano-Leon A, Forteza-Vila J. Influence of on-site cytopathology evaluation on the diagnostic accuracy of endoscopic ultrasound-guided fine needle aspiration (EUS-FNA) of solid pancreatic masses. *Am J Gastroenterol* 2011; **106**: 1705-1710 [PMID: 21483464 DOI: 10.1038/ajg.2011.119]

19 **Buxbaum JL**, Eloubeidi MA, Lane CJ, Varadarajulu S, Linder A, Crowe AE, Jhala D, Jhala NC, Crowe DR, Eltoum IA. Dynamic telecytology compares favorably to rapid onsite evaluation of endoscopic ultrasound fine needle aspirates. *Dig Dis Sci* 2012; **57**: 3092-3097 [PMID: 22729624 DOI: 10.1007/s10620-012-2275-4]

20 **Khurana KK**, Rong R, Wang D, Roy A. Dynamic telecytopathology for on-site preliminary diagnosis of endoscopic ultrasound-guided fine needle aspiration of pancreatic masses. *J Telemed Telecare* 2012; **18**: 253-259 [PMID: 22302762 DOI: 10.1258/jtt.2011.110706]

21 **Petrone MC**, Arcidiacono PG, Carrara S, Mezzi G, Doglioni C, Testoni PA. Does cytotechnician training influence the accuracy of EUS-guided fine-needle aspiration of pancreatic masses? *Dig Liver Dis* 2012; **44**: 311-314 [PMID: 22226546 DOI: 10.1016/j.dld.2011.12.001]

22 **Camellini L**, Carlinfante G, Azzolini F, Iori V, Cavina M, Sereni G, Decembrino F, Gallo C, Tamagnini I, Valli R, Piana S, Campari C, Gardini G, Sassatelli R. A randomized clinical trial comparing 22G and 25G needles in endoscopic ultrasound-guided fine-needle aspiration of solid lesions. *Endoscopy* 2011; **43**: 709-715 [PMID: 21611946 DOI: 10.1055/s-0030-1256482]

23 **Fabbri C**, Polifemo AM, Luigiano C, Cennamo V, Baccarini P, Collina G, Fornelli A, Macchia S, Zanini N, Jovine E, Fiscaletti M, Alibrandi A, D'Imperio N. Endoscopic ultrasound-guided fine needle aspiration with 22- and 25-gauge needles in solid pancreatic masses: a prospective comparative study with randomisation of needle sequence. *Dig Liver Dis* 2011; **43**: 647-652 [PMID: 21592873 DOI: 10.1016/j.dld.2011.04.005]

24 **Siddiqui UD**, Rossi F, Rosenthal LS, Padda MS, Murali-Dharan V, Aslanian HR. EUS-guided FNA of solid pancreatic masses: a prospective, randomized trial comparing 22-gauge and 25-gauge needles. *Gastrointest Endosc* 2009; **70**: 1093-1097 [PMID: 19640524 DOI: 10.1016/j.gie.2009.05.037]

25 **Wallace MB**, Kennedy T, Durkalski V, Eloubeidi MA, Etamad R, Matsuda K, Lewin D, Van Velse A, Hennesey W, Hawes RH, Hoffman BJ. Randomized controlled trial of EUS-guided fine needle aspiration techniques for the detection of malignant lymphadenopathy. *Gastrointest Endosc* 2001; **54**: 441-447 [PMID: 11577304]

26 **Puri R**, Vilmann P, Săftoiu A, Skov BG, Linnemann D, Hassan H, Garcia ES, Gorunescu F. Randomized controlled trial of endoscopic ultrasound-guided fine-needle sampling with or without suction for better cytological diagnosis. *Scand J Gastroenterol* 2009; **44**: 499-504 [PMID: 19117242 DOI: 10.1080/00365520802647392]

27 **Varadarajulu S**, Fockens P, Hawes RH. Best practices in endoscopic ultrasound-guided fine-needle aspiration. *Clin Gastroenterol Hepatol* 2012; **10**: 697-703 [PMID: 22475740 DOI: 10.1016/j.cgh.2012.03.017]

28 **Sahai AV**, Paquin SC, Gariépy G. A prospective comparison of endoscopic ultrasound-guided fine needle aspiration results obtained in the same lesion, with and without the needle stylet. *Endoscopy* 2010; **42**: 900-903 [PMID: 20725886 DOI: 10.1055/s-0030-1255676]

29 **Rastogi A**, Wani S, Gupta N, Singh V, Gaddam S, Reddymasu S, Ulusarac O, Fan F, Romanas M, Dennis KL, Sharma P, Bansal A, Oropeza-Vail M, Olyaee M. A prospective, single-blind, randomized, controlled trial of EUS-guided FNA with and without a stylet. *Gastrointest Endosc* 2011; **74**: 58-64 [PMID: 21514932 DOI: 10.1016/j.gie.2011.02.015]

30 **Mertz H**, Gautam S. The learning curve for EUS-guided FNA of pancreatic cancer. *Gastrointest Endosc* 2004; **59**: 33-37 [PMID: 14722544]

31 **Eloubeidi MA**, Tamhane A. EUS-guided FNA of solid pancreatic masses: a learning curve with 300 consecutive procedures. *Gastrointest Endosc* 2005; **61**: 700-708 [PMID: 15855975]

32 **Imaoka H**, Yamao K, Bhatia V, Shimizu Y, Yatabe Y, Koshikawa T, Kinoshita Y. Rare pancreatic neoplasms: the utility of endoscopic ultrasound-guided fine-needle aspiration-a large single center study. *J Gastroenterol* 2009; **44**: 146-153 [PMID: 19214677 DOI: 10.1007/s00535-008-2282-6]

33 **Gagovic V**, Spier BJ, DeLee RJ, Barancin C, Lindstrom M, Einstein M, Byrne S, Harter J, Agni R, Pfau PR, Frick TJ, Soni A, Gopal DV. Endoscopic ultrasound fine-needle aspiration characteristics of primary adenocarcinoma versus other malignant neoplasms of the pancreas. *Can J Gastroenterol* 2012; **26**: 691-696 [PMID: 23061060]

34 **Kulke MH**, Benson AB, Bergsland E, Berlin JD, Blaszkowsky LS, Choti MA, Clark OH, Doherty GM, Eason J, Emerson L, Engstrom PF, Goldner WS, Heslin MJ, Kandeel F, Kunz PL, Kuvshinoff BW, Moley JF, Pillarisetty VG, Saltz L, Schteingart DE, Shah MH, Shibata S, Strosberg JR, Vauthey JN, White R, Yao JC, Freedman-Cass DA, Dwyer MA. Neuroendocrine tumors. *J Natl Compr Canc Netw* 2012; **10**: 724-764 [PMID: 22679117]

35 **Larghi A**, Capurso G, Carnuccio A, Ricci R, Alfieri S, Galasso D, Lugli F, Bianchi A, Panzuto F, De Marinis L, Falconi M, Delle Fave G, Doglietto GB, Costamagna G, Rindi G. Ki-67 grading of nonfunctioning pancreatic neuroendocrine tumors on histologic samples obtained by EUS-guided fine-needle tissue acquisition: a

prospective study. *Gastrointest Endosc* 2012; **76**: 570-577 [PMID: 22898415 DOI: 10.1016/j.gie.2012.04.477]

36 **Unno J**, Kanno A, Masamune A, Kasajima A, Fujishima F, Ishida K, Hamada S, Kume K, Kikuta K, Hirota M, Motoi F, Unno M, Shimosegawa T. The usefulness of endoscopic ultrasound-guided fine-needle aspiration for the diagnosis of pancreatic neuroendocrine tumors based on the World Health Organization classification. *Scand J Gastroenterol* 2014; **49**: 1367-1374 [PMID: 25180490 DOI: 10.3109/00365521.2014.934909]

37 **Boni L**, Benevento A, Dionigi G, Cabrini L, Dionigi R. Primary pancreatic lymphoma. *Surg Endosc* 2002; **16**: 1107-1108 [PMID: 11984658 DOI: 10.1007/s00464-001-4247-1]

38 **Rossi ED**, Larghi A, Verna EC, Martini M, Galasso D, Carnuccio A, Larocca LM, Costamagna G, Fadda G. Endoscopic ultrasound-guided fine-needle aspiration with liquid-based cytologic preparation in the diagnosis of primary pancreatic lymphoma. *Pancreas* 2010; **39**: 1299-1302 [PMID: 20944491 DOI: 10.1097/MPA.0b013e3181dc694e]

39 **Beltrame V**, Gruppo M, Pastorelli D, Pizzi S, Merigliano S, Sperti C. Extra-gastrointestinal stromal tumor of the pancreas: case report and review of the literature. *World J Surg Oncol* 2014; **12**: 105 [PMID: 24755359 DOI: 10.1186/1477-7819-12-105]

40 **Volmar KE**, Jones CK, Xie HB. Metastases in the pancreas from nonhematologic neoplasms: report of 20 cases evaluated by fine-needle aspiration. *Diagn Cytopathol* 2004; **31**: 216-220 [PMID: 15452907 DOI: 10.1002/dc.20100]

41 **Minni F**, Casadei R, Perenze B, Greco VM, Marrano N, Margiotta A, Marrano D. Pancreatic metastases: observations of three cases and review of the literature. *Pancreatology* 2004; **4**: 509-520 [PMID: 15316227 DOI: 10.1159/000080248]

42 **Eloubeidi MA**, Varadarajulu S, Desai S, Wilcox CM. Value of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. *J Gastroenterol Hepatol* 2008; **23**: 567-570 [PMID: 18397485 DOI: 10.1111/j.1440-1746.2007.05119.x]

43 **DeWitt J**, McGreevy K, Sherman S, LeBlanc J. Utility of a repeated EUS at a tertiary-referral center. *Gastrointest Endosc* 2008; **67**: 610-619 [PMID: 18279866 DOI: 10.1016/j.gie.2007.09.037]

44 **Nicaud M**, Hou W, Collins D, Wagh MS, Chauhan S, Draganov PV. The utility of repeat endoscopic ultrasound-guided fine needle aspiration for suspected pancreatic cancer. *Gastroenterol Res Pract* 2010; **2010**: 268290 [PMID: 21234311 DOI: 10.1155/2010/268290]

45 **Laffan TA**, Horton KM, Klein AP, Berlanstein B, Siegelman SS, Kawamoto S, Johnson PT, Fishman EK, Hruban RH. Prevalence of unsuspected pancreatic cysts on MDCT. *AJR Am J Roentgenol* 2008; **191**: 802-807 [PMID: 18716113 DOI: 10.2214/AJR.07.3340]

46 **Lee KS**, Sekhar A, Rofsky NM, Pedrosa I. Prevalence of incidental pancreatic cysts in the adult population on MR imaging. *Am J Gastroenterol* 2010; **105**: 2079-2084 [PMID: 20354507 DOI: 10.1038/ajg.2010.122]

47 **Kimura W**, Nagai H, Kuroda A, Muto T, Esaki Y. Analysis of small cystic lesions of the pancreas. *Int J Pancreatol* 1995; **18**: 197-206 [PMID: 8708390 DOI: 10.1007/BF02784942]

48 **Kubo H**, Nakamura K, Itaba S, Yoshinaga S, Kinukawa N, Sadamoto Y, Ito T, Yonemasu H, Takayanagi R. Differential diagnosis of cystic tumors of the pancreas by endoscopic ultrasonography. *Endoscopy* 2009; **41**: 684-689 [PMID: 19670136 DOI: 10.1055/s-0029-1214952]

49 **But DY**, Poley JW. To fine needle aspiration or not? An endosonographer's approach to pancreatic cystic lesions. *Endosc Ultrasound* 2014; **3**: 82-90 [PMID: 24955337 DOI: 10.4103/2303-9027.124307]

50 **Crippa S**, Salvia R, Warshaw AL, Domínguez I, Bassi C, Falconi M, Thayer SP, Zamboni G, Lauwers GY, Mino-Kenudson M, Capelli P, Pederzoli P, Castillo CF. Mucinous cystic neoplasm of the pancreas is not an aggressive entity: lessons from 163 resected patients. *Ann Surg* 2008; **247**: 571-579 [PMID: 18362619 DOI: 10.1097/SLA.0b013e31811f4449]

51 **Cooper CL**, O'Toole SA, Kench JG. Classification, morphology and molecular pathology of premalignant lesions of the pancreas. *Pathology* 2013; **45**: 286-304 [PMID: 23442735 DOI: 10.1097/PAT.0b013e32835f2205]

52 **Salvia R**, Fernández-del Castillo C, Bassi C, Thayer SP, Falconi M, Mantovani W, Pederzoli P, Warshaw AL. Main-duct intraductal papillary mucinous neoplasms of the pancreas: clinical predictors of malignancy and long-term survival following resection. *Ann Surg* 2004; **239**: 678-685; discussion 685-687 [PMID: 15082972]

53 **van der Waaij LA**, van Dullemen HM, Porte RJ. Cyst fluid analysis in the differential diagnosis of pancreatic cystic lesions: a pooled analysis. *Gastrointest Endosc* 2005; **62**: 383-389 [PMID: 16111956]

54 **Brugge WR**, Lewandrowski K, Lee-Lewandrowski E, Centeno BA, Szydlo T, Regan S, del Castillo CF, Warshaw AL. Diagnosis of pancreatic cystic neoplasms: a report of the cooperative pancreatic cyst study. *Gastroenterology* 2004; **126**: 1330-1336 [PMID: 15131794]

55 **Khalid A**, Zahid M, Finkelstein SD, LeBlanc JK, Kaushik N, Ahmad N, Brugge WR, Edmundowicz SA, Hawes RH, McGrath KM. Pancreatic cyst fluid DNA analysis in evaluating pancreatic cysts: a report of the PANDA study. *Gastrointest Endosc* 2009; **69**: 1095-1102 [PMID: 19152896 DOI: 10.1016/j.gie.2008.07.033]

56 **Matthaei H**, Wylie D, Lloyd MB, Dal Molin M, Kemppainen J, Mayo SC, Wolfgang CL, Schulick RD, Langfield L, Andruss BF, Adai AT, Hruban RH, Szafranska-Schwarzbach AE, Maitra A. miRNA biomarkers in cyst fluid augment the diagnosis and management of pancreatic cysts. *Clin Cancer Res* 2012; **18**: 4713-4724 [PMID: 22723372 DOI: 10.1158/1078-0432.CCR-12-0035]

57 **Lee LS**, Szafranska-Schwarzbach AE, Wylie D, Doyle LA, Bellizzi AM, Kadiyala V, Suleiman S, Banks PA, Andruss BF, Conwell DL. Investigating MicroRNA Expression Profiles in Pancreatic Cystic Neoplasms. *Clin Transl Gastroenterol* 2014; **5**: e47 [PMID: 24476997 DOI: 10.1038/ctg.2013.18]

58 **Adler DG**, Jacobson BC, Davila RE, Hirota WK, Leighton JA, Qureshi WA, Rajan E, Zuckerman MJ, Fanelli RD, Baron TH, Faigel DO. ASGE guideline: complications of EUS. *Gastrointest Endosc* 2005; **61**: 8-12 [PMID: 15672049]

59 **Varadarajulu S**, Eloubeidi MA. Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas. *Gastrointest Endosc* 2004; **60**: 631-635 [PMID: 15472697]

60 **Das A**, Sivak MV, Chak A. Cervical esophageal perforation during EUS: a national survey. *Gastrointest Endosc* 2001; **53**: 599-602 [PMID: 11323585]

61 **Gress F**, Michael H, Gelrud D, Patel P, Gottlieb K, Singh F, Grendell J. EUS-guided fine-needle aspiration of the pancreas: evaluation of pancreatitis as a complication. *Gastrointest Endosc* 2002; **56**: 864-867 [PMID: 12447299 DOI: 10.1067/mge.2002.129602]

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REVIEW

Quality monitoring in colonoscopy: Time to act

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Abstract

Colonoscopy is the gold standard test for colorectal cancer screening. The primary advantage of colonoscopy as opposed to other screening modalities is the ability to provide therapy by removal of precancerous lesions at the time of detection. However, colonoscopy may miss clinically important neoplastic polyps. The value of colonoscopy in reducing incidence of colorectal cancer is dependent on many factors including, the patient, provider, and facility level. A high quality examination includes adequate bowel preparation, optimal colonoscopy technique, meticulous inspection during withdrawal, identification of subtle flat lesions, and complete polypectomy. Considerable variation among institutions and endoscopists has been reported in the literature. In attempt to diminish this disparity, various approaches have been advocated to improve the quality of colonoscopy. The overall impact of these interventions is not yet well defined. Implementing optimal education and training and subsequently analyzing the impact of these endeavors in improvement of quality will be essential to augment the utility of colonoscopy for the prevention of colorectal cancer.

Key words: Colonoscopy; Quality improvement; Cecal intubation rate; Adenoma detection rate

Core tip: Quality is a measure of actual performance compared to the defined standard as outlined by the medical community. Important quality measures in colonoscopy include informed consent, adequate bowel preparation, cecal intubation, withdrawal time, adenoma detection rate, appropriate screening and surveillance follow-up recommendations, and adverse events. The above quality measures could affect patient outcomes and therefore should be implemented and monitored regularly.

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INTRODUCTION

In 1998, the Institute of Medicine identified significant variations in practice, safety, and lack of accountability in healthcare, thereby highlighting the necessity of quality assurance[1]. Endoscopy is an important

modality in the diagnosis and management of digestive diseases. High quality endoscopy ensures that a patient receives an appropriately indicated procedure that is properly and effectively delivered with minimal risk. This satisfies the three parameters of quality outlined by the institute of medicine: safety, practice consistent with medical knowledge, and customization[2].

More than 14 million colonoscopies were performed in the United States in 2002, making it one of the most common procedures performed[3]. Colonoscopy is largely safe, effective, and well tolerated by patients with a major indication for colonoscopy of colorectal cancer screening and surveillance[4]. Colonoscopy is the only cancer-screening test that can both provide diagnosis and therapy as the adenoma-carcinoma sequence renders most colorectal cancer preventable by the identification and removal of adenomatous polyps[5].

The outcomes of health care are intimately linked to its quality. Many studies have shown that the quality of colonoscopy is directly linked to interval cancer, likely the result of missed lesions[6-8]. A high quality colonoscopy requires involvement of three different factors in order for the exam to be adequate: the patient (bowel preparation), the structure (facility, equipment), and the provider (competence). Each component is critically important to ensure that a malignancy or adenoma is detected. The efficacy to reduce colon cancer requires adequate visualization of the entire colon, diligence in examining the mucosa, and patient compliance. Based on the available literature and expert consensus, a joint task force of the American College of Gastroenterology (ACG) and the American Society for Gastrointestinal Endoscopy (ASGE) has proposed several quality measures to establish competence[9].

MEASURES OF QUALITY IN COLONOSCOPY

Pre-procedure

Prior to examination, potential risk factors that may increase complications should be identified. This includes use of antithrombotic therapy or significant medical comorbidities (heart disease, lung disease, renal failure). The American Society of Anesthesiology (ASA) classification is the most commonly employed system to identify patients at higher risk of developing endoscopy (and sedation) related complications. Those with a higher ASA class (Ⅲ or above) should be performed in a hospital as opposed to outpatient setting with consideration for anesthesia support.

Informed consent with discussion of risks, benefits, and alternatives should be discussed and documented. The risk of missed lesions may also be addressed, as no examination in medicine is infallible[10]. Tandem colonoscopy has demonstrated miss rates up to 27% for lesions ≤ 5 mm. Even for adenomas ≥ 1 cm, the miss rate has been calculated to be as high as 6%[11].

Quality of bowel preparation

Complete examination of the colon is feasible only with an adequate bowel preparation[12]. Inadequate bowel cleansing is associated with increased healthcare expenditure between 12% to 22% given altered recommendations for earlier follow-up[13]. Education on the importance of sufficient bowel cleansing should be addressed[14,15]. Patients with a lower socioeconomic status (and decreased health literacy)[16], history of constipation[17], diabetes[18], those on chronic narcotics, or prior history of inadequate bowel preparation have an increased probability for poor bowel preparation and should be recognized early. These patients should have modifications to their regimen such as following a low residue diet[19], and/or extended (two day) bowel preparation. Split-dose preparation yields improvement in bowel quality and should be universally applied to all patients[20].

Documentation of the bowel preparation is fundamental to the overall quality of the procedure[10]. The effectiveness of the bowel cleansing can be described with qualitative terms ranging from poor to excellent. An adequate preparation is defined by the ability to detect lesions ≥ 5 mm[21]. However, this format is not validated and subject to operator bias. Integration of a validated scale such as the Boston Bowel Preparation Scale[22] may reduce bias and aid in consistent and objective documentation.

Cecal intubation rate

Depth of maximal insertion should be documented in the text with support of endoscopic photographs. Cecal intubation with complete inspection of the cecal caput is imperative given the fact that many interval cancers occur in the proximal colon[23,24]. Two major landmarks confirm visualization of the cecum: the appendiceal orifice and ileocecal valve. A careful inspection of the cecal floor behind the ileocecal valve is very important. Current guidelines expect cecal intubation in ≥ 90% of cases overall and in ≥ 95% of screening colonoscopies[9]. In a large population based study, colonoscopy performed at an office or private setting in contrast to a hospital or academic institution was the strongest predictor for an incomplete examination[25].

Adenoma detection rate

Adenoma detection rate (ADR) is perhaps the most important quality metric of colonoscopy. It is defined as the percentage of colonoscopies in which at least one adenoma was identified and removed per colonoscopy. The prevalence of adenomas varies by age and gender. According to current recommended guidelines on quality indicators, among healthy asymptomatic patients undergoing screening colonoscopy, adenomas should be detected in ≥ 25% of men and ≥ 15% of women[9,26,27]. A landmark study by Kaminski *et al*[6]

Table 1 Colonoscopy screening and surveillance guidelines

Finding	Advised interval
No polyps/adenomas	10 yr
Single first degree relative with cancer (or adenomas) ⩾ 60 yr	10 yr (begin age 40)
Two or more first degree relatives with cancer (or adenomas) or one first degree relative diagnosed ⩽ 60 yr	5 yr (begin age 40)
Few (1-2), small tubular adenomas (< 1 cm)	5 yr
Advanced adenomatous lesions (> 1 cm or villous histology or high grade dysplasia) or > 3 adenomas	3 yr
Numerous (> 10) adenomas	Individualized approximately < 3 yr
HNPCC	1-2 yr (begin age 20-25)
Sessile adenomas > 2 cm, removed piecemeal	2-6 mo
Post cancer resection surveillance	Clear colon, then 1 yr, then 3 yr, then 5 yr

Joint guidelines from the American Cancer Society, the United States Multi-Society Task Force on Colorectal Cancer, and the American College of radiology. HNPCC: Hereditary nonpolyposis colorectal cancer.

validated that ADR is an independent predictor of the risk of interval cancer if ADR is less than 20%. Missed lesions have been hypothesized to be a principal contributor for interval cancer after colonoscopy[7], again highlighting the necessity of monitoring the ADR among individuals and the institutions.

The current benchmarks for ADR may be setting the standard too low. Multiple studies have shown much higher rates of adenoma detection[28-30] with significant variation among individual endoscopists. The endoscopist performing the procedure may have a stronger correlation with ADR more than previously identified traits such a patient's age or gender[31].

Unfortunately, despite the obvious strengths of this metric, it has some limitations. It is time intensive to calculate this measure because it requires manual integration of the endoscopy and pathology reports. ADR cannot be calculated in real-time as pathology findings are not available at the time of endoscopy. Hence, PDR has been advocated in some studies to be a surrogate for ADR[30,32]. The proposed benchmarks for PDR are 40% for men and 30% for women[33]. This method is certainly more convenient; however given high prevalence of hyperplastic polyps in the recto-sigmoid area and non-neoplastic polypectomy, there is risk for gaming the system by falsely inflating one's PDR.

The primary goal of screening and surveillance colonoscopy is detection and removal of all neoplastic colon polyps. However, ADR fails to distinguish endoscopists who identify more than one adenoma. Because every adenoma has risk of malignancy, endoscopists who are able to identify more adenomas per colonoscopy may be providing greater protection for colorectal cancer. Hence, novel scoring systems such as ADR-Plus[34] or mean adenoma per procedure (MAP)[35] have been proposed to provide greater discriminating ability among endoscopists. These models do provide more detail compared to ADR, however they carry the same burden of calculation, without clear benefit on outcomes.

Withdrawal time

Withdrawal time is the time at which the cecum is reached to when the colonoscope is withdrawn from the anus. The majority of detailed inspection of the colonic mucosa occurs during this phase. A landmark study by Barclay has demonstrated that there is increased detection of significant neoplastic lesions if the withdrawal time exceeds six minutes[36]. As a result, the United States Multi-Society Task Force on colorectal cancer recommends that withdrawal, excluding time for biopsy and polypectomy, should average between six to ten minutes[9]. Although this quality measure has been validated in some respects, it has significant limitations. For instance, an inefficient endoscopist may spend much longer than 6 min on withdrawal without complete visualization of the mucosa missing critical area between the haustral folds. A comprehensive examination includes careful examination of mucosa proximal to folds and flexures, better colonic distension, and washing of debris from the colon[37]. Ideally, rather than a quantitative requirement, focus should instead be on clear and effective visualization.

Screening and surveillance intervals

Screening and surveillance interval guidelines after colonoscopy have been published by the United States Multi-Society Task Force and are summarized in Table 1[38]. Compliance (with documentation) with these guidelines is an important quality measure. Adherence to guidelines is emphasized to decrease overuse of colonoscopy, which leads to increased exposure to potential procedural harm and drains resources that could be more effectively used. The efficiency and cost-effectiveness of colorectal cancer screening by colonoscopy is dependent upon the ability of the endoscopist to confidently follow established guidelines. For reasons unclear, studies have shown that postpolypectomy surveillance colonoscopy is frequently performed at shorter intervals[39]. Nonetheless, there are instances when repeat colonoscopy recommendations require an individualized approach based on clinical judgment that may differ than conventional guidelines; procedures performed at shorter or longer intervals than advised should be supported by written documentation. The variation discussed above underscores the need for

Table 2 Healthcare quality improvement projects[46]

Plan-Do-Study-Act (P-D-S-A)
Employs cycles of planning (P), small scale pilot testing (D), analysis of test results and lessons learned (S), followed by incorporation and maintenance of new processes into practice (A)
Useful when resources and time are limited and rapid stepwise improvement is desired
Lean method
Seeks to increase efficiency and reduce waste by excluding all processes, steps, or inputs that fail to contribute value to the end product
Useful when existing practices are deemed to be inefficient and cumbersome, with bottlenecks and excessive rework
Employs collaborative team input and process revision through value stream mapping
Six Sigma method
Intensively data driven approach to minimizing variation and thereby reducing defects or errors to improve quality
Use a cyclic approach referred to as the Define-Measure-Analyze-Improve-Control method
Employs more rigorous analytical tools and process control charting under the guidance of local experts
Especially appropriate for repetitive high frequency processes

quality monitoring of this aspect of colonoscopy.

Adverse events

Risk of complication is inherent to any procedure but endoscopists should be competent and proficient in their skills in order to maximize benefit while minimizing potential harm. Once a complication occurs however, it is important to document and monitor trends to ensure quality control. If rates exceed the established guidelines for an endoscopist or institution, investigation should be pursued to assess patient risk factors and procedure complexity to amend this situation.

Postpolypectomy bleeding is the common complication of a colonoscopy[40]. Typically, the risk of bleeding increases with increasing size of polyps, especially those located in the proximal colon. While the overall risk for postpolypectomy bleeding is around 1%[41,42], for polyps larger than 2 cm, bleeding rates are as high as 10%[40]. Bleeding can occur immediately or within 14 d of the procedure. Most bleeding stops spontaneously, however some patients require endoscopic evaluation. Therapy includes injection, cautery, or clipping. Data thus far is conflicting regarding the role of use of clips prophylactically[43,44].

Perforation is the most serious complication. The incidence of perforation due to colonoscopy is variable in the literature ranging between 1 in 500 to less than 1 in 1000[45]; about 5% of colonoscopic perforations are fatal[41,42]. During a diagnostic procedure, perforation can occur due to mechanical rupture with insertion primarily though the sigmoid colon, or may be secondary to barotrauma causing a rent in the cecum. Perforation can also occur with attempts to traverse a stricture. The greatest risk of perforation occurs with large polypectomies in the proximal colon where the walls are thinner.

THE PROCESS OF QUALITY IMPROVEMENT

Quality improvement refers to monitoring the performance, making continuous refinements, and then further assessing the outcomes of the interventions taken. As mentioned previously, there is marked variation in quality in colonoscopy. As a result, continuous quality improvement is essential to the success of colonoscopy.

Continuous tracking of performance for high volume procedures can be challenging. Monitoring quality metrics is time intensive and costly because it often requires data collection from multiple sources. Automated data collection *via* modern electronic endoscopic databases assist with this process, yet some deficiencies still exist. This includes integration of pathology findings to determine ADR, an important quality metric. Infrequent and delayed occurrences such as adverse events are also difficult to capture. Episodic audits of sequential procedures on a monthly, quarterly, or annual basis are one option to accruing representative data samples[46].

Methods used in quality improvement projects are outlined in Table 2. The essential elements include collecting information about standards, assembling data about current practices, identifying gaps in performance, executing a performance strategy, followed by reassessment, and further testing.

FUTURE AREAS FOR IMPROVEMENT

There are several patient-related, procedural-related, and endoscopist performance-related factors that account for inconsistency. In an editorial by Douglas Rex, he tabulated multiple questions to improve detection during colonoscopy[47]. Review of this editorial provides important hypotheses that warrant further investigation to improve quality.

Patient related improvements include health literacy on the benefits of colorectal cancer screening. Increasing awareness leads to increased attendance for screening examinations[48]. Better compliance with bowel cleansing will have innumerable benefits as poor bowel preparation prolongs procedure time, reduces detection of polyps, and increases likelihood of an incomplete procedure[14,49]. Education on quality markers will encourage patients to seek high quality

endoscopists.

One procedural related method that may improve the quality of colonoscopy includes the use of the water method. Rather than the use of air insufflation, which causes sharp angulations, water infusion results in the straightening of the sigmoid colon and other angulations easing insertion. Studies have shown aid with technically difficult colonoscopies[50], decreased pain, and lower requirements for sedation[51]. Future prospective studies are needed to assess the true value of water immersion. Another technique proposed is use of a cap-fitted colonoscopy. A cap may ease insertion by creating a distance between the instrument tip and colonic mucosa, thus facilitating navigation through angulation[52]. Data has shown shorter intubation times as well as avoidance of a failed or incomplete procedure with use of this method[53]. Cap-fitted colonoscopy may also assist with detection of lesions between the haustral folds though studies have had conflicting results in regards to overall adenoma detection[54-56].

Technology to aid with adenoma detection includes chromoendoscopy and the Third Eye Retroscope (Avantis Medical, Sunnyvale, California, United States). Chromoendoscopy has been advocated for use in order to identify subtle flat lesions[57]. Chromoendoscopy includes use of a colored dye that is sprayed into the colon or electronic light variation such as narrow band imaging (Olympus America, Center Valley, Pennsylvania, United States). Studies thus far have shown marginal benefit with only an improvement in the detection of diminutive lesions[58-60]. The Third Eye Retroscope is passed down the colonoscope channel and provides a continuous retrospective view on a second monitor[61]. A randomized control trial showed improved adenoma detection however with a longer withdrawal time[62]. This technology also requires accessing the accessory (and suction) channel making it a bit tedious in practice. One recent development is known as the full spectrum endoscopy (FUSE; EndoChoice, GA, United States). While a standard forward viewing colonoscope visualizes 170° of the colon, the FUSE instead has a more comprehensive view with the capability to capture 330° of the mucosa. This is accomplished by the addition of imagers on the sides of the tip of the scope to provide three images on adjacent monitors. The result is a lower miss rate of adenomas (7% *vs* 41%; $P < 0.00001$)[63]. Thus far, these technologies are not yet supported for incorporation into routine care. They may however, have a role for patients with increased risk for malignancy and/or endoscopists with low adenoma detection rates.

The quality of the examination by the proficient endoscopist is a significant predictor of adenoma detection therefore should be the focus of quality improvement efforts[64]. Internal audits are necessary to identify weaknesses in the practice. For instance, several studies have found that physician fatigue has an impact on adenoma detection with less adenomas found during afternoon procedures[65]. This phenomenon improves if endoscopists work in shorter shifts such as half-day blocks[66]. Direct observation and feedback has had variable results on outcomes[67]. In a study by Imperiali *et al*[68], less experienced endoscopists had more time dedicated to endoscopy with intermittent supervision, and their skills were regularly audited. Completion rates improved, variability between endoscopist polyp detection decreased, but no change in overall adenoma detection was observed[68].

A controversial issue is the endoscopic training of nongastroenterologists. The suggested threshold number for competence in colonoscopy is 200 procedures[69]. However, this quota may be misleading, as most trainees require many more procedures than dictated to achieve competence. Studies have shown an increase in interval cancer among nongastroenterologists[70]. This issue should be resolved through a collaboration of gastroenterology and nongastroenterology training programs to define uniformity to grant involvement in endoscopy.

In accordance with the changing paradigm of healthcare, rather than the fee-for-service model which rewards volume, a pay-for-performance reimbursement method will become the primary financial incentive with a focus more on value[71]. Within this model, satisfying national quality metrics may have a role in compensation as well. Several national endoscopic benchmarking programs are now in effect around the world. For instance, the GI Quality Improvement Consortium is a non-profit collaboration between the ASGE and ACG. This program facilitates data submission to various institutions, including the Physicians Consortium for Performance Improvement[46].

CONCLUSION

Quality measurement and improvement are essential components of a colonoscopy program. Quality is a multifactorial and dynamic process that requires regular monitoring to ensure adherence to national standards. Although several challenges exist, development and implementation of educational tools and improved endoscopic technology are imperative to enhance the benefits of colonoscopy, thereby reducing the incidence and mortality attributed to colon cancer.

REFERENCES

1 **Chassin MR**, Galvin RW. The urgent need to improve health care quality. Institute of Medicine National Roundtable on Health Care Quality. *JAMA* 1998; **280**: 1000-1005 [PMID: 9749483]
2 Crossing the Quality Chasm: A New Health System for the 21st Century. Washington (DC), 2001
3 **Seeff LC**, Richards TB, Shapiro JA, Nadel MR, Manninen DL, Given LS, Dong FB, Winges LD, McKenna MT. How many endoscopies are performed for colorectal cancer screening? Results from CDC's survey of endoscopic capacity. *Gastroenterology* 2004; **127**: 1670-1677 [PMID: 15578503]

4 **Rex DK**, Johnson DA, Lieberman DA, Burt RW, Sonnenberg A. Colorectal cancer prevention 2000: screening recommendations of the American College of Gastroenterology. American College of Gastroenterology. *Am J Gastroenterol* 2000; **95**: 868-877 [PMID: 10763931 DOI: 10.1111/j.1572-0241.2000.02059.x]

5 **Zauber AG**, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF, Shi W, Bond JH, Schapiro M, Panish JF, Stewart ET, Waye JD. Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. *N Engl J Med* 2012; **366**: 687-696 [PMID: 22356322 DOI: 10.1056/NEJMoa1100370]

6 **Kaminski MF**, Regula J, Kraszewska E, Polkowski M, Wojciechowska U, Didkowska J, Zwierko M, Rupinski M, Nowacki MP, Butruk E. Quality indicators for colonoscopy and the risk of interval cancer. *N Engl J Med* 2010; **362**: 1795-1803 [PMID: 20463339 DOI: 10.1056/NEJMoa0907667]

7 **Bressler B**, Paszat LF, Chen Z, Rothwell DM, Vinden C, Rabeneck L. Rates of new or missed colorectal cancers after colonoscopy and their risk factors: a population-based analysis. *Gastroenterology* 2007; **132**: 96-102 [PMID: 17241863 DOI: 10.1053/j.gastro.2006.10.027]

8 **Singh H**, Nugent Z, Demers AA, Bernstein CN. Rate and predictors of early/missed colorectal cancers after colonoscopy in Manitoba: a population-based study. *Am J Gastroenterol* 2010; **105**: 2588-2596 [PMID: 20877348 DOI: 10.1038/ajg.2010.390]

9 **Rex DK**, Petrini JL, Baron TH, Chak A, Cohen J, Deal SE, Hoffman B, Jacobson BC, Mergener K, Petersen BT, Safdi MA, Faigel DO, Pike IM. Quality indicators for colonoscopy. *Am J Gastroenterol* 2006; **101**: 873-885 [PMID: 16635231 DOI: 10.1111/j.1572-0241.2006.00673.x]

10 **Rex DK**. Avoiding and defending malpractice suits for postcolonoscopy cancer: advice from an expert witness. *Clin Gastroenterol Hepatol* 2013; **11**: 768-773 [PMID: 23376796 DOI: 10.1016/j.cgh.2013.01.027]

11 **Rex DK**, Cutler CS, Lemmel GT, Rahmani EY, Clark DW, Helper DJ, Lehman GA, Mark DG. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterology* 1997; **112**: 24-28 [PMID: 8978338]

12 **Froehlich F**, Wietlisbach V, Gonvers JJ, Burnand B, Vader JP. Impact of colonic cleansing on quality and diagnostic yield of colonoscopy: the European Panel of Appropriateness of Gastrointestinal Endoscopy European multicenter study. *Gastrointest Endosc* 2005; **61**: 378-384 [PMID: 15758907]

13 **Rex DK**, Imperiale TF, Latinovich DR, Bratcher LL. Impact of bowel preparation on efficiency and cost of colonoscopy. *Am J Gastroenterol* 2002; **97**: 1696-1700 [PMID: 12135020 DOI: 10.1111/j.1572-0241.2002.05827.x]

14 **Spiegel BM**, Talley J, Shekelle P, Agarwal N, Snyder B, Bolus R, Kurzbard N, Chan M, Ho A, Kaneshiro M, Cordasco K, Cohen H. Development and validation of a novel patient educational booklet to enhance colonoscopy preparation. *Am J Gastroenterol* 2011; **106**: 875-883 [PMID: 21483463 DOI: 10.1038/ajg.2011.75]

15 **Modi C**, Depasquale JR, Digiacomo WS, Malinowski JE, Engelhardt K, Shaikh SN, Kothari ST, Kottam R, Shakov R, Maksoud C, Baddoura WJ, Spira RS. Impact of patient education on quality of bowel preparation in outpatient colonoscopies. *Qual Prim Care* 2009; **17**: 397-404 [PMID: 20051190]

16 **Nguyen DL**, Wieland M. Risk factors predictive of poor quality preparation during average risk colonoscopy screening: the importance of health literacy. *J Gastrointestin Liver Dis* 2010; **19**: 369-372 [PMID: 21188326]

17 **Ness RM**, Manam R, Hoen H, Chalasani N. Predictors of inadequate bowel preparation for colonoscopy. *Am J Gastroenterol* 2001; **96**: 1797-1802 [PMID: 11419832 DOI: 10.1111/j.1572-0241.2001.03874.x]

18 **Van Dongen M**. Enhancing bowel preparation for colonoscopy: an integrative review. *Gastroenterol Nurs* 2012; **35**: 36-44 [PMID: 22306728]

19 **Wu KL**, Rayner CK, Chuah SK, Chiu KW, Lu CC, Chiu YC. Impact of low-residue diet on bowel preparation for colonoscopy. *Dis Colon Rectum* 2011; **54**: 107-112 [PMID: 21160321]

20 **Gurudu SR**, Ramirez FC, Harrison ME, Leighton JA, Crowell MD. Increased adenoma detection rate with system-wide implementation of a split-dose preparation for colonoscopy. *Gastrointest Endosc* 2012; **76**: 603-608.e1 [PMID: 22732876 DOI: 10.1016/j.gie.2012.04.456]

21 **Rex DK**, Bond JH, Winawer S, Levin TR, Burt RW, Johnson DA, Kirk LM, Litlin S, Lieberman DA, Waye JD, Church J, Marshall JB, Riddell RH. Quality in the technical performance of colonoscopy and the continuous quality improvement process for colonoscopy: recommendations of the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2002; **97**: 1296-1308 [PMID: 12094842 DOI: 10.1111/j.1572-0241.2002.05812.x]

22 **Lai EJ**, Calderwood AH, Doros G, Fix OK, Jacobson BC. The Boston bowel preparation scale: a valid and reliable instrument for colonoscopy-oriented research. *Gastrointest Endosc* 2009; **69**: 620-625 [PMID: 19136102 DOI: 10.1016/j.gie.2008.05.057]

23 **Brenner H**, Chang-Claude J, Seiler CM, Rickert A, Hoffmeister M. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. *Ann Intern Med* 2011; **154**: 22-30 [PMID: 21200035]

24 **Baxter NN**, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009; **150**: 1-8 [PMID: 19075198]

25 **Shah HA**, Paszat LF, Saskin R, Stukel TA, Rabeneck L. Factors associated with incomplete colonoscopy: a population-based study. *Gastroenterology* 2007; **132**: 2297-2303 [PMID: 17570204 DOI: 10.1053/j.gastro.2007.03.032]

26 **Johnson DA**, Gurney MS, Volpe RJ, Jones DM, VanNess MM, Chobanian SJ, Avalos JC, Buck JL, Kooyman G, Cattau EL. A prospective study of the prevalence of colonic neoplasms in asymptomatic patients with an age-related risk. *Am J Gastroenterol* 1990; **85**: 969-974 [PMID: 2375325]

27 **Schoenfeld P**, Cash B, Flood A, Dobhan R, Eastone J, Coyle W, Kikendall JW, Kim HM, Weiss DG, Emory T, Schatzkin A, Lieberman D. Colonoscopic screening of average-risk women for colorectal neoplasia. *N Engl J Med* 2005; **352**: 2061-2068 [PMID: 15901859 DOI: 10.1056/NEJMoa042990]

28 **Imperiale TF**, Glowinski EA, Juliar BE, Azzouz F, Ransohoff DF. Variation in polyp detection rates at screening colonoscopy. *Gastrointest Endosc* 2009; **69**: 1288-1295 [PMID: 19481649 DOI: 10.1016/j.gie.2007.11.043]

29 **Boroff ES**, Gurudu SR, Hentz JG, Leighton JA, Ramirez FC. Polyp and adenoma detection rates in the proximal and distal colon. *Am J Gastroenterol* 2013; **108**: 993-999 [PMID: 23567353 DOI: 10.1038/ajg.2013.68]

30 **Patel NC**, Islam RS, Wu Q, Gurudu SR, Ramirez FC, Crowell MD, Faigel DO. Measurement of polypectomy rate by using administrative claims data with validation against the adenoma detection rate. *Gastrointest Endosc* 2013; **77**: 390-394 [PMID: 23199647 DOI: 10.1016/j.gie.2012.09.032]

31 **Chen SC**, Rex DK. Endoscopist can be more powerful than age and male gender in predicting adenoma detection at colonoscopy. *Am J Gastroenterol* 2007; **102**: 856-861 [PMID: 17222317 DOI: 10.1111/j.1572-0241.2006.01054.x]

32 **Francis DL**, Rodriguez-Correa DT, Buchner A, Harewood GC, Wallace M. Application of a conversion factor to estimate the adenoma detection rate from the polyp detection rate. *Gastrointest Endosc* 2011; **73**: 493-497 [PMID: 21353846 DOI: 10.1016/j.gie.2011.01.005]

33 **Williams JE**, Le TD, Faigel DO. Polypectomy rate as a quality measure for colonoscopy. *Gastrointest Endosc* 2011; **73**: 498-506 [PMID: 20970795 DOI: 10.1016/j.gie.2010.08.008]

34 **Wang HS**, Pisegna J, Modi R, Liang LJ, Atia M, Nguyen M, Cohen H, Ohning G, van Oijen M, Spiegel BM. Adenoma detection rate is necessary but insufficient for distinguishing high versus low endoscopist performance. *Gastrointest Endosc* 2013; **77**: 71-78 [PMID: 23261096 DOI: 10.1016/j.gie.2012.08.038]

35 **Lee TJ**, Rutter MD, Blanks RG, Moss SM, Goddard AF, Chilton A, Nickerson C, McNally RJ, Patnick J, Rees CJ. Colonoscopy quality measures: experience from the NHS Bowel Cancer Screening

Programme. *Gut* 2012; **61**: 1050-1057 [PMID: 21940723 DOI: 10.1136/gutjnl-2011-300651]
36 **Barclay RL**, Vicari JJ, Doughty AS, Johanson JF, Greenlaw RL. Colonoscopic withdrawal times and adenoma detection during screening colonoscopy. *N Engl J Med* 2006; **355**: 2533-2541 [PMID: 17167136 DOI: 10.1056/NEJMoa055498]
37 **Rex DK**. Colonoscopic withdrawal technique is associated with adenoma miss rates. *Gastrointest Endosc* 2000; **51**: 33-36 [PMID: 10625792]
38 **Lieberman DA**, Rex DK, Winawer SJ, Giardiello FM, Johnson DA, Levin TR. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2012; **143**: 844-857 [PMID: 22763141 DOI: 10.1053/j.gastro.2012.06.001]
39 **Mysliwiec PA**, Brown ML, Klabunde CN, Ransohoff DF. Are physicians doing too much colonoscopy? A national survey of colorectal surveillance after polypectomy. *Ann Intern Med* 2004; **141**: 264-271 [PMID: 15313742]
40 **Sorbi D**, Norton I, Conio M, Balm R, Zinsmeister A, Gostout CJ. Postpolypectomy lower GI bleeding: descriptive analysis. *Gastrointest Endosc* 2000; **51**: 690-696 [PMID: 10840301]
41 **Nivatvongs S**. Complications in colonoscopic polypectomy. An experience with 1,555 polypectomies. *Dis Colon Rectum* 1986; **29**: 825-830 [PMID: 3491746]
42 **Silvis SE**, Nebel O, Rogers G, Sugawa C, Mandelstam P. Endoscopic complications. Results of the 1974 American Society for Gastrointestinal Endoscopy Survey. *JAMA* 1976; **235**: 928-930 [PMID: 128642]
43 **Liaquat H**, Rohn E, Rex DK. Prophylactic clip closure reduced the risk of delayed postpolypectomy hemorrhage: experience in 277 clipped large sessile or flat colorectal lesions and 247 control lesions. *Gastrointest Endosc* 2013; **77**: 401-407 [PMID: 23317580 DOI: 10.1016/j.gie.2012.10.024]
44 **Feagins LA**, Nguyen AD, Iqbal R, Spechler SJ. The prophylactic placement of hemoclips to prevent delayed post-polypectomy bleeding: an unnecessary practice? A case control study. *Dig Dis Sci* 2014; **59**: 823-828 [PMID: 24526499 DOI: 10.1007/s10620-014-3055-0]
45 **Gatto NM**, Frucht H, Sundararajan V, Jacobson JS, Grann VR, Neugut AI. Risk of perforation after colonoscopy and sigmoidoscopy: a population-based study. *J Natl Cancer Inst* 2003; **95**: 230-236 [PMID: 12569145]
46 **Petersen BT**. Quality assurance for endoscopists. *Best Pract Res Clin Gastroenterol* 2011; 25: 349-360 [PMID: 21764003 DOI: 10.1016/j.bpg.2011.05.003]
47 **Rex DK**. Improving detection during colonoscopy: multiple pathways for investigation. *J Clin Gastroenterol* 2011; **45**: 207-209 [PMID: 21307698]
48 **Wardle J**, Williamson S, McCaffery K, Sutton S, Taylor T, Edwards R, Atkin W. Increasing attendance at colorectal cancer screening: testing the efficacy of a mailed, psychoeducational intervention in a community sample of older adults. *Health Psychol* 2003; **22**: 99-105 [PMID: 12558207]
49 **Harewood GC**, Sharma VK, de Garmo P. Impact of colonoscopy preparation quality on detection of suspected colonic neoplasia. *Gastrointest Endosc* 2003; **58**: 76-79 [PMID: 12838225 DOI: 10.1067/mge.2003.294]
50 **Falchuk ZM**, Griffin PH. A technique to facilitate colonoscopy in areas of severe diverticular disease. *N Engl J Med* 1984; **310**: 598 [PMID: 6694718 DOI: 10.1056/NEJM198403013100919]
51 **Leung CW**, Kaltenbach T, Soetikno R, Wu KK, Leung FW, Friedland S. Water immersion versus standard colonoscopy insertion technique: randomized trial shows promise for minimal sedation. *Endoscopy* 2010; **42**: 557-563 [PMID: 20593332 DOI: 10.1055/s-0029-1244231]
52 **Dai J**, Feng N, Lu H, Li XB, Yang CH, Ge ZZ. Transparent cap improves patients' tolerance of colonoscopy and shortens examination time by inexperienced endoscopists. *J Dig Dis* 2010; **11**: 364-368 [PMID: 21091899 DOI: 10.1111/j.1751-2980.2010.00460.x]
53 **Tee HP**, Corte C, Al-Ghamdi H, Prakoso E, Darke J, Chettiar R, Rahman W, Davison S, Griffin SP, Selby WS, Kaffes AJ. Prospective randomized controlled trial evaluating cap-assisted colonoscopy vs standard colonoscopy. *World J Gastroenterol* 2010; **16**: 3905-3910 [PMID: 20712051]
54 **Matsushita M**, Hajiro K, Okazaki K, Takakuwa H, Tominaga M. Efficacy of total colonoscopy with a transparent cap in comparison with colonoscopy without the cap. *Endoscopy* 1998; **30**: 444-447 [PMID: 9693890 DOI: 10.1055/s-2007-1001305]
55 **Takeuchi Y**, Inoue T, Hanaoka N, Higashino K, Iishi H, Chatani R, Hanafusa M, Kizu T, Ishihara R, Tatsuta M, Shimokawa T, Uedo N. Autofluorescence imaging with a transparent hood for detection of colorectal neoplasms: a prospective, randomized trial. *Gastrointest Endosc* 2010; **72**: 1006-1013 [PMID: 21034901 DOI: 10.1016/j.gie.2010.06.055]
56 **Hewett DG**, Rex DK. Cap-fitted colonoscopy: a randomized, tandem colonoscopy study of adenoma miss rates. *Gastrointest Endosc* 2010; **72**: 775-781 [PMID: 20579648 DOI: 10.1016/j.gie.2010.04.030]
57 **Vemulapalli KC**, Rex DK. Evolving techniques in colonoscopy. *Curr Opin Gastroenterol* 2011; **27**: 430-438 [PMID: 21785352 DOI: 10.1097/MOG.0b013e328349cfc0]
58 **East JE**, Ignjatovic A, Suzuki N, Guenther T, Bassett P, Tekkis PP, Saunders BP. A randomized, controlled trial of narrow-band imaging vs high-definition white light for adenoma detection in patients at high risk of adenomas. *Colorectal Dis* 2012; **14**: e771-e778 [PMID: 22958651 DOI: 10.1111/codi.12014]
59 **Pohl J**, Schneider A, Vogell H, Mayer G, Kaiser G, Ell C. Pancolonic chromoendoscopy with indigo carmine versus standard colonoscopy for detection of neoplastic lesions: a randomised two-centre trial. *Gut* 2011; **60**: 485-490 [PMID: 21159889 DOI: 10.1136/gut.2010.229534]
60 **Paggi S**, Radaelli F, Amato A, Meucci G, Mandelli G, Imperiali G, Spinzi G, Terreni N, Lenoci N, Terruzzi V. The impact of narrow band imaging in screening colonoscopy: a randomized controlled trial. *Clin Gastroenterol Hepatol* 2009; **7**: 1049-1054 [PMID: 19577008 DOI: 10.1016/j.cgh.2009.06.028]
61 **Triadafilopoulos G**, Li J. A pilot study to assess the safety and efficacy of the Third Eye retrograde auxiliary imaging system during colonoscopy. *Endoscopy* 2008; **40**: 478-482 [PMID: 18543136 DOI: 10.1055/s-2007-995811]
62 **Leufkens AM**, DeMarco DC, Rastogi A, Akerman PA, Azzouzi K, Rothstein RI, Vleggaar FP, Repici A, Rando G, Okolo PI, Dewit O, Ignjatovic A, Odstrcil E, East J, Deprez PH, Saunders BP, Kalloo AN, Creel B, Singh V, Lennon AM, Siersema PD. Effect of a retrograde-viewing device on adenoma detection rate during colonoscopy: the TERRACE study. *Gastrointest Endosc* 2011; **73**: 480-489 [PMID: 21067735 DOI: 10.1016/j.gie.2010.09.004]
63 **Gralnek IM**, Siersema PD, Halpern Z, Segol O, Melhem A, Suissa A, Santo E, Sloyer A, Fenster J, Moons LM, Dik VK, D'Agostino RB, Rex DK. Standard forward-viewing colonoscopy versus full-spectrum endoscopy: an international, multicentre, randomised, tandem colonoscopy trial. *Lancet Oncol* 2014; **15**: 353-360 [PMID: 24560453 DOI: 10.1016/S1470-2045(14)70020-8]
64 **Millan MS**, Gross P, Manilich E, Church JM. Adenoma detection rate: the real indicator of quality in colonoscopy. *Dis Colon Rectum* 2008; **51**: 1217-1220 [PMID: 18500502 DOI: 10.1007/s10350-008-9315-3]
65 **Chan MY**, Cohen H, Spiegel BM. Fewer polyps detected by colonoscopy as the day progresses at a Veteran's Administration teaching hospital. *Clin Gastroenterol Hepatol* 2009; **7**: 1217-1123; quiz 1143 [PMID: 19631284 DOI: 10.1016/j.cgh.2009.07.013]
66 **Gurudu SR**, Ratuapli SK, Leighton JA, Heigh RI, Crowell MD. Adenoma detection rate is not influenced by the timing of colonoscopy when performed in half-day blocks. *Am J Gastroenterol* 2011; **106**: 1466-1471 [PMID: 21502998 DOI: 10.1038/ajg.2011.125]
67 **Rex DK**, Hewett DG, Raghavendra M, Chalasani N. The impact of videorecording on the quality of colonoscopy performance: a pilot study. *Am J Gastroenterol* 2010; **105**: 2312-2317 [PMID: 21048675 DOI: 10.1038/ajg.2010.245]

68 **Imperiali G**, Minoli G, Meucci GM, Spinzi G, Strocchi E, Terruzzi V, Radaelli F. Effectiveness of a continuous quality improvement program on colonoscopy practice. *Endoscopy* 2007; **39**: 314-318 [PMID: 17273959 DOI: 10.1055/s-2006-945196]

69 **Sedlack RE**. Training to competency in colonoscopy: assessing and defining competency standards. *Gastrointest Endosc* 2011; **74**: 355-366.e1-2 [PMID: 21514931 DOI: 10.1016/j.gie.2011.02.019]

70 **Rabeneck L**, Paszat LF, Saskin R. Endoscopist specialty is associated with incident colorectal cancer after a negative colonoscopy. *Clin Gastroenterol Hepatol* 2010; **8**: 275-279 [PMID: 19879970 DOI: 10.1016/j.cgh.2009.10.022]

71 **Hewett DG**, Rex DK. Improving colonoscopy quality through health-care payment reform. *Am J Gastroenterol* 2010; **105**: 1925-1933 [PMID: 20551937 DOI: 10.1038/ajg.2010.247]

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REVIEW

Review of the diagnosis and management of gastrointestinal bezoars

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Abstract

The formation of a bezoar is a relatively infrequent disorder that affects the gastrointestinal system. Bezoars are mainly classified into four types depending on the material constituting the indigestible mass of the bezoar: phytobezoars, trichobezoars, pharmacobezoars, and lactobezoars. Gastric bezoars often cause ulcerative lesions in the stomach and subsequent bleeding, whereas small intestinal bezoars present with small bowel obstruction and ileus. A number of articles have emphasized the usefulness of Coca-Cola® administration for the dissolution of phytobezoars. However, persimmon phytobezoars may be resistant to such dissolution treatment because of their harder consistency compared to other types of phytobezoars. Better understanding of the etiology and epidemiology of each type of bezoar will facilitate prompt diagnosis and management. Here we provide an overview of the prevalence, classification, predisposing factors, and manifestations of bezoars. Diagnosis and management strategies are also discussed, reviewing mainly our own case series. Recent progress in basic research regarding persimmon phytobezoars is also briefly reviewed.

Key words: Bezoars; Gastrointestinal endoscopy; Persimmon phytobezoar; Trichobezoar; Endoscopic removal; Gastric ulcer; Ileus

Core tip: Among the gastrointestinal bezoars, phytobezoars, which consist of indigestible plant materials, are the most common. An administration of Coca-Cola®

is believed to be the primary choice for phytobezoar treatment because it is safe, inexpensive, and effective. However, persimmon phytobezoars (diospyrobezoars) are often resistant to Coca-Cola® dissolution and may require different treatment. Endoscopic fragmentation or surgical removal should be applied in urgent cases, such as those manifesting gastrointestinal bleeding and/or ileus, and in patients with refractory bezoars.

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INTRODUCTION

A bezoar is an indigestible conglomeration trapped in the gastrointestinal tract. This indigestible mass can be formed by a variety of materials that were intentionally or accidentally ingested. Representative substances forming bezoars include plant materials such as fibers, skins and seeds of vegetables and fruits (*i.e.*, phytobezoars), ingested hair (*i.e.*, trichobezoars), medications (*i.e.*, pharmacobezoars), and milk protein in milk-fed infants (*i.e.*, lactobezoars)[1]. Bezoars can be formed and found in any part of the gastrointestinal tract, but the stomach is the most common. Once the diagnosis of bezoar is made, the bezoar is generally dissolved or removed because it can cause gastric outlet obstruction, ileus, ulcerations due to pressure necrosis, and subsequent gastrointestinal bleeding. Here we review relevant clinical studies, case reports and basic research findings, using mainly our recent studies[2-4], for a better understanding of the etiology and epidemiology of this disease entity.

PREVALENCE

Bezoars of the gastrointestinal tract are a relatively rare disease entity, with a variable incidence among studies[5]. In 1978, Kadian *et al*[6] reported that they found six cases of gastric bezoars in a four-year period during which time 1400 gastroscopies were done (0.43% of the gastroscopies). In 1987, Ahn *et al*[7] reported a similar incidence of 0.43% (14/3247 esophagogastroduodenoscopy examinations) over a seven-year period. More recently, Mihai *et al*[8] noted that there were 49 cases of gastric bezoars over a period of 20 years (0.068% of all endoscopies).

Although the majority of bezoars are found in the stomach, bezoars sometimes move from the stomach into the small intestine, or they can be primarily formed in the small intestine. Such small intestinal bezoars occasionally cause small bowel obstruction and ileus. Yakan *et al*[9] reviewed 432 cases of small bowel obstruction treated within 10 years; of these, 14 (3.2%) cases were caused by phytobezoars. In a meta-analysis by Ghosheh *et al*[10] reviewing 19 reported studies published from 1994 to 2005, laparoscopy was attempted in 1061 patients presenting with acute small bowel obstruction, and bezoars represented the 5th most common cause, accounting for 0.8%[11].

Overall, bezoars can be found in the stomach in less than 0.5% of individuals undergoing esophagogastroduodenoscopy examinations and in the small intestine in 0.4%-4.8% of all cases presenting with intestinal obstruction[9-13]. However, the prevalence of bezoars likely varies among ethnic groups and geographic locations, since the occurrence rate of phytobezoar, the most common type of bezoar, is mostly reflected by food cultures. For example, multiple cases of persimmon phytobezoar (diospyrobezoar) have been reported in regions where the residents frequently consume fresh persimmon fruits and dried persimmons, such as South Korea, Japan, Israel, Spain, Turkey, and Southeastern United States[3,14-19].

BEZOAR CLASSIFICATION

Phytobezoar

Among the four types of bezoars, phytobezoars are the most common[20]. Celery, pumpkins, grape skins, prunes, raisins and, in particular, persimmons are representative causatives of phytobezoars[14]. Some of these foods contain high amount of cellulose, hemicellulose, lignin, and tannins (leucoanthocyanins and catechins), and these nondigestible food materials are the main components of phytobezoars[1,21,22]. Persimmon phytobezoars, *i.e.*, diospyrobezoars, are formed after a frequent consumption of persimmons (Figure 1). The skin of unripe persimmons contains high concentrations of the persimmon tannin. Upon reaction with stomach acid, persimmon tannin is believed to polymerize and form a conglomerate in which cellulose, hemicelluloses, and various proteins are accumulated[20,23]. For example, Holloway *et al*[21] investigated the plant fiber content in a gastric phytobezoar by using the acid and neutral detergent method. The gastric phytobezoar was composed of approx, 11% cellulose, 5% hemicellulose, and 2% lignin. In a thin-layer chromatography analysis, phytobezoar tissue contained only polymerized tannins, without tannin monomers. Maki *et al*[24] succeeded in generating an artificial mass *in vitro* that mimicked a phytobezoar by using persimmon skin pieces, hydrochloric acid, and high-molecular-weight organic polymers. In light of the basic research findings, we speculate that persimmon tannin plays a vital role in the formation of phytobezoars acting as cementing agents that hold undigestible plant fibers together. However, the precise mechanism of the emergence of a phytobezoar is still unknown.

Trichobezoar

A trichobezoar is a hair ball trapped in the gastroin-

testinal tract, mainly in the stomach. Trichobezoar is a rare condition, nearly always diagnosed in young females[25-30]. Psychiatric comorbidities that involve strong urges to pull out one's own hair (trichotillomania) and eat it (trichophagia) are observed in these patients. Due to its enzyme-resistant properties and smooth, slippery surface, human hair cannot be digested and it can be stagnant in the gastrointestinal system. Consequently, eaten hairs retain and accumulate between the gastric mucosal folds and finally lead to the formation of a hair ball together with food and mucus[25]. In some cases, the hair ball extends from the stomach into the small intestines and colon. This condition is named Rapunzel syndrome, which was first described by Vaughan *et al*[31] in 1968[32].

Pharmacobezoar

Pharmacobezoars are an uncommon complication caused by conglomerations of medications or medication vehicles in the gastrointestinal tract. Bulk-forming laxatives, *e.g.*, perdium and psyllium, and guar gum appear to contribute to the formation of pharmacobezoars because of their hygroscopic properties and bulk-forming nature[1,33-37]. Extended-release drug products are other candidate causatives for bezoars[38-40]. The development of time-release technology enabled drug tablets/capsules to be slowly dissolved and gradually release active ingredients of the medication. Extended-release drugs, *e.g.*, nifedipine and verapamil, are coated with cellulose acetate, a synthetic chemical compound derived from the plant substance cellulose. Cellulose acetate may aggregate and lead to bezoar formation in the gastrointestinal tract. Enteric coatings, which use a polymer barrier to stabilize drug tablets at the highly acidic pH found in the stomach, are dissolved at a less acidic pH in the small intestine. Because of the insolubility of the carrying vehicle of enteric-coated medications, *e.g.*, aspirin, they can also be responsible for bezoar formation[39].

Lactobezoar

A lactobezoar is an undigested mass composed of milk and mucus components[41]. In clear contrast to the other types of bezoars, virtually all patients affected with a lactobezoar are milk-fed infants. The pathogenesis is likely multifactorial and includes both exogenous risk factors (*i.e.*, the composition of synthetic milk, medications lowering gastric motility and secretion, and methodologies of feeding) and endogenous risk factors (*i.e.*, dehydration, premature birth, and the subsequent insufficient activity and capacity of the digestive tract)[42-44]. Heinz-Erian *et al*[42] reviewed 96 published cases since the first report in 1959 and noted that most cases were published in the period 1975-1985, whereas only 26 cases have been reported since 1986. The reasons for the infrequency of lactobezoar cases in recent years have not been revealed, but the improvement of synthetic milk composition and advances in premature infant management have probably affected the prevalence.

Other types of bezoar

Varieties of substances other than those responsible for the aforementioned four types of bezoars (*i.e.*, plant materials, hair, medications, and artificial milk) have been reported as a source of bezoars. Such bizarre materials include plastic[45], metals[46], parasitic worms (ascaris)[47], and even toilet paper[48]. Theoretically, all indigestible food materials and foreign bodies can cause a mass formation together with mucus and semi-digested foodstuffs.

STRUCTURE OF PERSIMMON PHYTOBEZOAR

Compared with other phytobezoars, persimmon phytobezoars are more difficult to dissolve or break up into small pieces due to their hard consistency. In addition, persimmon phytobezoars usually have a black or darkish-brown color (Figure 1). We recently investigated persimmon phytobezoar fragments by microscopy, transmission electron microscopy, energy dispersive X-ray spectroscopy, and infrared spectroscopy and revealed the unique structure and components that cause the characteristic hard consistency and dark color[2]. In this section, we briefly introduce our analysis regarding the microstructure of persimmon phytobezoar fragments.

First, the bezoar fragments were analyzed by scanning electron microscopy (SEM). The SEM analysis revealed a high-density, continuous layer approx. 20- to 50-μm thick that formed the exterior of the phytobezoar. Close-up observation revealed that aggregated microgranules constituted the exterior surface. These microgranules were stuck together and created an almost seamless structure with a few slits. In contrast, the density of the inner part of the persimmon phytobezoar was low. The inner part consisted of sheet-like structures with curved or wavy shapes. The wiggly arrangement of the sheet-like structures resulted in unoccupied areas existed between the sheets. These microscopic features indicate that the persimmon phytobezoar's resistance to mechanical and chemical forces was rendered by almost seamless, dense layers of the exterior surface.

Secondly, to investigate the chemical components that constitute the surface structure and the inner part of the persimmon phytobezoar, we performed an infrared spectroscopy analysis. The surface layer and the inner part of the persimmon phytobezoar were manually segmented with a surgical knife. Both parts were air-dried and analyzed by infrared spectroscopy. The spectra obtained from the surface and the inner parts of the persimmon phytobezoar were quite similar to that of persimmon juice. The persimmon juice was extracted from green, unripe persimmon

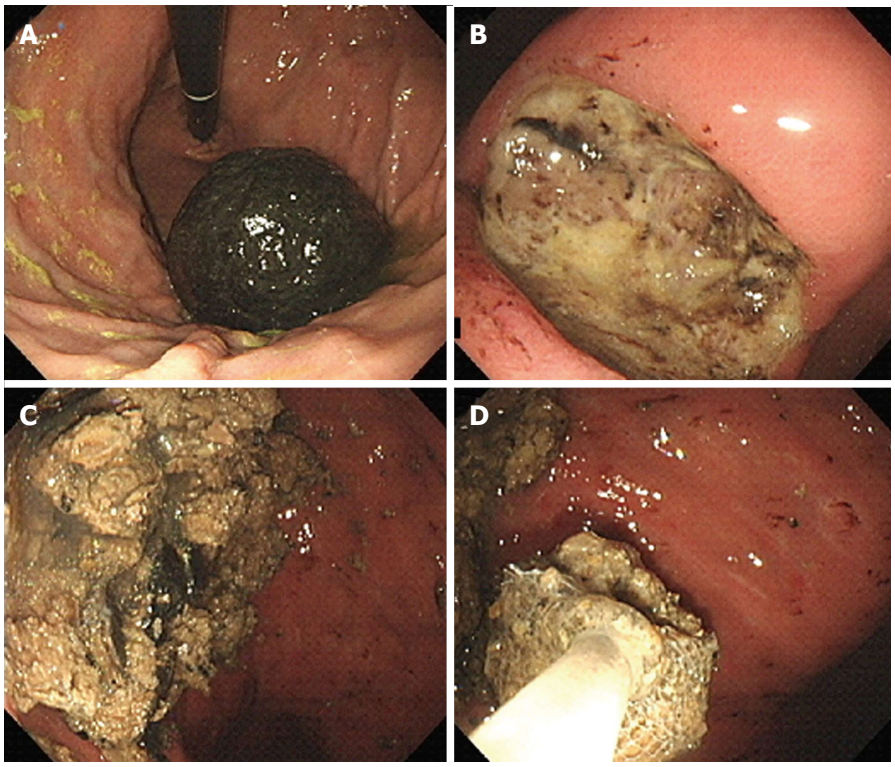

Figure 1 Endoscopic images of a persimmon phytobezoar. A: A large, black bezoar is seen in the gastric fundus; B: A peptic ulcer is also observed in the gastric angle; C: Fragmentation of the bezoar was performed by endoscopy forceps and polypectomy snares; D: The fragments were removed by a retrieval net device and used in the subsequent *in vitro* analysis.

fruits that contained plenty of tannin. This juice can be commercially purchased in Japan as a natural dyestuff and as a coating material for fabric, paper, and wood. The striking resemblance of spectra between the persimmon juice and the phytobezoar fragments indicates that a quite high concentration of persimmon tannin exists in a phytobezoar. It also suggests the importance of persimmon tannin in the pathogenesis of phytobezoars.

Thirdly, to compare the elemental composition of the surface and the inner part of the phytobezoar, we used S4800 scanning electron microscopy and energy dispersive X-ray spectroscopy (EDX) (EDAX Genesis APEX2 system, Ametek, Paoli, PA). The net intensity of each element was measured at five different points on the surface and the inner part, respectively. We analyzed the spectrum of the EDX results using Genesys software (Ametek). The amount of each element was quantified by the standardless EDAX ZAF quantification method. As a result, higher amounts of sulphur and iron were detected in the surface layer compared to the inner part (Table 1). We speculate that the iron deposition and resulting compound, iron(Ⅲ) tannate, are responsible for the black color of the persimmon phytobezoar surface. In our study, yttrium, aluminum, and osmium were detected in the persimmon phytobezoar, in addition to the major elements such as carbon, oxygen, sodium and sulfur. Generally, edible plants have yttrium at a concentration of 20-100 ppm[49]. The seeds of woody plants have high amounts, up to 700 ppm. Aluminum is also contained in foods and food additives. Osmium was probably contaminated during the process of sample preparation for the SEM analysis, because it was used as a fixing agent.

A limitation associated with our study is that the phytobezoar examined was obtained from a single patient. Since the structure of phytobezoars presumably varies among patients, an analysis of the ultrastructure would ideally include phytobezoars extracted from several different patients. Another subject of great interest is the structure and components of other types of bezoars (*i.e.*, trichobezoars, pharmacobezoars, and lactobezoars). Although the formation of bezoars is a relatively infrequent disorder, further *in vitro* investigations could provide findings that contribute to the management of phytobezoars.

PATIENT SUSCEPTIBILITY

Bezoars are believed to form as a complication of delayed gastric emptying. Predisposed risk factors include prior gastric surgery such as partial gastrectomy, vagotomy and pyloroplasty, peptic ulcer disease, chronic gastritis, Crohn's disease, carcinoma of the gastrointestinal tract, dehydration and hypothyroidism[46,50]. These conditions lead to reduced gastric acidity, gastric stasis, loss of pyloric function, and/or pyloric stenosis. Elderly individuals and diabetic patients with neuropathy or myotonic dystrophy have

Table 1 Net intensity of elements determined by energy-dispersive X-ray spectroscopy in a persimmon phytobezoar

	Surface layer	Inner part	*P* value
C	52.91 ± 13.88	62.30 ± 15.77	0.35
O	22.42 ± 5.95	43.71 ± 14.56	< 0.05
Na	12.77 ± 5.09	21.24 ± 6.26	< 0.05
Al	9.98 ± 2.55	13.01 ± 2.64	0.1
Y	160.62 ± 29.73	209.37 ± 38.48	0.06
S	16.96 ± 3.22	5.27 ± 1.95	< 0.01
Fe	9.88 ± 1.69	2.02 ± 1.17	< 0.01
Os	45.02 ± 3.96	60.35 ± 6.26	< 0.01

For comparisons, statistical analyses were performed by *t* tests. C: Carbon; O: Oxygen; Na: Sodium; Al: Aluminum; Y: Yttrium; S: Sulfur; Fe: Iron; Os: Osmium.

impaired gastric motility[1,12,51,52].

In our previous study, we reviewed 19 Japanese patients with gastrointestinal bezoars and presented their clinical characteristics[3]. To date, we have collected an additional 12 cases. A summary of the 31 cases (13 males and 18 females) is shown in Table 2. In accord with previous studies, the histories of our patient series included diabetes mellitus (*n* = 3, 9.7%) and surgery of the gastrointestinal tract (*n* = 11, 35.5%). Notably, except for the 10-year-old patient with a trichobezoar, all patients were 61 years of age or older. Consequently, the potential development of bezoars in elderly individuals and patients with underlying disease that causes poor gastric motility should be borne in mind by clinicians.

Table 2 Clinical characteristics of bezoar patients

	n (%)
Total	31
Female	18 (58.1)
Median age (yr, range)	74 (10-93)
Past histories	
Diabetes mellitus	3 (9.7)
Surgery of gastrointestinal tract	11 (35.5)
Symptoms	
Pain	11 (35.5)
Bloody or tarry stool	5 (16.1)
Abdominal fullness	5 (16.1)
Discomfort	5 (16.1)
Anemia	4 (12.9)
Difficulty of swallowing	3 (9.7)
Hematemesis	3 (9.7)
Nausea	3 (9.7)
Anorexia	1 (3.2)
Faint	1 (3.2)
None	3 (9.7)
Bezoar location	
Stomach	29 (93.5)
Small intestine	2 (6.5)
Diagnosis modality	
Esophagogastroduodenoscopy	23 (74.2)
Computed tomography	8 (25.8)
Complications of bezoar	
Gastric ulcer	20[1] (64.5)
Ileus	3[1] (9.7)
Reflux esophagitis	1 (3.2)
Acute gastric mucosal lesions	1 (3.2)
Duodenal ulcer	1 (3.2)
None	6 (19.4)

[1]One patient presented with both gastric ulcer and ileus.

MANIFESTATIONS AND DIAGNOSIS

Bezoars can be asymptomatic or present with a variety of gastrointestinal symptoms. In our series of 31 patients with gastrointestinal bezoars, pain (*n* = 11), bloody or tarry stool (*n* = 5), abdominal fullness (*n* = 5), discomfort (*n* = 5), anemia (*n* = 4), difficulty swallowing (*n* = 3), hematemesis (*n* = 3), nausea (*n* = 3), anorexia (*n* = 1), and fainting (*n* = 1) were observed as initial presentations (Table 2). In contrast, bezoars were coincidentally found in asymptomatic patients (*n* = 5) by esophagogastroduodenoscopy or computed tomography (CT) scans performed during a health check-up or follow-up of other diseases. Symptoms related to gastrointestinal bleeding such as hematemesis, bloody or tarry stool, anemia, and fainting are the result of the development of ulceration in the gastric mucosa due to pressure necrosis induced by the bezoar[1]. As shown in Table 2, gastric ulcers were observed in 20 of the 31 patients (64.5%) by esophagogastroduodenoscopy. Lee *et al*[53] also documented a high rate of gastric ulcers as a complication of bezoars (41.2%, 7/17 cases). Obstruction of the gastrointestinal tract is another vital manifestation caused by bezoars, particularly by small intestinal bezoars.

Endoscopic examinations play the most important role in the detection of gastric bezoars, as well as in the treatment of this disease. A phytobezoar is typically observed in the gastric fundus as a single mass, but it can be multiple. The color is diverse depending on the materials constituting the phytobezoar, ranging from beige, tan, ocher, yellow green, to black[3]. As described above, the black color of persimmon phytobezoar's surface is probably imparted by iron(III) tannate (Figure 1A)[2].

CT scanning is useful to detect both gastric and small intestinal bezoars. Phytobezoars are visualized by CT scan as an ovoid or round occupational mass in the gastrointestinal tract with air bubbles retained inside and a mottled appearance[54,55]. A CT scan is particularly valuable in patients requiring the surgical removal of small intestinal bezoars, not only because it demonstrates the obstructed site of the intestines; it also enables the visualization of multiple bezoars[19].

TREATMENT OF BEZOARS

Overview

The currently available treatment options for a gastric phytobezoar include dissolution of the bezoar by Coca-Cola®, removal by endoscopic devices, laparotomy, and laparoscopic surgery. It should be noted that persimmon phytobezoars are often resistant to chemical dissolution

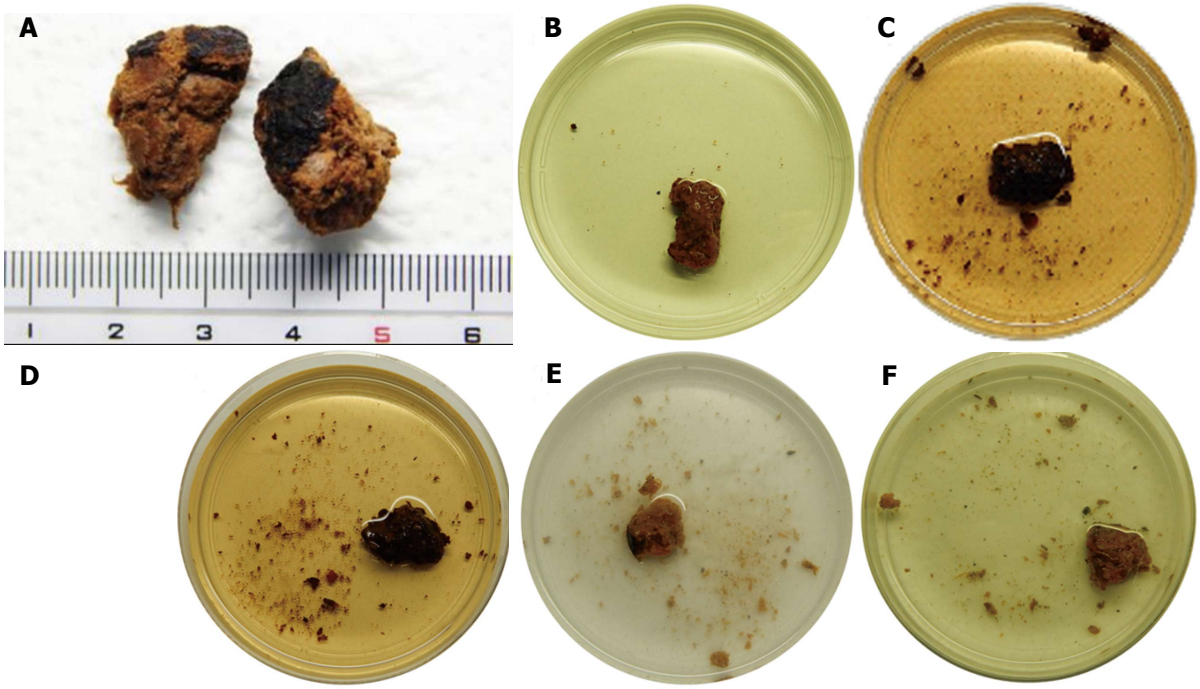

Figure 2 Photographs of the *in vitro* experiment. A: Endoscopically extracted fragments of the gastric bezoar were used; B: Representative photographs of the bezoar fragments incubated at 37 ℃ with gentle swirling for 12 h with double-distilled water; C: Bezoar fragments after incubation with Coca-Cola®; D: Bezoar fragments after incubation with Coca-Cola Zero®; E: Bezoar fragments after incubation with a digestive enzymes supplement including cellulase; F: Bezoar fragments after incubation with papain. The bezoar fragments were clearly more softened and more fragmented after 12-h incubation with Coca-Cola® or Coca-Cola Zero® than with the other agents.

because of their hard consistency, and they are thus usually removed endoscopically or surgically[53,55].

Intestinal bezoars are generally removed by a surgical procedure, since patients with this type of bezoar often present with intestinal obstruction and ileus.

Coca-Cola

The first successful treatment achieved with Coca-Cola® lavage was reported in 2002 by Ladas *et al*[56]. In a recent review by Ladas *et al*[56], they summarized 24 publications including 46 patients and noted that Coca-Cola® administration resulted in phytobezoar resolution in 91.3% of the cases, either as a sole treatment or in combination with an endoscopic procedure[20]. The protocol for Coca-Cola® administration has varied among authors[53]. Ladas *et al*[56] performed gastric lavage *via* nasogastric tubes with 3000 mL of Coca-Cola® administered over 12 h. Hayashi *et al*[57] reported that the peroral intake of 500-1000 mL/d of Coca-Cola® for 3 wk resulted in a decrease in size and softened structure of the phytobezoar. Mihai *et al*[8] described 12 patients treated with 4800 mL of Coca-Cola® ingestion over 12 h (100 mL every 15 min); complete dissolution of the bezoar was observed in 5 patients (42%), and fragmentation of the bezoar was found in 5 patients (42%). In the latest review, Ladas *et al*[20] recommended gastric lavage with 3000 mL of Coca-Cola® for 12 h, or drinking 3000 mL of Coca-Cola® over 12 h. The adequate dose and timing of Coca-Cola® administration should be investigated, because no standard protocol for bezoar treatment has been established to date.

In our recent paper, we investigated persimmon phytobezoar dissolubility by Coca-Cola® *in vitro*[4]. A gastric persimmon phytobezoar was fragmented by endoscopy forceps and polypectomy snares (Figure 1C) and extracted with a retrieval net device (Figures 1D and 2A). A fragment and hydrochloric acid-potassium chloride buffer (pH 2.0) was put into each of several tubes. Double-distilled water, Coca-Cola®, Coca-Cola Zero®, a digestive enzyme supplement containing cellulase, or papain supplement was added to the tube. After a 12-h incubation, the contents of the tubes were gently decanted into 100-mm polystyrene dishes, and photographs of these dishes were taken. Representative images of each group at post-incubation are shown in Figures 2B-2F. The particles of broken bezoar were fewest in the control (Figure 2B).

By contrast, more particles of the broken bezoar were observed after incubation with Coca-Cola® (Figure 2C) or Coca-Cola Zero® (Figure 2D), even compared to cellulase (Figure 2E) or papain (Figure 2F). Next, the undissolved bezoar fragments were extracted, and their weights were measured after 30 min of air-drying and compared the values with the weight at pre-incubation. The phytolytic activities of the solvents are summarized in Figure 3. Bezoar fragments showed significantly better dissolubility in Coca-Cola Zero® (16.1% ± 0.4%) than in water (7.0% ± 5.3%) ($P < 0.05$, t test). The dissolubility in Coca-Cola® (18.5% ± 5.8%) was also higher than that in cellulase (10.1

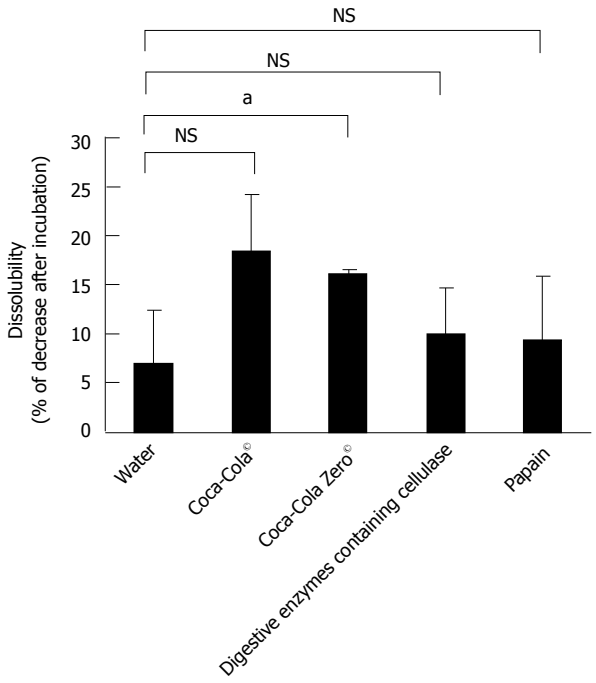

Figure 3 The dissolubility of bezoar fragments. The mean dissolubility of bezoar fragments was highest by Coca-Cola®, but the difference between Coca-Cola® and water was not significant (P = 0.06) due to the relatively large standard deviation. NS: Not significant. $^{a}P < 0.05$.

± 4.5%), papain (9.5% ± 6.5%), and water, though the difference between Coca-Cola® and water was not significant (P = 0.06) due to the relatively large standard deviation. Overall, our study obtained the first evidence of the comparative benefits of Coca-Cola® beverages. In addition, Coca-Cola® and Coca-Cola Zero® showed equal phytolytic activities *in vitro*.

Although the mechanism has not been fully elucidated, it has been speculated that some ingredients in Coca-Cola® play a key role in bezoar dissolution. Such hypotheses include enhanced bezoar digestion by the mucolytic effect of sodium bicarbonate and/or by the acidifying effect of carbonic acid and phosphoric acid. Destruction of the bezoar may also be assisted by the carbon dioxide bubbles, which penetrate into the bezoar through the microscopic pores on its surface[5,20,56,58,59]. Diet Coke®, Coca-Cola Light®, and Coca-Cola Zero® all contain these ingredients. Since the clinical success of bezoar dissolution by Diet Coke®, Coca-Cola Light®, and Coca-Cola Zero® was documented in previous reports, several authors have speculated that these sugar-free beverages have the same effect of bezoar dissolution as the regular version of Coca-Cola®[5,60]. Although our study was conducted using the phytobezoar obtained from a single patient, the results confirmed this speculation, revealing almost equal bezoar dissolubility between Coca-Cola® and Coca-Cola Zero®. A future study should determine whether or not other carbonated beverages such as Pepsi-Cola® and carbonated water have the same lytic action against phytobezoars.

Despite the number of reports describing a successful treatment outcome of phytobezoars, however, persimmon phytobezoars may not be dissolved by Coca-Cola® beverages alone because of their hard consistency. For example, Lee *et al*[53] reported that complete dissolution by Coca-Cola® administration was observed in 4/6 patients (66.7%) with non-persimmon phytobezoars, whereas Coca-Cola® was completely ineffective in all 11 patients with persimmon phytobezoars (0%) in whom this method was attempted. For such phytobezoars that are resistant to chemical dissolution, endoscopic fragmentation and removal in combination with or without Coca-Cola® dissolution is generally effective[55].

Papain

Papain, an enzyme extracted from the Carica papaya plant, has been used as an alternative enzymatic therapy for bezoars. Generally, papain rapidly hydrolyzes a variety of proteins based on the proteolytic activity. Several authors have described bezoar dissolution by the oral administration of Adolph's Meat Tenderizer or gastric lavage with the tenderizing agent[61]. However, papain is no longer included in Adolph's Meat Tenderizer, because the manufacturer changed the chief ingredient from papain to bromelain, which is another proteolytic enzyme contained in pineapples. Papain is currently used in other products for tenderizing meat, in clarifying beer, and in biochemical research involving the analysis of proteins. Papain is thus still commercially available, but physicians should keep in mind that adverse events such as gastric ulceration and esophageal perforation following papain therapy have been documented[62,63].

In our previous study, papain powders were extracted from a capsule of dietary supplement, but the bezoar dissolubility in papain was not significantly higher than that in water (Figures 2 and 3)[4]. The insufficient dissolubility of bezoars in papain is contradictory to the previous successful clinical outcomes. We speculate that this might be due to the small dose size of the active enzymes in a dietary supplement capsule. An excess doses of papain supplement may be effective for the dissolution of bezoars, but it is impractical in a clinical setting because the maximum dose of papain for safe ingestion have not been elucidated.

Cellulase

Cellulase has been widely used for phytobezoar treatment, since vegetables and fruits contain large amounts of cellulose. The enhancement of phytobezoar digestion by cellulase may originate in its degradation activity against cellulose by cleaving the glycosidic bond. A successful outcome of bezoar treatment with tablet-form gastroenterase (containing pepsin, pancreatic enzyme concentrate, cellulase, and dehydrocholic acid) was described in the 1970s[64,65]. However, these tablets have been discontinued. Additionally, in many countries, cellulase is not readily available for ingestion as a commercial product, or even as a medication under prescription[60]. For example,

in the United States, cellulase is only available as a dietary supplement in combination with other digestive enzymes. In our previous study, however, one capsule of cellulase supplement was not effective for the lysis of bezoar fragments (Figures 2 and 3)[4].

Endoscopic removal

Endoscopic fragmentation has often been applied for gastric bezoars. Various types of endoscopy devices including biopsy forceps, alligator forceps, a polypectomy snare, a basket catheter, an argon plasma coagulation device and an electrohydraulic lithotripsy device have been used for fragmentation[3]. Kurt *et al*[66] recently reported the first patient with a gastric bezoar successfully treated with a bezoaratom, an oval polyfilament snare device specifically designed for the treatment of bezoars. Endoscopic spraying or the endoscopic injection of Coca-Cola® into bezoars probably assists fragmentation *via* lytic activity for gastrointestinal bezoars[20,67]. It should be noted that persimmon phytobezoars may require multiple sessions of endoscopic treatment to be completely broken down because of the hard consistency[3].

Trichobezoars are resistant to enzymatic degradation and pharmacotherapy. Endoscopic fragmentation is generally ineffective due to the high density of the hair conglomerate. In a review of the 40 reported trichobezoar cases, endoscopic removal was successful in only two of the cases; the other cases required laparotomy or laparoscopic surgery[35]. In our experience, however, we achieved fragmentation of trichobezoar in one patient by using an electrosurgical knife[3]. Electrosurgical knives developed for endoscopic submucosal dissection may thus be useful for treating trichobezoars.

Surgical removal

Surgical removal is inevitable for cases presenting with ileus or patients with refractory bezoars. Bezoars were traditionally managed by open surgical retrieval (laparotomy). Recent papers emphasized the importance of a minimally invasive surgical approach by laparoscopy in the management of gastrointestinal bezoars[54,68-70]. Intraoperative endoscopic removal has also been reported[71].

Other treatment strategies

In some patients, the administration of prokinetic agents was reportedly effective in resolving the gastric bezoar[3]. As described above, a reduction in the evacuation of indigestible foods due to insufficient gastric motor activity can lead to bezoar formation. Prokinetic agents such as itopride, mosapride, and metoclopramide may improve gastric emptying and facilitate the break-down of a bezoar by enhancing contractions of the gastrointestinal tract and increasing their frequency, if the bezoar is soft enough to be digested with gastrointestinal peristalsis.

Spontaneous disappearance of a bezoar under the absence of specific treatment was also observed in some patients[3,6]. The etiology of the bezoars and the mechanisms underlying how the bezoars were digested in these patients remain to be determined. However, careful follow-up without any specific treatment is a possible option in the management of bezoar patients, if they are in stable condition[6].

CONCLUSION

We reviewed the prevalence, classification, structure, predisposing factors, manifestations, diagnosis, and treatment strategies of gastrointestinal bezoars. Endoscopy and CT play key roles in the detection and management of bezoars. The administration of Coca-Cola® is currently the primary choice for phytobezoar treatment because it is safe, inexpensive, and effective. Endoscopic fragmentation or surgical removal should be applied in urgent cases, such as those manifesting gastrointestinal bleeding and/or ileus, and patients with refractory bezoars.

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REFERENCES

1 **Sanders MK**. Bezoars: from mystical charms to medical and nutritional management. *Pract Gastroenterol* 2004; **18**: 37-50

2 **Iwamuro M**, Urata H, Furutani M, Kawai Y, Shiraha H, Takaki A, Okada H, Yamamoto K. Ultrastructural analysis of a gastric persimmon phytobezoar. *Clin Res Hepatol Gastroenterol* 2014; **38**: e85-e87 [PMID: 24360625 DOI: 10.1016/j.clinre.2013.11.005]

3 **Iwamuro M**, Tanaka S, Shiode J, Imagawa A, Mizuno M, Fujiki S, Toyokawa T, Okamoto Y, Murata T, Kawai Y, Tanioka D, Okada H, Yamamoto K. Clinical characteristics and treatment outcomes of nineteen Japanese patients with gastrointestinal bezoars. *Intern Med* 2014; **53**: 1099-1105 [PMID: 24881731 DOI: 10.2169/internalmedicine.53.2114]

4 **Iwamuro M**, Kawai Y, Shiraha H, Takaki A, Okada H, Yamamoto K. In vitro analysis of gastric phytobezoar dissolubility by coca-cola, coca-cola zero, cellulase, and papain. *J Clin Gastroenterol* 2014; **48**: 190-191 [PMID: 24045274 DOI: 10.1097/MCG.0b013e3182a39116]

5 **Ertuğrul G**, Coşkun M, Sevinç M, Ertuğrul F, Toydemir T. Treatment of gastric phytobezoars with Coca-Cola given via oral route: a case report. *Int J Gen Med* 2012; **5**: 157-161 [PMID: 22393302 DOI: 10.2147/IJGM.S29453]

6 **Kadian RS**, Rose JF, Mann NS. Gastric bezoars--spontaneous

resolution. *Am J Gastroenterol* 1978; **70**: 79-82 [PMID: 696718]
7 **Ahn YH**, Maturu P, Steinheber FU, Goldman JM. Association of diabetes mellitus with gastric bezoar formation. *Arch Intern Med* 1987; **147**: 527-528 [PMID: 3827430 DOI: 10.1001/archinte.1987.00370030131025]
8 **Mihai C**, Mihai B, Drug V, Cijevschi Prelipcean C. Gastric bezoars--diagnostic and therapeutic challenges. *J Gastrointestin Liver Dis* 2013; **22**: 111 [PMID: 23539409]
9 **Yakan S**, Sirinocak A, Telciler KE, Tekeli MT, Deneçli AG. A rare cause of acute abdomen: small bowel obstruction due to phytobezoar. *Ulus Travma Acil Cerrahi Derg* 2010; **16**: 459-463 [PMID: 21038126]
10 **Ghosheh B**, Salameh JR. Laparoscopic approach to acute small bowel obstruction: review of 1061 cases. *Surg Endosc* 2007; **21**: 1945-1949 [PMID: 17879114 DOI: 10.1007/s00464-007-9575-3]
11 **de Toledo AP**, Rodrigues FH, Rodrigues MR, Sato DT, Nonose R, Nascimento EF, Martinez CA. Diospyrobezoar as a cause of small bowel obstruction. *Case Rep Gastroenterol* 2012; **6**: 596-603 [PMID: 23271989 DOI: 10.1159/000343161]
12 **Cifuentes Tebar J**, Robles Campos R, Parrilla Paricio P, Lujan Mompean JA, Escamilla C, Liron Ruiz R, Pellicer Franco EM. Gastric surgery and bezoars. *Dig Dis Sci* 1992; **37**: 1694-1696 [PMID: 1425068 DOI: 10.5009/gnl.2014.8.4.400]
13 **Acar T**, Tuncal S, Aydin R. An unusual cause of gastrointestinal obstruction: bezoar. *N Z Med J* 2003; **116**: U422 [PMID: 12740615]
14 **Moffat JH**, Fraser WP. Gastric Bezoar. *Can Med Assoc J* 1962; **87**: 813-814 [PMID: 20327264]
15 **Park SE**, Ahn JY, Jung HY, Na S, Park SJ, Lim H, Choi KS, Lee JH, Kim do H, Choi KD, Song HJ, Lee GH, Kim JH. Clinical outcomes associated with treatment modalities for gastrointestinal bezoars. *Gut Liver* 2014; **8**: 400-407 [PMID: 25071905]
16 **Gayà J**, Barranco L, Llompart A, Reyes J, Obrador A. Persimmon bezoars: a successful combined therapy. *Gastrointest Endosc* 2002; **55**: 581-583 [PMID: 11923779 DOI: 10.1067/mge.2002.122332]
17 **Moriel EZ**, Ayalon A, Eid A, Rachmilewitz D, Krausz MM, Durst AL. An unusually high incidence of gastrointestinal obstruction by persimmon bezoars in Israeli patients after ulcer surgery. *Gastroenterology* 1983; **84**: 752-755 [PMID: 6825987]
18 **Granot E**, Fich A, Ayalon A, Manny J, Winograd I, Schwartz J, Rachmilewitz D. An epidemic of persimmon bezoars in Israel. *Isr J Med Sci* 1984; **20**: 167-169 [PMID: 6706544]
19 **Altintoprak F**, Degirmenci B, Dikicier E, Cakmak G, Kivilcim T, Akbulut G, Dilek ON, Gunduz Y. CT findings of patients with small bowel obstruction due to bezoar: a descriptive study. *ScientificWorldJournal* 2013; **2013**: 298392 [PMID: 23690741 DOI: 10.1155/2013/298392]
20 **Ladas SD**, Kamberoglou D, Karamanolis G, Vlachogiannakos J, Zouboulis-Vafiadis I. Systematic review: Coca-Cola can effectively dissolve gastric phytobezoars as a first-line treatment. *Aliment Pharmacol Ther* 2013; **37**: 169-173 [PMID: 23252775 DOI: 10.1111/apt.12141]
21 **Holloway WD**, Lee SP, Nicholson GI. The composition and dissolution of phytobezoars. *Arch Pathol Lab Med* 1980; **104**: 159-161 [PMID: 6892599]
22 **Matsuo T**, Ito S. The chemical structure of kaki-tannin from immature fruit of the persimmon. *Agric Biol Chem* 1978; **126**: 421-424
23 **Krausz MM**, Moriel EZ, Ayalon A, Pode D, Durst AL. Surgical aspects of gastrointestinal persimmon phytobezoar treatment. *Am J Surg* 1986; **152**: 526-530 [PMID: 3777332 DOI: 10.1016/0002-9610(86)90221-7]
24 **Maki T**, Suzuki N. Experimental formation of persimmon-bezoar. *Tohoku J Exp Med* 1965; **86**: 168-177 [PMID: 5835264 DOI: 10.1620/tjem.86.168]
25 **Gorter RR**, Kneepkens CM, Mattens EC, Aronson DC, Heij HA. Management of trichobezoar: case report and literature review. *Pediatr Surg Int* 2010; **26**: 457-463 [PMID: 20213124 DOI: 10.1007/s00383-010-2570-0]
26 **Diefenbach GJ**, Reitman D, Williamson DA. Trichotillomania: a challenge to research and practice. *Clin Psychol Rev* 2000; **20**: 289-309 [PMID: 10779896 DOI: 10.1016/S0272-7358(98)00083-X]
27 **Carr JR**, Sholevar EH, Baron DA. Trichotillomania and trichobezoar: a clinical practice insight with report of illustrative case. *J Am Osteopath Assoc* 2006; **106**: 647-652 [PMID: 17192451]
28 **Bouwer C**, Stein DJ. Trichobezoars in trichotillomania: case report and literature overview. *Psychosom Med* 1998; **60**: 658-660 [PMID: 9773774]
29 **Sehgal VN**, Srivastava G. Trichotillomania +/- trichobezoar: revisited. *J Eur Acad Dermatol Venereol* 2006; **20**: 911-915 [PMID: 16922936]
30 **DeBakey M**, Ochsner A. Part 1: Bezoars and concretions. *Surgery* 1938; **4**: 934-963
31 **Vaughan ED**, Sawyers JL, Scott HW. The Rapunzel syndrome. An unusual complication of intestinal bezoar. *Surgery* 1968; **63**: 339-343 [PMID: 5638179]
32 **Naik S**, Gupta V, Naik S, Rangole A, Chaudhary AK, Jain P, Sharma AK. Rapunzel syndrome reviewed and redefined. *Dig Surg* 2007; **24**: 157-161 [PMID: 17476105 DOI: 10.1159/000102098]
33 **Stack PE**, Thomas E. Pharmacobezoar: an evolving new entity. *Dig Dis* 1995; **13**: 356-364 [PMID: 8590522 DOI: 10.1159/000171515]
34 **Schneider RP**. Perdiem causes esophageal impaction and bezoars. *South Med J* 1989; **82**: 1449-1450 [PMID: 2814636 DOI: 10.1097/00007611-198911000-00032]
35 **Frohna WJ**. Metamucil bezoar: an unusual cause of small bowel obstruction. *Am J Emerg Med* 1992; **10**: 393-395 [PMID: 1616534 DOI: 10.1016/0735-6757(92)90030-2]
36 **Agha FP**, Nostrant TT, Fiddian-Green RG. "Giant colonic bezoar": a medication bezoar due to psyllium seed husks. *Am J Gastroenterol* 1984; **79**: 319-321 [PMID: 6711534]
37 **Oka A**, Ishihara S, Kinoshita Y. An unusual case of a gastric foreign body. *Gastroenterology* 2013; **145**: 1206, 1500-1501 [PMID: 24409485]
38 **Taylor JR**, Streetman DS, Castle SS. Medication bezoars: a literature review and report of a case. *Ann Pharmacother* 1998; **32**: 940-946 [PMID: 9762382 DOI: 10.1345/aph.17420]
39 **Stack PE**, Patel NR, Young MF, Ferslew KE, Thomas E. Pharmacobezoars--the irony of the antidote: first case report of nifedipine XL bezoar. *J Clin Gastroenterol* 1994; **19**: 264-265 [PMID: 7806842 DOI: 10.1097/00004836-199410000-00020]
40 **Chung M**, Reitberg DP, Gaffney M, Singleton W. Clinical pharmacokinetics of nifedipine gastrointestinal therapeutic system. A controlled-release formulation of nifedipine. *Am J Med* 1987; **83**: 10-14 [PMID: 3503594 DOI: 10.1016/0002-9343(87)90630-9]
41 **Levkoff AH**, Gadsden RH, Hennigar GR, Webb CM. Lactobezoar and gastric perforation in a neonate. *J Pediatr* 1970; **77**: 875-877 [PMID: 5537311 DOI: 10.1016/S0022-3476(70)80252-9]
42 **Heinz-Erian P**, Gassner I, Klein-Franke A, Jud V, Trawoeger R, Niederwanger C, Mueller T, Meister B, Scholl-Buergi S. Gastric lactobezoar - a rare disorder? *Orphanet J Rare Dis* 2012; **7**: 3 [PMID: 22216886 DOI: 10.1186/1750-1172-7-3]
43 **Bos ME**, Wijnen RM, de Blaauw I. Gastric pneumatosis and rupture caused by lactobezoar. *Pediatr Int* 2013; **55**: 757-760 [PMID: 23789736 DOI: 10.1111/ped.12164]
44 **WOLF RS**, BRUCE J. Gastrotomy for lactobezoar in a newborn infant. *J Pediatr* 1959; **54**: 811-812 [PMID: 13655177 DOI: 10.1016/S0022-3476(59)80150-5]
45 **Yeh J**, Saul T, Gingrich A, Wassermann J. Bezoar. *J Emerg Med* 2013; **45**: 615-616 [PMID: 23890688 DOI: 10.1016/j.jemermed.2013.02.003]
46 **Kumar GS**, Amar V, Ramesh B, Abbey RK. Bizarre metal bezoar: a case report. *Indian J Surg* 2013; **75**: 356-358 [PMID: 24426615 DOI: 10.1007/s12262-012-0706-2]
47 **Zheng PP**, Wang BY, Wang F, Ao R, Wang Y. Esophageal space-occupying lesion caused by Ascaris lumbricoides. *World J Gastroenterol* 2012; **18**: 1552-1554 [PMID: 22509089 DOI: 10.3748/wjg.v18.i13.1552]
48 **Goldman RD**, Schachter P, Katz M, Bilik R, Avigad I. A bizarre bezoar: case report and review of the literature. *Pediatr Surg Int* 1998; **14**: 218-219 [PMID: 9880754 DOI: 10.1007/s003830050492]
49 **Daane AH**. Yttrium. In: The Encyclopedia of the Chemical

Elements, edited by Hampel CA. New York, NY: Reinhold Book Corporation, 1968
50 **LaFountain J**. Could your patient's bowel obstruction be a bezoar? *Todays Surg Nurse* 1999; **21**: 34-37 [PMID: 10232288]
51 **Campos RR**, Paricio PP, Albasini JLA, Riquelme Riquelme J, Cifuentes Tebar J, Luján Mompeán JA. Gastrointestinal bezoars. Presentation of 60 cases. *Dig Surg* 1990; **7**: 39-44 [DOI: 10.1159/000171939]
52 **Simsek Z**, Altinbas A, Yuksel I, Yuksel O. Effective treatment with pineapple juice in small bowel obstruction due to phytobezoar in a gastrectomized patient. *Dig Endosc* 2011; **23**: 197 [PMID: 21429030 DOI: 10.1111/j.1443-1661.2010.01059.x]
53 **Lee BJ**, Park JJ, Chun HJ, Kim JH, Yeon JE, Jeen YT, Kim JS, Byun KS, Lee SW, Choi JH, Kim CD, Ryu HS, Bak YT. How good is cola for dissolution of gastric phytobezoars? *World J Gastroenterol* 2009; **15**: 2265-2269 [PMID: 19437568 DOI: 10.3748/wjg.15.2265]
54 **Sharma D**, Srivastava M, Babu R, Anand R, Rohtagi A, Thomas S. Laparoscopic treatment of gastric bezoar. *JSLS* 2010; **14**: 263-267 [PMID: 20932381 DOI: 10.4293/108680810X12785289144566]
55 **Zhang RL**, Yang ZL, Fan BG. Huge gastric disopyrobezoar: a case report and review of literatures. *World J Gastroenterol* 2008; **14**: 152-154 [PMID: 18176981 DOI: 10.3748/wjg.14.152]
56 **Ladas SD**, Triantafyllou K, Tzathas C, Tassios P, Rokkas T, Raptis SA. Gastric phytobezoars may be treated by nasogastric Coca-Cola lavage. *Eur J Gastroenterol Hepatol* 2002; **14**: 801-803 [PMID: 12169994 DOI: 10.1097/00042737-200207000-00017]
57 **Hayashi K**, Ohara H, Naitoh I, Okumura F, Andoh T, Itoh T, Nakazawa T, Joh T. Persimmon bezoar successfully treated by oral intake of Coca-Cola: a case report. *Cases J* 2008; **1**: 385 [PMID: 19077219 DOI: 10.1186/1757-1626-1-385]
58 **Chung YW**, Han DS, Park YK, Son BK, Paik CH, Jeon YC, Sohn JH. Huge gastric diospyrobezoars successfully treated by oral intake and endoscopic injection of Coca-Cola. *Dig Liver Dis* 2006; **38**: 515-517 [PMID: 16330268 DOI: 10.1016/j.dld.2005.10.024]
59 **Sanderson I**, Ibberson O, Fish EB. Gastric phytobezoar following gastrectomy. *Can Med Assoc J* 1971; **104**: 1115 passim [PMID: 5580753]
60 **Kramer SJ**, Pochapin MB. Gastric phytobezoar dissolution with ingestion of diet coke and cellulase. *Gastroenterol Hepatol* (N Y) 2012; **8**: 770-772 [PMID: 24672417]
61 **Dwivedi AJ**, Chahin F, Agrawal S, Patel J, Khalid M, Lakra Y. Gastric phytobezoar: treatment using meat tenderizer. *Dig Dis Sci* 2001; **46**: 1013-1015 [PMID: 11341642]
62 **Dugan FA**, Lilly JO, McCaffery TD. Dissolution of a phytobezoar with short-term medical management. *South Med J* 1972; **65**: 313-316 [PMID: 5016447 DOI: 10.1097/00007611-197203000-00013]
63 **Holsinger JW**, Fuson RL, Sealy WC. Esophageal perforation following meat impaction and papain ingestion. *JAMA* 1968; **204**: 734-735 [DOI: 10.1001/jama.1968.03140210090027]
64 **Bruck HM**. Letter: Gastric phytobezoar. *JAMA* 1975; **231**: 26 [PMID: 1243563 DOI: 10.1001/jama.1975.03240130020017]
65 **Gold MH**, Patteson TE, Green GI. Cellulase bezoar injection: a new endoscopic technique. *Gastrointest Endosc* 1976; **22**: 200-202 [PMID: 1269883 DOI: 10.1016/S0016-5107(76)73753-2]
66 **Kurt M**, Posul E, Yilmaz B, Korkmaz U. Endoscopic removal of gastric bezoars: an easy technique. *Gastrointest Endosc* 2014; In press
67 **Lin CS**, Tung CF, Peng YC, Chow WK, Chang CS, Hu WH. Successful treatment with a combination of endoscopic injection and irrigation with coca cola for gastric bezoar-induced gastric outlet obstruction. *J Chin Med Assoc* 2008; **71**: 49-52 [PMID: 18218561 DOI: 10.1016/S1726-4901(08)70073-X]
68 **Kannan NL**, Singaraju H, Sim SW. Laparoscopic-assisted removal of gastric trichobezoar: a novel technique to reduce operative complications and time. *J Pediatr Surg* 2013; **48**: 1826-1827 [PMID: 23932631 DOI: 10.1016/j.jpedsurg.2013.05.069]
69 **Javed A**, Agarwal AK. A modified minimally invasive technique for the surgical management of large trichobezoars. *J Minim Access Surg* 2013; **9**: 42-44 [PMID: 23626422 DOI: 10.4103/0972-9941.107142]
70 **Nirasawa Y**, Mori T, Ito Y, Tanaka H, Seki N, Atomi Y. Laparoscopic removal of a large gastric trichobezoar. *J Pediatr Surg* 1998; **33**: 663-665 [PMID: 9574777 DOI: 10.1016/S0022-3468(98)90342-6]
71 **Gong EJ**, Jung HY, Kim do H, Lim H, Song KB. Intraoperative endoscopic removal of a duodenal bezoar in a patient with intestinal malrotation. *Gastrointest Endosc* 2014; **80**: 346; discussion 347 [PMID: 24726265 DOI: 10.1016/j.gie.2014.02.028]

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REVIEW

Endoscopic diagnosis and management of type I neuroendocrine tumors

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Abstract

Type I gastric neuroendocrine tumors (TI-GNETs) are related to chronic atrophic gastritis with hypergastrinemia and enterochromaffin-like cell hyperplasia. The incidence of TI-GNETs has significantly increased, with the great majority being TI-GNETs. TI-GNETs present as small (< 10 mm) and multiple lesions endoscopically and are generally limited to the mucosa or submucosa. Narrow band imaging and high resolution magnification endoscopy may be helpful for the endoscopic diagnosis of TI-GNETs. TI-GNETs are usually histologically classified by World Health Organization criteria as G1 tumors. Therefore, TI-GNETs tend to display nearly benign behavior with a low risk of progression or metastasis. Several treatment options are currently available for these tumors, including surgical resection, endoscopic resection, and endoscopic surveillance. However, debate persists about the best management technique for TI-GNETs.

Key words: Gastric neuroendocrine tumor; Narrow band imaging; Magnifying endoscopy; Endoscopic submucosal dissection; Endoscopic surveillance

Core tip: The incidence of type I gastric neuroendocrine tumors (TI-GNETs) has significantly increased, TI-GNETs are the most frequently diagnosed of all GNETs, accounting for about 70%-80%. Endoscopically, TI-GNETs are present as small (< 10 mm), polypoid lesions or, more frequently, as smooth, rounded submucosal lesions. Especially, narrow band imaging and high resolution magnification endoscopy may be helpful for the endoscopic diagnosis of TI-GNETs. TI-GNETs tend to display a nearly benign behavior and a low risk of progression or metastasis in spite of submucosal invasion. Therefore, endoscopic submucosal dissection is a feasible technique for the removal of TI-GNETs.

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INTRODUCTION

Neuroendocrine tumors (NETs), originally termed

Table 1 Characteristics of gastric neuroendocrine tumors

Characteristic	Type Ⅰ GNETs	Type Ⅱ GNETs	Type Ⅲ GNETs
Proportion of all GNETs	70%-80%	5%-10%	10%-15%
Associated disease	Chronic atrophic gastritis	MEN type 1/ZES	None
Gender	Women > men	Women = men	Women < men
Tumor number	⩾ 1	⩾ 1	1
Tumor size	< 10 mm	< 10 mm	Often > 20 mm
Tumor location	Fundus or corpus	Fundus or corpus	Any region
Histology	Well differentiated	Well differentiated	From well to poorly differentiated
Invasion depth	Mucosa or submucosa	Mucosa or submucosa	Any depth
Serum gastrin level	High	High	Normal
Gastric pH	Low	High	Normal
Metastasis risk	2%-5%	10%-20%	> 50%
Tumor-related death	0	< 10%	25%-30%
Prognosis	Excellent	Good	Poor

GNET: Gastric neuroendocrine tumor; MEN: Multiple endocrine neoplasia; ZES: Zollinger-Ellison syndrome.

carcinoid tumors, arise from neuroendocrine cells of the diffuse neuroendocrine system[1]. NETs are rare neoplasms; however, the incidence of gastrointestinal NETs (GNET) is gradually increasing with all NETs[2,3], while the ratio of GNETs to all GI NETs has increased according to the latest reports[4-9]. This increase in the incidence of GNETs reflects the true increase (that the incidence of GNET is increasing); however, this also might be related to improvements in diagnostic technology including endoscopy and increased GNET awareness. Because of the increasing incidence and prevalence, GNETs represent a substantial clinical problem.

GNETs are classified into three distinct subgroups: types Ⅰ to Ⅲ[10]. Table 1 shows the clinical characteristics of these three types[11-19]. Type Ⅰ GNETs (TI-GNETs) arise in patients with chronic atrophic gastritis (CAG), including autoimmune gastritis (AIG; *i.e.*, type-A gastritis) and *Helicobacter pylori (H. pylori)*-associated atrophic gastritis. Most TI-GNETs are small (< 10 mm), multiple, located within the gastric fundus or corpus, and limited to the mucosa or submucosa. TI-GNETs comprise the great majority (70%-80%) of GNETs. TI-GNETs are generally considered benign, with low metastasis rates and a 100% long-term survival rate.

Type Ⅱ GNETs, which account for 5%-6% of all GNETs, are associated with the gastrin-secreting neoplasms in multiple endocrine neoplasia-Zollinger-Ellison syndrome (MEN-ZES). Therefore, hyperacidity-induced peptic ulceration is often seen in patients with type Ⅱ GNETs. Type Ⅱ GNETs are also small, multiple, and considered benign. However, the survival rate of patients with type Ⅱ GNETs is lower than that of patients with type Ⅰ because of the course of the gastrinoma[20].

On the contrary, type Ⅲ GNETs are sporadic tumors whose development is unrelated to gastrin conditions. Type Ⅲ NETs are often single and large, have a diameter around 20 mm, and comprise approximately 10%-15% of all GNETs. These GNETs behave more aggressively and are usually metastatic and spread to the regional lymph nodes or liver.

This review focuses on TI-GNET pathogenesis, endoscopic diagnosis, and management.

TI-GNET PATHOGENESIS

TI-GNETs are associated with CAG, which leads to hypergastrinemia and enterochromaffin-like (ECL) cell hyperplasia. The loss of fundic glands seen in CAG results in a lack of acid production (achlorhydria). In response to achlorhydria, antral G-cells undergo hyperplasia and secrete more gastrin, resulting in hypergastrinemia. Gastrin stimulates gastric epithelial cell proliferation and acts as a trophic factor for ECL cells and leads to ECL cell hyperplasia. Therefore, hypergastrinemia results in the progression to TI-GNET development.

In either AIG- or *H. pylori*-associated gastritis, under the CAG condition, a lack of gastric acid production results in hypergastrinemia and leads to TI-GNET progression. In the AIG, anti-parietal cell antibody acts on gastric parietal cells, leading to acid secretion disorder and resulting in more gastrin secretion by antral G-cells. The role of *H. pylori* in TI-GNET development is unclear. However, it is well known that *H. pylori* infection induces hypergastrinemia[21,22]. *H. pylori* induces gastric mucosal atrophy, resulting in low acid output[23]. The negative feedback loop created by this low acid output causes hypergastrinemia. One possible mechanism is that antibodies against *H. pylori* may act like those against parietal cells[24-26]. Furthermore, *H. pylori* lipopolysaccharide stimulates DNA synthesis in ECL cells, suggesting that it may contribute to ECL cell hyperplasia[27]. Some reports have suggested that *H. pylori* infection might be a risk factor for TI-GNET in humans due to hypergastrinemia[28,29]. However, a minority of patients with CAG had TI-GNETs; therefore, it has been proposed that other cofactors (*i.e.*, Reg[30], mcl-1[31], *MEN-1* gene mutation[32]) might play a role in TI-GNET development.

Proton pump inhibitors (PPI) create hypergastrinemia secondary to gastric hypoacidity. Therefore, PPI treatment causes ECL hyperplasia in rats[33,34]. In humans, there are some case reports of GNETs that developed after long-term PPI treatment[35-38], and one revealed disappearance of the tumors after PPI treatment discontinuation[38]. However, the number of reports about GNETs compared to those on PPI users remains very small, and it is generally accepted that continual PPI use is not associated with GNET development in

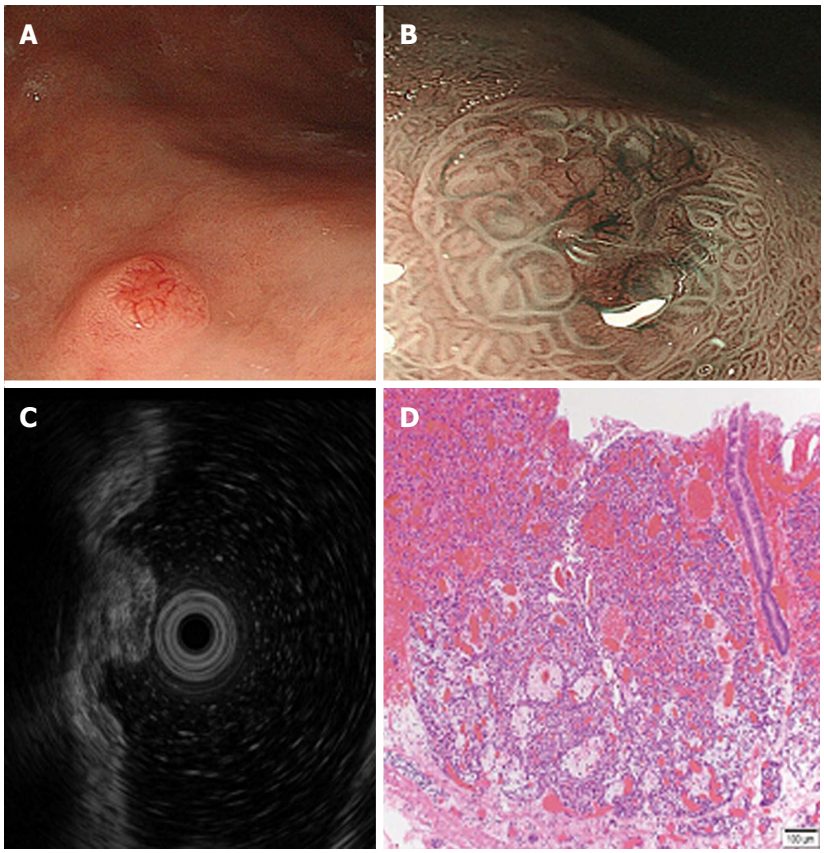

Figure 1 Type Ⅰ gastric neuroendocrine tumor. A: Conventional endoscopic image taken under white light. A hemispherical reddish polyp with a central depression is visible; B: Magnifying endoscopic image taken with a narrow band imaging system. Gastric pit-like structures present on the tumor's surface, except for the central depression. In the central depression, the pit-like structure was not present, whereas dilated blackish-brown subepithelial vessels with cork-screw capillaries are visible; C: Endoscopic ultrasound showing a hypoechoic intramural structure in the second layer of the tumor; D: Histological appearance. Magnification (40 ×) of a hematoxylin-and-eosin–stained section of the tumor revealing a gastric neuroendocrine tumor limited to the mucosa.

humans.

TI-GNET DIAGNOSIS

Clinical features

Most patients with TI-GNETs have no specific symptoms related to "carcinoid syndrome"[39,40] such as flushing, tachycardia, and diarrhea. However, those with TI-GNET have nonspecific symptoms (nausea, abdominal pain, dyspepsia)[41] or pernicious anemia complicated by AIG. Therefore, TI-GNETs are detected incidentally during esophagogastroduodenoscopy.

TI-GNETs are more prevalent in women[14,16], a finding that is attributed to the fact that AIG occurs more commonly in females[42]. AIG is also substantially more common in patients with other autoimmune-related diseases (type 1 diabetes mellitus[43], autoimmune thyroiditis[44], and primary biliary cirrhosis[45]) than in the healthy population. Therefore, the existence of TI-GNETs should be also appropriately investigated in patients with those diseases. Moreover, under the condition of CAG, the stomach becomes unable to produce sufficient amounts of pepsinogen and pepsin due to gastric chief cell injury. Therefore, patients with CAG show the low pepsinogen Ⅰ level and pepsinogen Ⅰ/Ⅱ ratio on serological testing[46], while the measurement of pepsinogen Ⅰ level and pepsinogen Ⅰ/Ⅱ ratio might be helpful for distinguishing TI-GNETs from the other two GNET types.

Serum chromogranin A (CgA) levels are increased in patients with TI-GNETs[39]. However, an elevated serum CgA level is not specific to GNETs. Therefore, measuring CgA is not recommended as a routine screening but rather as a surveillance marker for monitoring GNET progression.

Endoscopy

TI-GNETs are often small (< 10 mm), multiple, and found in the gastric corpus or fundus. Endoscopically, TI-GNETs present as polypoid lesions or, more frequently, as smooth and rounded submucosal lesions[47] and may appear yellow or red in color. A depression can sometimes be seen at the center of the tumor. The use of high-resolution magnifying endoscopy (ME) and narrow band imaging (NBI) might be helpful for the endoscopic diagnosis of GNETs[48]. The ME with NBI approach provides very clear images of the fine superficial structure and microvasculature of the gastric mucosa. Endoscopic TI-GNET images are shown in Figure 1. Endoscopy with white light revealed

Table 2 Histological grading of gastrointestinal neuroendocrine neoplasms

ENETS grading	Mitotic index (× 10 HPF)	Ki-67 proliferation index (%)	WHO classification 2010
G1	< 2	≤ 2	NET G1 (carcinoid)
G2	2-20	3-20	NET G2
G3	> 20	> 20	NEC G3; large-cell or small-cell type

ENETS: European neuroendocrine tumor society; HPF: High power field; NET: Neuroendocrine tumor; NEC: Neuroendocrine carcinoma.

a hemispherical reddish polyp with or without a central depression (Figure 1A). Most of the GNET surface is covered with normal mucosa; therefore, gastric pits can be visualized in ME using the NBI system. However, in the area of the central depression, gastric glands vanish, so the gastric pits cannot be visualized. The tumor grows expansively beneath the epithelium; therefore, abnormally dilated subepithelial vessels with blackish-brown or cyan corkscrew-shaped capillaries are visible (Figure 1B). This finding reflects the fact that the tumor grew beneath the epithelium without a gland structure. Differential diagnoses include gastric lymphoma and metastatic lesions (breast cancer, lung cancer, and melanoma), which also present as protruding tumors covered with non-tumorous mucosa.

Endoscopic ultrasonography (EUS) is useful for judging GNET invasion depth[49]. On EUS, GNETs are commonly seen in the second (deeper mucosa) or third (submucosa) echo layer and have a hypoechoic intramural structure (Figure 1C). The tumors generally have a hypoechoic structure with uniform echotexture. The tumor margins are typically well defined and smooth, and the overall shape is round and oval. A 20 MHz frequency ultrasound probe is generally useful for the evaluation of small GNETs; however, lesions > 20 mm may require the use of a lower frequency (12 MHz) probe[50].

Additionally, as documented above, the greater portions of these tumors are covered with normal mucosa; therefore, the collection of adequate endoscopic biopsy specimens in the deeper cut is required for diagnosis. Sampling biopsy should be taken of not only the TI-GNET lesion but also each antrum and corpus/fundus to assess for the presence of atrophic gastritis and hyperplastic/dysplastic proliferation of ECL cells as TI-GNET precursors[51].

Histology

TI-GNETs are composed of small uniform cells in nests and infiltrating strands with a ribbon-like, tubular, or acinar pattern (Figure 1D). According to the European Neuroendocrine Tumor Society (ENETS) consensus proposal in 2006, NETs are classified by counting mitosis and Ki67 index (Table 2)[52]. Based on this grading method, in 2010, the World Health Organization (WHO) classification[53], histological classification of NETs is based on proliferation and differentiation: G1 NET, G2 NET, neuroendocrine carcinoma (NEC), mixed adenoneuroendocrine carcinoma, and hyperplastic and pre-neoplastic lesions. A G3 tumor classified by ENETS criteria would correspond to NEC on WHO criteria. Histologically, most TI-GNETs are G1 NETs.

Other imaging

Computed tomography or magnetic resonance imaging can provide useful information about local spread and distal metastasis to aid with tumor staging. The role of fludeoxyglucose positron emission tomography is unclear in the assessment of TI-GNETs[54]. Findings of somatostatin receptor scintigraphy, also known as an octreoscan, are often negative in TI-GNETs[55] because this method cannot usually identify small GI-NETs.

TI-GNET MANAGEMENT

The clinical management and treatment of TI-GNETs depends on tumor size and the presence of risk factors such as muscular wall infiltration, increased proliferation, and/or metastasis. Simple surveillance or endoscopic resection (ER) is generally recommended for TI-GNETs < 10 mm that have not invaded the muscularis propria or otherwise metastasized. The treatment of TI-GNETs 10-20 mm that are limited to the submucosa is controversial: ENETS guidelines recommend ER, whereas National Comprehensive Cancer Network (NCCN) guidelines[56] recommend both ER and endoscopic surveillance. Patients with TI-GNETs measuring > 20 mm, or those that have invaded beyond the submucosa, or have multiple lesions that are unsuitable for ER generally require surgical resection.

Endoscopic resection

Hitherto, endoscopic mucosal resection (EMR) has been recommended and is performed, as it is the most useful method of mucosal resection for local TI-GNETs. However, TI-GNETs frequently invade the submucosa; therefore, they are difficult to remove completely, even when small, using snare polypectomy or conventional EMR. In contrast, endoscopic submucosal dissection (ESD) is a feasible technique for the removal of tumors such as TI-GNETs within the submucosal layer. Recent reports have shown that the complete resection rate of GNETs using ESD was superior to that using EMR[57,58].

Surgical resection

Surgical resection is generally recommended for TI-GNETs > 20 mm in diameter or those that have invaded beyond the submucosa[52,56]. Moreover, surgery should also be performed in the presence of lymph nodal, distant disease spread, or poorly differentiated neoplasms[51]. For surgical therapy, local resection and/or antrectomy to reduce gastrin levels should

be chosen. Antrectomy removes G-cell–mediated hypergastrinemia; however, it might not effectively prevent recurrence and/or metastasis[59]. This suggests that TI-GNETs can grow autonomously independent of gastrin and beyond the gastrin responsive growing point. In the case of TI-GNET recurrence or persistence after local resection and antrectomy, total gastrectomy would be needed.

Medical management

Somatostatin analogs (SSAs) act on G-cells to inhibit gastrin secretion and play a role in reducing ECL cell hyperplasia. SSA treatment effectively reduces TI-GNET number and size[60-62]. However, its use cannot be recommended due to its short-term effects (*i.e.*, the tumor recurs after its cessation)[63] and its relatively high cost. Recently, natazepide (YF476), a peripheral gastrin (CCK-B) receptor antagonist, has been reported to suppress gastric acid output and ECL cell proliferation and reduce TI-GNET size and number[64]. However, there is no study on the long-term administration or large studies on CCK-B receptor antagonist treatment for TI-GNETs.

TI-GNET PROGNOSIS AND FOLLOW-UP STRATEGY

Patients with TI-GNETs generally have an excellent prognosis; in fact, disease-specific survival approaches 100%[39,40,59,60,65-74]. Tumor size and depth predict lymph node metastasis for GNETs[75], and presence of metastasis was the only factor that influenced long-term prognosis of patients with GNETs[40]. Moreover, histological tumor grading is well correlated with patient survival[68]. Therefore, the assessment of tumor metastasis, size, depth, and histological grade may predict patient prognosis. In fact, metastatic TI-GNETs are related to tumor size ⩾ 1 cm, an elevated Ki-67 index, and high serum gastrin levels[76]. On the other hand, TI-GNET recurrence rates are relatively high; however, recurrent lesions are small, indolent, and unrelated to prognosis[39,72].

Post-treatment ENETS guidelines propose that endoscopic surveillance be provided every 12 mo for patients with recurrent TI-GNET and every 24 mo for patients without recurrence[51]. NCCN guidelines recommend that patients with small (< 20 mm) TI-GNETs who did not require ER or treatment be evaluated using patient history and a physical examination every 6-12 mo[56]. The guidelines also recommend that follow-up endoscopy be performed every 6-12 mo for the first 3 years and annually thereafter if no evidence of recurrence or progression is seen[56]. However, an optimal follow-up schedule as a clinical standard has yet to be established.

CONCLUSION

The incidence of NETs has increased significantly, and the vast majority of NETs are TI-GNETs. TI-GNETs present as small (< 10 mm) and multiple lesions that are generally limited to the mucosa or submucosa. TI-GNETs tend to display a nearly benign behavior and a low risk of progression or metastasis. Several treatment options are currently available for TI-GNETs; however, their optimal management has not yet been established. Further studies on TI-GNETs are needed to develop new promising management strategies for patients with TI-GNETs.

In routine clinical practice, the careful observation of the gastric mucosa in CAG and the knowledge of the endoscopic characteristic of TI-GNETs would be required for detection of TI-GNETs. When it exists, it would be important to choose appropriate treatment after the assessment of the size, invasion, metastasis and histological grading of the tumors.

REFERENCES

1 **Solcia E**, Arnold R, Capella C, klimstra DS, Klöppel G, Komminoth P, Rindi G. Neuroendocrine neoplasms of the stomach. In: Bosman FT, Carneiro F, Hruban RH, Theise ND (ed). WHO classification of Tumours of the digestive system. Lyon: IARC, 2010: 64-68

2 **Lawrence B**, Gustafsson BI, Chan A, Svejda B, Kidd M, Modlin IM. The epidemiology of gastroenteropancreatic neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; **40**: 1-18, vii [PMID: 21349409 DOI: 10.1016/j.ecl.2010.12.005]

3 **Yao JC**, Hassan M, Phan A, Dagohoy C, Leary C, Mares JE, Abdalla EK, Fleming JB, Vauthey JN, Rashid A, Evans DB. One hundred years after "carcinoid": epidemiology of and prognostic factors for neuroendocrine tumors in 35,825 cases in the United States. *J Clin Oncol* 2008; **26**: 3063-3072 [PMID: 18565894 DOI: 10.1200/JCO.2007.15.4377]

4 **Ellis L**, Shale MJ, Coleman MP. Carcinoid tumors of the gastrointestinal tract: trends in incidence in England since 1971. *Am J Gastroenterol* 2010; **105**: 2563-2569 [PMID: 20823835 DOI: 10.1038/ajg.2010.341]

5 **Modlin IM**, Lye KD, Kidd M. A 50-year analysis of 562 gastric carcinoids: small tumor or larger problem? *Am J Gastroenterol* 2004; **99**: 23-32 [PMID: 14687136]

6 **Ito T**, Sasano H, Tanaka M, Osamura RY, Sasaki I, Kimura W, Takano K, Obara T, Ishibashi M, Nakao K, Doi R, Shimatsu A, Nishida T, Komoto I, Hirata Y, Nakamura K, Igarashi H, Jensen RT, Wiedenmann B, Imamura M. Epidemiological study of gastroenteropancreatic neuroendocrine tumors in Japan. *J Gastroenterol* 2010; **45**: 234-243 [PMID: 20058030 DOI: 10.1007/s00535-009-0194-8]

7 **Niederle MB**, Hackl M, Kaserer K, Niederle B. Gastroenteropancreatic neuroendocrine tumours: the current incidence and staging based on the WHO and European Neuroendocrine Tumour Society classification: an analysis based on prospectively collected parameters. *Endocr Relat Cancer* 2010; **17**: 909-918 [PMID: 20702725 DOI: 10.1677/ERC-10-0152]

8 **Cho MY**, Kim JM, Sohn JH, Kim MJ, Kim KM, Kim WH, Kim H, Kook MC, Park do Y, Lee JH, Chang H, Jung ES, Kim HK, Jin SY, Choi JH, Gu MJ, Kim S, Kang MS, Cho CH, Park MI, Kang YK, Kim YW, Yoon SO, Bae HI, Joo M, Moon WS, Kang DY, Chang SJ. Current Trends of the Incidence and Pathological Diagnosis of Gastroenteropancreatic Neuroendocrine Tumors (GEP-NETs) in Korea 2000-2009: Multicenter Study. *Cancer Res Treat* 2012; **44**: 157-165 [PMID: 23091441 DOI: 10.4143/crt.2012.44.3.157]

9 **Caldarella A**, Crocetti E, Paci E. Distribution, incidence, and prognosis in neuroendocrine tumors: a population based study from a cancer registry. *Pathol Oncol Res* 2011; **17**: 759-763 [PMID: 21476126 DOI: 10.1007/s12253-011-9382-y]

10 **Rindi G**, Luinetti O, Cornaggia M, Capella C, Solcia E.

Three subtypes of gastric argyrophil carcinoid and the gastric neuroendocrine carcinoma: a clinicopathologic study. *Gastroenterology* 1993; **104**: 994-1006 [PMID: 7681798]
11 **Nikou GC**, Angelopoulos TP. Current concepts on gastric carcinoid tumors. *Gastroenterol Res Pract* 2012; **2012**: 287825 [PMID: 23316222 DOI: 10.1155/2012/287825]
12 **Basuroy R**, Srirajaskanthan R, Prachalias A, Quaglia A, Ramage JK. Review article: the investigation and management of gastric neuroendocrine tumours. *Aliment Pharmacol Ther* 2014; **39**: 1071-1084 [PMID: 24628514 DOI: 10.1111/apt.12698]
13 **Li TT**, Qiu F, Qian ZR, Wan J, Qi XK, Wu BY. Classification, clinicopathologic features and treatment of gastric neuroendocrine tumors. *World J Gastroenterol* 2014; **20**: 118-125 [PMID: 24415864 DOI: 10.3748/wjg.v20.i1.118]
14 **Massironi S**, Sciola V, Spampatti MP, Peracchi M, Conte D. Gastric carcinoids: between underestimation and overtreatment. *World J Gastroenterol* 2009; **15**: 2177-2183 [PMID: 19437556]
15 **Zhang L**, Ozao J, Warner R, Divino C. Review of the pathogenesis, diagnosis, and management of type I gastric carcinoid tumor. *World J Surg* 2011; **35**: 1879-1886 [PMID: 21559999 DOI: 10.1007/s00268-011-1137-0]
16 **Scherübl H**, Cadiot G, Jensen RT, Rösch T, Stölzel U, Klöppel G. Neuroendocrine tumors of the stomach (gastric carcinoids) are on the rise: small tumors, small problems? *Endoscopy* 2010; **42**: 664-671 [PMID: 20669078 DOI: 10.1055/s-0030-1255564]
17 **Kaltsas G**, Grozinsky-Glasberg S, Alexandraki KI, Thomas D, Tsolakis AV, Gross D, Grossman AB. Current concepts in the diagnosis and management of type 1 gastric neuroendocrine neoplasms. *Clin Endocrinol* (Oxf) 2014; **81**: 157-168 [PMID: 24750249 DOI: 10.1111/cen.12476]
18 **O'Toole D**, Delle Fave G, Jensen RT. Gastric and duodenal neuroendocrine tumours. *Best Pract Res Clin Gastroenterol* 2012; **26**: 719-735 [PMID: 23582915 DOI: 10.1016/j.bpg.2013.01.002]
19 **Dakin GF**, Warner RR, Pomp A, Salky B, Inabnet WB. Presentation, treatment, and outcome of type 1 gastric carcinoid tumors. *J Surg Oncol* 2006; **93**: 368-372 [PMID: 16550587]
20 **Meko JB**, Norton JA. Management of patients with Zollinger-Ellison syndrome. *Annu Rev Med* 1995; **46**: 395-411 [PMID: 7598474]
21 **Chittajulla RS**, Ardill JES, McColl KEL. The degree of hypergastrinemia induced by Helicobacter pylori is the same in duodenal ulcer patients and asymptomatic volunteers. *Eur J Gastroenterol* 1992; **4**: 49-53
22 **Smith JT**, Pounder RE, Nwokolo CU, Lanzon-Miller S, Evans DG, Graham DY, Evans DJ. Inappropriate hypergastrinaemia in asymptomatic healthy subjects infected with Helicobacter pylori. *Gut* 1990; **31**: 522-525 [PMID: 2351302]
23 **El-Omar EM**, Oien K, El-Nujumi A, Gillen D, Wirz A, Dahill S, Williams C, Ardill JE, McColl KE. Helicobacter pylori infection and chronic gastric acid hyposecretion. *Gastroenterology* 1997; **113**: 15-24 [PMID: 9207257]
24 **Faller G**, Steininger H, Kränzlein J, Maul H, Kerkau T, Hensen J, Hahn EG, Kirchner T. Antigastric autoantibodies in Helicobacter pylori infection: implications of histological and clinical parameters of gastritis. *Gut* 1997; **41**: 619-623 [PMID: 9414967]
25 **Claeys D**, Faller G, Appelmelk BJ, Negrini R, Kirchner T. The gastric H+,K+-ATPase is a major autoantigen in chronic Helicobacter pylori gastritis with body mucosa atrophy. *Gastroenterology* 1998; **115**: 340-347 [PMID: 9679039]
26 **Negrini R**, Savio A, Poiesi C, Appelmelk BJ, Buffoli F, Paterlini A, Cesari P, Graffeo M, Vaira D, Franzin G. Antigenic mimicry between Helicobacter pylori and gastric mucosa in the pathogenesis of body atrophic gastritis. *Gastroenterology* 1996; **111**: 655-665 [PMID: 8780570]
27 **Kidd M**, Miu K, Tang LH, Perez-Perez GI, Blaser MJ, Sandor A, Modlin IM. Helicobacter pylori lipopolysaccharide stimulates histamine release and DNA synthesis in rat enterochromaffin-like cells. *Gastroenterology* 1997; **113**: 1110-1117 [PMID: 9322505]
28 **Solcia E**, Rindi G, Fiocca R, Villani L, Buffa R, Ambrosiani L, Capella C. Distinct patterns of chronic gastritis associated with carcinoid and cancer and their role in tumorigenesis. *Yale J Biol Med* 1992; **65**: 793-804; discussion 827-829 [PMID: 1341079]
29 **Sato Y**, Iwafuchi M, Ueki J, Yoshimura A, Mochizuki T, Motoyama H, Sugimura K, Honma T, Narisawa R, Ichida T, Asakura H, Van Thiel DH. Gastric carcinoid tumors without autoimmune gastritis in Japan: a relationship with Helicobacter pylori infection. *Dig Dis Sci* 2002; **47**: 579-585 [PMID: 11911346]
30 **Higham AD**, Bishop LA, Dimaline R, Blackmore CG, Dobbins AC, Varro A, Thompson DG, Dockray GJ. Mutations of RegIalpha are associated with enterochromaffin-like cell tumor development in patients with hypergastrinemia. *Gastroenterology* 1999; **116**: 1310-1318 [PMID: 10348814]
31 **Pritchard DM**, Berry D, Przemeck SM, Campbell F, Edwards SW, Varro A. Gastrin increases mcl-1 expression in type I gastric carcinoid tumors and a gastric epithelial cell line that expresses the CCK-2 receptor. *Am J Physiol Gastrointest Liver Physiol* 2008; **295**: G798-G805 [PMID: 18719002 DOI: 10.1152/ajpgi.00015.2008]
32 **D'Adda T**, Keller G, Bordi C, Höfler H. Loss of heterozygosity in 11q13-14 regions in gastric neuroendocrine tumors not associated with multiple endocrine neoplasia type 1 syndrome. *Lab Invest* 1999; **79**: 671-677 [PMID: 10378509]
33 **Bakke I**, Qvigstad G, Brenna E, Sandvik AK, Waldum HL. Gastrin has a specific proliferative effect on the rat enterochromaffin-like cell, but not on the parietal cell: a study by elutriation centrifugation. *Acta Physiol Scand* 2000; **169**: 29-37 [PMID: 10759608]
34 **Larsson H**, Carlsson E, Mattsson H, Lundell L, Sundler F, Sundell G, Wallmark B, Watanabe T, Håkanson R. Plasma gastrin and gastric enterochromaffinlike cell activation and proliferation. Studies with omeprazole and ranitidine in intact and antrectomized rats. *Gastroenterology* 1986; **90**: 391-399 [PMID: 3510144]
35 **Dawson R**, Manson JM. Omeprazole in oesophageal reflux disease. *Lancet* 2000; **356**: 1770-1771 [PMID: 11095286]
36 **Haga Y**, Nakatsura T, Shibata Y, Sameshima H, Nakamura Y, Tanimura M, Ogawa M. Human gastric carcinoid detected during long-term antiulcer therapy of H2 receptor antagonist and proton pump inhibitor. *Dig Dis Sci* 1998; **43**: 253-257 [PMID: 9512115]
37 **Jianu CS**, Fossmark R, Viset T, Qvigstad G, Sørdal O, Mårvik R, Waldum HL. Gastric carcinoids after long-term use of a proton pump inhibitor. *Aliment Pharmacol Ther* 2012; **36**: 644-649 [PMID: 22861200 DOI: 10.1111/apt.12012]
38 **Food and Drug Administration**. FDA Background. Omeprazole Magensium (Prilosec 1 TM) Astra Zeneca with Proctor and Gamble. For the Joint Meeting of the Nonprescription Drugs Advisory Committee and the Gastrointestinal Drugs Advisory Committee. On October 20, 2000
39 **Ravizza D**, Fiori G, Trovato C, Fazio N, Bonomo G, Luca F, Bodei L, Pelosi G, Tamayo D, Crosta C. Long-term endoscopic and clinical follow-up of untreated type 1 gastric neuroendocrine tumours. *Dig Liver Dis* 2007; **39**: 537-543 [PMID: 17433795]
40 **Borch K**, Ahrén B, Ahlman H, Falkmer S, Granérus G, Grimelius L. Gastric carcinoids: biologic behavior and prognosis after differentiated treatment in relation to type. *Ann Surg* 2005; **242**: 64-73 [PMID: 15973103]
41 **Granberg D**, Wilander E, Stridsberg M, Granerus G, Skogseid B, Oberg K. Clinical symptoms, hormone profiles, treatment, and prognosis in patients with gastric carcinoids. *Gut* 1998; **43**: 223-228 [PMID: 10189848]
42 **Soykan I**, Yakut M, Keskin O, Bektaş M. Clinical profiles, endoscopic and laboratory features and associated factors in patients with autoimmune gastritis. *Digestion* 2012; **86**: 20-26 [PMID: 22710370 DOI: 10.1159/000338295]
43 **De Block CE**, De Leeuw IH, Van Gaal LF. Autoimmune gastritis in type 1 diabetes: a clinically oriented review. *J Clin Endocrinol Metab* 2008; **93**: 363-371 [PMID: 18029461]
44 **Lam-Tse WK**, Batstra MR, Koeleman BP, Roep BO, Bruining MG, Aanstoot HJ, Drexhage HA. The association between autoimmune thyroiditis, autoimmune gastritis and type 1 diabetes. *Pediatr Endocrinol Rev* 2003; **1**: 22-37 [PMID: 16437010]

45 **Mörk H**, Jakob F, al-Taie O, Gassel AM, Scheurlen M. Primary biliary cirrhosis and gastric carcinoid: a rare association? *J Clin Gastroenterol* 1997; **24**: 270-273 [PMID: 9252858]

46 **Samloff IM**, Varis K, Ihamaki T, Siurala M, Rotter JI. Relationships among serum pepsinogen I, serum pepsinogen II, and gastric mucosal histology. A study in relatives of patients with pernicious anemia. *Gastroenterology* 1982; **83**: 204-209 [PMID: 7084603]

47 **Ichikawa J**, Tanabe S, Koizumi W, Kida Y, Imaizumi H, Kida M, Saigenji K, Mitomi H. Endoscopic mucosal resection in the management of gastric carcinoid tumors. *Endoscopy* 2003; **35**: 203-206 [PMID: 12584637]

48 **Singh R**, Yao K, Anagnostopoulos G, Kaye P, Ragunath K. Microcarcinoid tumor diagnosed with high-resolution magnification endoscopy and narrow band imaging. *Endoscopy* 2008; **40** Suppl 2: E12 [PMID: 18278715 DOI: 10.1055/s-2007-995393]

49 **Karaca C**, Turner BG, Cizginer S, Forcione D, Brugge W. Accuracy of EUS in the evaluation of small gastric subepithelial lesions. *Gastrointest Endosc* 2010; **71**: 722-727 [PMID: 20171632]

50 **Kojima T**, Takahashi H, Parra-Blanco A, Kohsen K, Fujita R. Diagnosis of submucosal tumor of the upper GI tract by endoscopic resection. *Gastrointest Endosc* 1999; **50**: 516-522 [PMID: 10502173]

51 **Delle Fave G**, Kwekkeboom DJ, Van Cutsem E, Rindi G, Kos-Kudla B, Knigge U, Sasano H, Tomassetti P, Salazar R, Ruszniewski P. ENETS Consensus Guidelines for the management of patients with gastroduodenal neoplasms. *Neuroendocrinology* 2012; **95**: 74-87 [PMID: 22262004 DOI: 10.1159/000335595]

52 **Rindi G**, Klöppel G, Alhman H, Caplin M, Couvelard A, de Herder WW, Erikssson B, Falchetti A, Falconi M, Komminoth P, Körner M, Lopes JM, McNicol AM, Nilsson O, Perren A, Scarpa A, Scoazec JY, Wiedenmann B. TNM staging of foregut (neuro)endocrine tumors: a consensus proposal including a grading system. *Virchows Arch* 2006; **449**: 395-401 [PMID: 16967267]

53 **Rindi G**, Arnold R, Bosman FT, Capella C, klimstra DS, Klöppel G, Komminoth P, Solcia E. Nomenclature and classification of neuroendocrine neoplasms of the digestive system. In: WHO Classification of Tumours of the Digestive System, 4th ed. Lyon: International Agency for Research on cancer (IARC), 2010: 13-14

54 **Bushnell DL**, Baum RP. Standard imaging techniques for neuroendocrine tumors. *Endocrinol Metab Clin North Am* 2011; **40**: 153-62, ix [PMID: 21349416 DOI: 10.1016/j.ecl.2010.12.002]

55 **Gibril F**, Reynolds JC, Lubensky IA, Roy PK, Peghini PL, Doppman JL, Jensen RT. Ability of somatostatin receptor scintigraphy to identify patients with gastric carcinoids: a prospective study. *J Nucl Med* 2000; **41**: 1646-1656 [PMID: 11037994]

56 **Kulke MH**, Benson AB, Bergsland E, Berlin JD, Blaszkowsky LS, Choti MA, Clark OH, Doherty GM, Eason J, Emerson L, Engstrom PF, Goldner WS, Heslin MJ, Kandeel F, Kunz PL, Kuvshinoff BW, Moley JF, Pillarisetty VG, Saltz L, Schteingart DE, Shah MH, Shibata S, Strosberg JR, Vauthey JN, White R, Yao JC, Freedman-Cass DA, Dwyer MA. Neuroendocrine tumors. *J Natl Compr Canc Netw* 2012; **10**: 724-764 [PMID: 22679117]

57 **Sato Y**, Takeuchi M, Hashimoto S, Mizuno K, Kobayashi M, Iwafuchi M, Narisawa R, Aoyagi Y. Usefulness of endoscopic submucosal dissection for type I gastric carcinoid tumors compared with endoscopic mucosal resection. *Hepatogastroenterology* 2013; **60**: 1524-1529 [PMID: 23933946 DOI: 10.5754/hge121185]

58 **Kim HH**, Kim GH, Kim JH, Choi MG, Song GA, Kim SE. The efficacy of endoscopic submucosal dissection of type I gastric carcinoid tumors compared with conventional endoscopic mucosal resection. *Gastroenterol Res Pract* 2014; **2014**: 253860 [PMID: 24693280 DOI: 10.1155/2014/253860]

59 **Gladdy RA**, Strong VE, Coit D, Allen PJ, Gerdes H, Shia J, Klimstra DS, Brennan MF, Tang LH. Defining surgical indications for type I gastric carcinoid tumor. *Ann Surg Oncol* 2009; **16**: 3154-3160 [PMID: 19727959 DOI: 10.1245/s10434-009-0687-y]

60 **Thomas D**, Tsolakis AV, Grozinsky-Glasberg S, Fraenkel M, Alexandraki K, Sougioultzis S, Gross DJ, Kaltsas G. Long-term follow-up of a large series of patients with type 1 gastric carcinoid tumors: data from a multicenter study. *Eur J Endocrinol* 2013; **168**: 185-193 [PMID: 23132699 DOI: 10.1530/EJE-12-0836]

61 **Grozinsky-Glasberg S**, Kaltsas G, Gur C, Gal E, Thomas D, Fichman S, Alexandraki K, Barak D, Glaser B, Shimon I, Gross DJ. Long-acting somatostatin analogues are an effective treatment for type 1 gastric carcinoid tumours. *Eur J Endocrinol* 2008; **159**: 475-482 [PMID: 18662970 DOI: 10.1530/EJE-08-0420]

62 **Campana D**, Nori F, Pezzilli R, Piscitelli L, Santini D, Brocchi E, Corinaldesi R, Tomassetti P. Gastric endocrine tumors type I: treatment with long-acting somatostatin analogs. *Endocr Relat Cancer* 2008; **15**: 337-342 [PMID: 18310299 DOI: 10.1677/ERC-07-0251]

63 **Jianu CS**, Fossmark R, Syversen U, Hauso Ø, Fykse V, Waldum HL. Five-year follow-up of patients treated for 1 year with octreotide long-acting release for enterochromaffin-like cell carcinoids. *Scand J Gastroenterol* 2011; **46**: 456-463 [PMID: 21133821 DOI: 10.3109/00365521.2010.539255]

64 **Fossmark R**, Sørdal Ø, Jianu CS, Qvigstad G, Nordrum IS, Boyce M, Waldum HL. Treatment of gastric carcinoids type 1 with the gastrin receptor antagonist netazepide (YF476) results in regression of tumours and normalisation of serum chromogranin A. *Aliment Pharmacol Ther* 2012; **36**: 1067-1075 [PMID: 23072686 DOI: 10.1111/apt.12090]

65 **Sato Y**, Imamura H, Kaizaki Y, Koizumi W, Ishido K, Kurahara K, Suzuki H, Fujisaki J, Hirakawa K, Hosokawa O, Ito M, Kaminishi M, Furuta T, Chiba T, Haruma K. Management and clinical outcomes of type I gastric carcinoid patients: retrospective, multicenter study in Japan. *Dig Endosc* 2014; **26**: 377-384 [PMID: 24188531 DOI: 10.1111/den.12197]

66 **Hosokawa O**, Kaizaki Y, Hattori M, Douden K, Hayashi H, Morishita M, Ohta K. Long-term follow up of patients with multiple gastric carcinoids associated with type A gastritis. *Gastric Cancer* 2005; **8**: 42-46 [PMID: 15747174]

67 **Kim BS**, Oh ST, Yook JH, Kim KC, Kim MG, Jeong JW, Kim BS. Typical carcinoids and neuroendocrine carcinomas of the stomach: differing clinical courses and prognoses. *Am J Surg* 2010; **200**: 328-333 [PMID: 20385369 DOI: 10.1016/j.amjsurg.2009.10.028]

68 **La Rosa S**, Inzani F, Vanoli A, Klersy C, Dainese L, Rindi G, Capella C, Bordi C, Solcia E. Histologic characterization and improved prognostic evaluation of 209 gastric neuroendocrine neoplasms. *Hum Pathol* 2011; **42**: 1373-1384 [PMID: 21531442 DOI: 10.1016/j.humpath.2011.01.018]

69 **Schindl M**, Kaserer K, Niederle B. Treatment of gastric neuroendocrine tumors: the necessity of a type-adapted treatment. *Arch Surg* 2001; **136**: 49-54 [PMID: 11146777]

70 **Gough DB**, Thompson GB, Crotty TB, Donohue JH, Kvols LK, Carney JA, Grant CS, Nagorney DM. Diverse clinical and pathologic features of gastric carcinoid and the relevance of hypergastrinemia. *World J Surg* 1994; **18**: 473-479; discussion 479-480 [PMID: 7725731]

71 **Merola E**, Sbrozzi-Vanni A, Panzuto F, D'Ambra G, Di Giulio E, Pilozzi E, Capurso G, Lahner E, Bordi C, Annibale B, Delle Fave G. Type I gastric carcinoids: a prospective study on endoscopic management and recurrence rate. *Neuroendocrinology* 2012; **95**: 207-213 [PMID: 21811050 DOI: 10.1159/000329043]

72 **Vannella L**, Sbrozzi-Vanni A, Lahner E, Bordi C, Pilozzi E, Corleto VD, Osborn JF, Delle Fave G, Annibale B. Development of type I gastric carcinoid in patients with chronic atrophic gastritis. *Aliment Pharmacol Ther* 2011; **33**: 1361-1369 [PMID: 21492197 DOI: 10.1111/j.1365-2036.2011.04659.x]

73 **Uygun A**, Kadayifci A, Polat Z, Yilmaz K, Gunal A, Demir H, Bagci S. Long-term results of endoscopic resection for type I gastric neuroendocrine tumors. *J Surg Oncol* 2014; **109**: 71-74 [PMID: 24165913 DOI: 10.1002/jso.23477]

74 **Rappel S**, Altendorf-Hofmann A, Stolte M. Prognosis of gastric carcinoid tumours. *Digestion* 1995; **56**: 455-462 [PMID: 8536814]

75 **Saund MS**, Al Natour RH, Sharma AM, Huang Q, Boosalis VA, Gold JS. Tumor size and depth predict rate of lymph node metastasis and utilization of lymph node sampling in surgically managed gastric carcinoids. *Ann Surg Oncol* 2011; **18**: 2826-2832

[PMID: 21455598 DOI: 10.1245/s10434-011-1652-0]
76 **Grozinsky-Glasberg S**, Thomas D, Strosberg JR, Pape UF, Felder S, Tsolakis AV, Alexandraki KI, Fraenkel M, Saiegh L, Reissman P, Kaltsas G, Gross DJ. Metastatic type 1 gastric carcinoid: a real threat or just a myth? *World J Gastroenterol* 2013; **19**: 8687-8695 [PMID: 24379587 DOI: 10.3748/wjg.v19.i46.8687]

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REVIEW

Endoscopic ultrasound guided drainage of pancreatic fluid collections: Assessment of the procedure, technical details and review of the literature

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Abstract

Endoscopic ultrasound (EUS) guided drainage of pancreatic fluid collections (PFC) has become increasingly popular and become first line management option in many centers. Use of therapeutic echoendoscopes has greatly increased the applicability of EUS guided transmural drainage. Drainage is indicated in symptomatic PFCs, PFC related infection, bleed, luminal obstruction, fistulization and biliary obstruction. EUS guided transmural drainage of PFCs is preferred in patients with non bulging lesions, portal hypertension, bleeding tendency and in those whom conventional drainage has failed. In the present decade significant progress has been made in minimally invasive endoscopic techniques. There are newer stent designs, access devices and techniques for more efficient drainage of PFCs. In this review, we discuss the EUS guided drainage of PFCs in acute pancreatitis.

Key words: Acute pancreatitis; Pancreatic fluid collections; Endoscopic ultrasound-guided drainage

Core tip: Endoscopic ultrasound guided drainage has become first line option in the management of pancreatic fluid collections in acute pancreatitis. There are many new stent designs and techniques available that has made the procedure and its outcome more impressive. In this manuscript we present a concise review on this topic.

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INTRODUCTION

Acute pancreatitis (AP) is sometimes accompanied by

Table 1 Classification of pancreatic fluid collections as per revised Atlanta classification

Acute pancreatitis
Interstitial edematous pancreatitis
Necrotizing pancreatitis (pancreatic necrosis and/or peripancreatic necrosis)
Sterile necrosis
Infected necrosis
Fluid collections during acute pancreatitis
< 4 wk after onset of acute pancreatitis
Acute peripancreatic fluid collection
ANC
⩾ 4 wk after onset of acute pancreatitis
Pancreatic pseudocyst
WOPN

ANC: Acute necrotic collection; WOPN: Walled-off pancreatic necrosis.

local complications in the form of fluid collections and necrosis. The local complications seen with AP include acute pancreatic fluid collections (PFCs), pancreatic pseudocysts, acute necrotic collections (ANCs), and walled off pancreatic necrosis (WOPN). The nature and sites of PFCs are diverse as are the management options. The recent revision of Atlanta classification has reclassified these fluid collections[1]. Acute PFCs develop in the early phase of interstitial edematous AP, and they lack a wall and are confined by the fascial planes (Table 1). They are generally not complicated and usually resolve without intervention[2]. PFCs that persist for longer than 4 wk usually develop a defined wall and are described as pancreatic pseudocysts. Pseudocysts are less commonly seen with AP; they are more common with chronic pancreatitis. ANC refers to those developing in cases of necrotizing pancreatitis. When the ANCs persist for more than 4 wk they develop into WOPN. ANC and WOPN have variable amount of necrosis and the chances of infection and complications are higher. PFCs are also seen with post-operative complications and abdominal trauma[3-6]. In this review, we will confine the discussion to AP related PFC.

There have been a lot of controversies in identifying PFCs that require intervention. The recent data indicate drainage in PFCs that are symptomatic. Other indications include PFC related infection, bleed, luminal obstruction, fistulization, and biliary obstruction[7-11]. Size alone is not a criterion for drainage of PFCs, but those larger than 6 cm are usually symptomatic. The methods of drainage include, percutaneous radiologic, endoscopic and surgical. Each of these modalities has advantages and disadvantages. A recent retrospective study comparing the two nonsurgical techniques; percutaneous radiologic *vs* endoscopic drainage (conventional transluminal drainage by forward-viewing endoscopy or endoscopic ultrasound-guided drainage) in PFC showed no significant difference between technical success rates[12]. However, percutaneous drainage was associated with a higher re-intervention rate, longer hospital stay, and increased number of subsequent abdominal imaging studies[12]. The authors concluded that, overall endoscopic drainage should be the preferred method. Another recent prospective randomized controlled trial regarding surgical drainage *vs* endoscopic ultrasound (EUS)-guided drainage for symptomatic PFCs revealed that both groups were comparable in treatment success, complications, or re-interventions. But the duration of hospitalization was less, the physical and mental health scores were better, and the total mean costs were lower for the EUS group[13]. There was also no recurrence in PFCs following endoscopic drainage, thereby showing that surgical drainage is not superior in outcome. The authors concluded that, In view of less invasiveness, lower costs, lower re-interventions, and lower morbidity endoscopic drainage should be considered as the first-line method in the management of PFCs.

Endoscopic drainage is performed by transmural route or endoscopic retrograde cholangiopancreatography (ERCP) guided transpapillary route. Transmural drainage is done for PFCs close to the lumen and can be performed by conventional method (using duodenoscope) or under EUS guidance[14,15]. The specific advantages of EUS guided intervention are: (1) EUS can confirm the presence of PFCs and distinguish it from cystic neoplasms, true cysts, gall bladder and other lymphovascular structures[16]; (2) EUS can identify the presence of solid necrotic material inside the collection. Extensive necrotic debris warrant more aggressive debridement; (3) EUS can identify the presence of any intervening vessels or organs that can be damaged at the time of puncture of PFC[17,18]; and (4) EUS is of extreme importance in localizing "non-bulging" PFCs and determining the correct site of approach into these lesions. Non-bulging PFC are present in 40% of cases[19,20]. Clinical success occurs in 70% to 87%, and complications in 11% to 34% of patients undergoing EUS drainage[7,21,22]. Improvement in techniques, availability of new accessories, stent designs and development of exchange free access devices have increased the safety and efficacy of EUS guided PFC drainage. Disadvantages of EUS drainage include the complications in the form of bleed, secondary infection, luminal perforation and stent migration. Multiloculated collections may fail to resolve completely with conventional EUS draining techniques. Lesions not close to luminal wall may not be accessible to EUS drainage.

Prerequisites for EUS drainage

The PFCs are considered for endoscopic drainage when they are symptomatic, demonstrate a well-formed wall and are located in an endoscopically accessible location (within 1 cm of the luminal wall)[7-11]. Computed tomography (CT) or magnetic resonance imaging is performed before drainage. They help in delineation of the anatomy and PFC. With expertise PFCs that have failed drainage by other methods and those in unusual locations are also considered for drainage[7,16,23]. Many experts recommend assessment of the main pancreatic duct at the time of PFC drainage with ERCP as uniden-

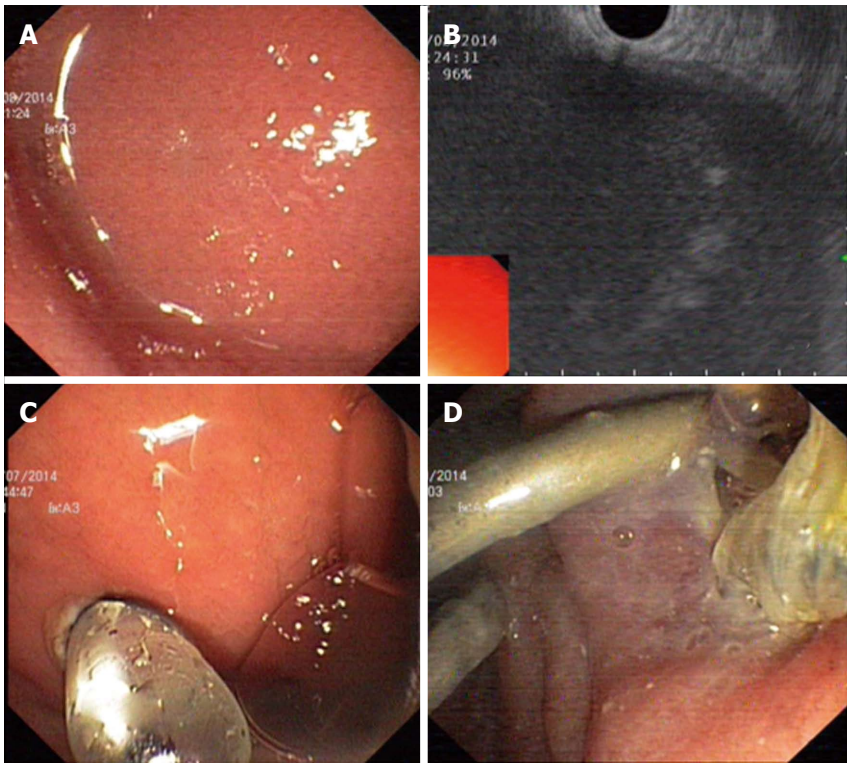

Figure 1 Endoscopic view of intragastric bulge due to pancreatic fluid collections (A), endosonographic view of pancreatic fluid collections (B), Dilation of fistula with Controlled radial expansion (CRE™) catheter balloon (C), Placement of double pigtail plastic stents through the fistula (D).

tified pancreatic duct stricture or leak may result in failure of resolution or recurrence of PFC[16,24,25].

TECHNIQUE OF EUS GUIDED DRAINAGE OF PFC

EUS guided PFC drainage is performed under conscious sedation in the left lateral position or under general anesthesia (Figures 1 and 2). Most endoscopists prefer fluoroscopy suite for procedure, since in some cases the radiologic view can be helpful either for insertion of the stent or for completing the drainage with cyst irrigation and/or additional stent placement. After identification of cyst in relation to luminal wall, evaluate the cyst with the linear array echoendoscope (with a channel size of at least 3 mm to allow placement of 10 French stents) looking for a site with optimal contact with the gastric or duodenal wall, assess with doppler to eliminate interposition of large vessels, evaluate distance of PFC to the gut wall, presence of solid debris inside the cyst, evidence of portal hypertension, communication of the cyst with the pancreatic duct and presence of coexistent biliary disease (such as common bile duct stones)[25]. After this, identify an adequate point to puncture; where there are no intervening blood vessels and the distance between the gut lumen and the PFC is less than one centimeter. Thereafter a 19 G needle (Wilson-Cook, Winston-Salem, NC, United States) is introduced through the working channel of the endoscope and pseudocyst is punctured under real-time guidance, it is preferable to have a fixed and straightened position of echoendoscope. After removing the needle stylet, aspirate at least ten cc of pseudocyst contents for Grams stain, culture and analysis for determination of amylase, carcino embryonic antigen levels, and other tests as per the clinical indication.

Afterwards, introduce a guide-wire (Jagwire, Boston Scientific Corp, Natick, MA, United States) through the needle under real-time ultrasonographic and fluoroscopic guidance. Without losing the endoscope position we remove the needle, leaving the guide-wire in place, and a 6 F cystotome is passed over guide-wire to puncture bowel wall and cyst wall, this establishes a fistula. Some authors have used tapered cannula or needle knife. This fistula track is further dilated with either a 6 or 8 mm biliary balloon dilatation catheter (Hurricane Rx, Boston Scientific Corp, Cork, Ireland) over the wire or 12-15 mm CRE balloon (Boston Scientific Corp, Cork, Ireland) under endoscopic or EUS view[20]. After obliteration of waist, the balloon is deflated and a lot of pseudocyst contents usually drains into the stomach and it must be aspirated. Once there is a clear vision of the fistula, a double pigtail stent (Solus, Cook Medical, Limerick, Ireland) are inserted over the wire and placed through the fistula, connecting the pseudocyst and the gastric lumen or appropriately sized self-expandable metal stents (SEMS) are placed depending on cyst contents. In order to insert more stents, we have to re cannulate the fistula and again insert the guide wire into the cyst to be able to introduce a second stent or a nasocystic catheter. We repeat this maneuver as many times as the number of

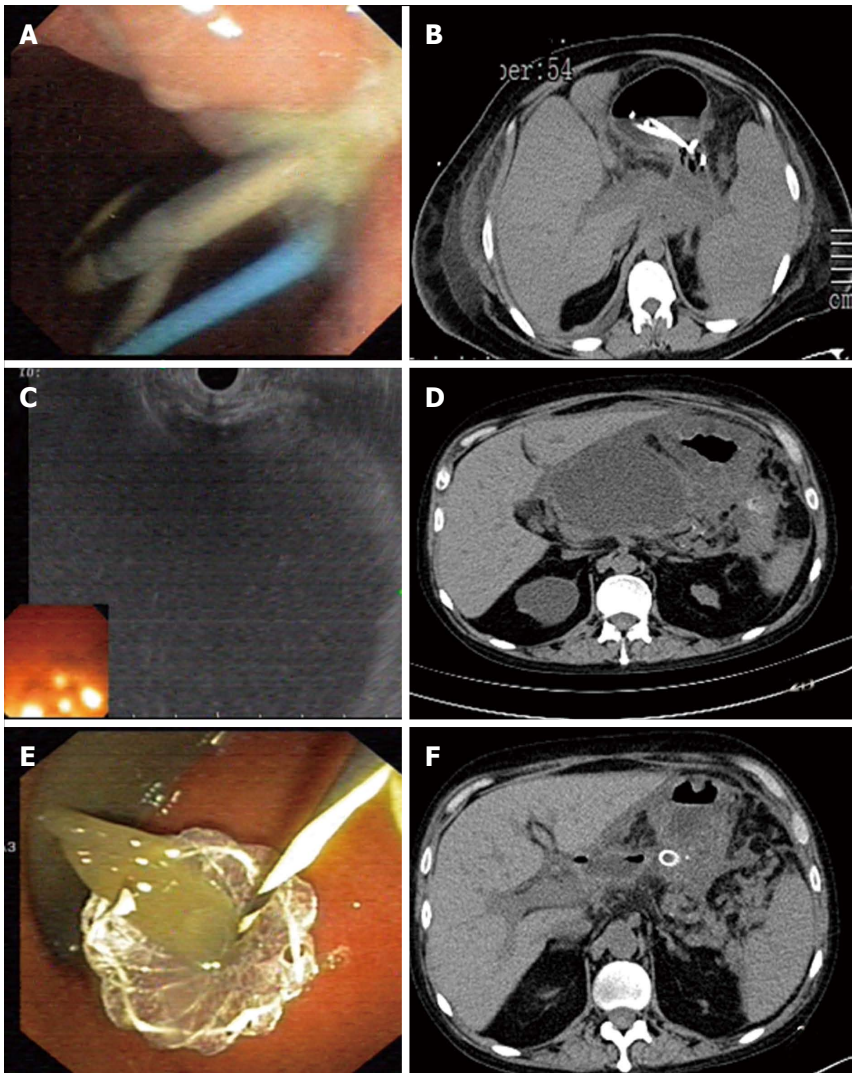

Figure 2 Placement of double pigtail plastic stent and nasocystic drain (A), computed tomography view of pancreatic fluid collections after insertion of stent and nasocystic drain (B), endosonographic view of pancreatic fluid collections before drainage (C), computed tomography view of pancreatic fluid collections before drainage (D), Placement of NAGI stent into pancreatic fluid collections (E), computed tomography view after placement of NAGI stent (F).

stents we want to place.

Normally 2 to 3 stents, 10 F diameter and 5 cm long are placed into the PFC. The patient resumes oral feeding several hours after the exploration and is discharged 48-72 h later if there are no procedure-related complications. Patients needs follow up on four weekly basis with cross sectional imaging. All the stents can be removed after confirmation of the resolution of collection and after ensuring the integrity of pancreatic duct[23]. We routinely remove stent at three months and SEMS at 8 wk. New accessories include modified access needles (19 G needle, Grosse, Daldorf, Germany, loaded with a modified 7- or 10-Fr stent and a Teflon pusher catheter, Wilson-Cook)[25,26], exchange free access design, NAVIX (Xlumena Inc., Mountain View, CA, United States)[27,28] and Giovannini Needle Wire Oasis a needle wire device (Cook Endoscopy, Winston-Salem, NC, United States)[29]. Some authors recommend placement of a nasocystic catheter in the presence of solid debris inside the cyst that allows nasocystic lavage[30].

REVIEW OF LITERATURE

There are reports of PFC drainage through stomach that date back to early 1990s (Table 2). Grimm *et al*[31] successfully created a fistula between the stomach and a cyst with a linear echoendoscope. Binmoeller *et al*[21] in 1995 had reported a series (n = 27) of EUS guided drainage of pancreatic pseudocysts with a success rate of 78%. Over years the technique and accessories evolved and with the advent of the therapeutic linear echoendoscope with larger working channels of 3.7 or 3.8 mm, successful drainage with placement of multiple large-bore stents without changing the scope became feasible. In 2001, Giovannini *et al*[32] reported 88.5% success rate (n = 35) in patients undergoing the drainage of pseudocyst or pancreatic abscess. One patient had pneumo-peritoneum that resolved with conservative care and four had failure

Table 2 Summary of technical success, clinical success and complications with endoscopic ultrasound-guided drainage of pancreatic fluid collection

Ref. (number of cases)	Type of study	Technical Success (%)	Clinical Success (%)	Complications (%)	Complications
Grimm *et al*[31], 1992 (1)	Retrospective	100	100	0	Nil
Binmoeller *et al*[21], 1995 (27)	Retrospective	93	78	7	Bleeding (*n* = 2)
Giovannini *et al*[32], 2001 (35)	Prospective	100	89	3	Pneumoperitoneum (*n* = 1)
Azar *et al*[33], 2006 (23)	Retrospective	91	82	4	Pneumoperitoneum (*n* = 1)
Antillon *et al*[19], 2006 (33)	Prospective	94	87	15	Bleeding (*n* = 4), pneumoperitoneum (*n* = 1)
Krüger *et al*[34], 2006 (35)	Prospective	94	88	0	Nil
Kahaleh *et al*[35], 2006 (46)	Prospective	100	93.5	20	Superinfection (*n* = 4), bleeding (*n* = 2), pneumoperitoneum (*n* = 2) stent migration (*n* = 1)
Hookey *et al*[22], 2006 (32)	Retrospective	96	93	9	Pneumoperitoneum (*n* = 2), bleeding (*n* = 1)
Lopes *et al*[36], 2007 (51)	Retrospective	94	84	4	Pneumoperitoneum (*n* = 1), migration (*n* = 1)
Varadarajulu *et al*[37], 2007(21)	Prospective	100	95	0	None
Barthet *et al*[38], 2008 (28)	Prospective	100	89	18	Superinfection (*n* = 5)
Varadarajulu *et al*[39], 2008 (24)	Randomized controlled trial	100	96	0	Nil
Park *et al*[40], 2009 (31)	Randomized controlled trial	94	89	7	Minor bleeding (*n* = 1), stent migration (*n* = 1)
Zheng *et al*[41], 2011 (21)	Retrospective	90.5	90.5	19	Stent blockade (*n* = 2), Infection (*n* = 2)
Varadarajulu *et al*[42], 2011 (148)	Prospective	100	98	5	Infection (*n* = 4), perforation (*n* = 2), bleeding (*n* = 1), stent migration (*n* = 1)
Bakker *et al*[43], 2012 (10)	Randomized controlled trial	90	80	20	Pancreatic fistula (*n* = 1), death from multiorgan failure (*n* = 1)
Seewald *et al*[44], 2012 (80)	Retrospective	97	84	26	Bleeding (*n* = 12), perforation (*n* = 7), portal air embolism (*n* = 1), ogilvie syndrome (*n* = 1)
Fabbri *et al*[45], 2012 (22)	Prospective	100	77	14	Superinfection (*n* = 1), superinfection and stent migration (*n* = 1), failed stent removal (*n* = 1)
Itoi *et al*[46], 2012 (15)	Retrospective	100	100	7	Stent migration (*n* = 1)
Berzosa *et al*[47], 2012 (7)	Retrospective	100	100	0	None
Penn *et al*[48], 2012 (20)	Prospective	100	85	15	Superinfection (*n* = 2), pancreatitis (*n* = 1)
Mangiavillano *et al*[49], 2012 (21)	Prospective	85.7	81	4.8	Bleeding (*n* = 1)
Weilert *et al*[27], 2012 (18)	Prospective	100	77.8	5.6	Tract dehiscence (*n* = 1)
Gornals *et al*[28], 2012 (9)	Prospective	89	89	11.1	Tension pneumothorax (*n* = 1)
Puri *et al*[50], 2012 (40)	Prospective	100	97	5	Pneumoperitoneum n-1, infection (*n* = 1)
Siddiqui *et al*[51], 2013 (87)	Retrospective	99	79	18	Stent occlusion (*n* = 16)
Lin *et al*[52], 2014 (93)	Retrospective	95	95	12	Secondary infection (*n* = 11)

Table modified from the tables described by Fabri *et al*[8] and Singhal *et al*[25].

requiring surgery[32]. None of the patients developed bleed. In 2006, Azar *et al*[33] using a therapeutic linear echoendoscope described a new technique of introducing a 19-gauge needle and guide-wire into the PFC followed by creation of a fistula with a cystoenterostome. Maximum upto four stents were placed through the tract after balloon dilation. They reported successful drainage (*n* = 23) of pancreatic pseudocysts in 91.3% patients with only a single case of significant pneumo-peritoneum. Another study by Krüger *et al*[34] described EUS-guided drainage with placement of 8.5 Fr stents (*n* = 34). The procedure was successful in 88%. There was recurrence (12%) over next 2 years, and cyst resolution of pseudocyst was increased in 30% with cyst irrigation. Hookey *et al*[22] described EUS-guided drainage of PFC (*n* = 116) which included acute pseudocysts, necrosis, and abscess. They noted 29/32 (90.6%) success. Of these patients, 20 had non bulging lesions. 4 (12.5%) patients had recurrence and 3 (9.4%) had complications[22].

In 2006, Kahaleh *et al*[35] reported a prospective comparative study of non EUS guided *vs* EUS guided drainage. 53/99 patients underwent non EUS guided, and rest EUS guided drainage. Those with visible bulge and no portal hypertension were included in the former group. The outcomes at 6 mo (84% *vs* 91%) and overall complications (18% *vs* 19%) were comparable in the two groups. They reported that the choice between these two techniques, therefore, depends on individual patient characteristics and availability of skilled EUS intervention. They recommended EUS guided drainage for non-bulging collections and those at risk for bleeding[35]. Another study by Varadarajulu *et al*[39] in 2008 compared EUS and conventional transmural drainage of pancreatic pseudocysts. Only 5/15 patients had successful drainage with the conventional method, and all of them had complete drainage on cross over to EUS. Major procedure related bleed was seen in 2 patients in the conventional drainage group. The authors concluded that EUS

guided drainage should be the first option.

In a prospective randomized controlled trial by Park *et al*[40], patients with pancreatic pseudocysts (*n* = 60) were randomly allotted to conventional drainage (*n* = 29) and EUS guided drainage groups (*n* = 31). In an intention-to-treat analysis, the technical success of the procedure was more for EUS guided drainage (94%) than for conventional drainage (72%, *P* = 0.039). With the failure of conventional drainage (n = 8), crossover to EUS guided drainage was made, which was successful in all. Complications in both groups were comparable (7% *vs* 10%, *P* = 0.67). Long term clinical success on per protocol analysis was comparable in both groups (89% *vs* 86%, *P* = 0.69). The authors concluded that EUS guided drainage, and conventional transmural drainage can both be considered first-line methods, but with non bulging cysts the former should be preferred.

In another study by Varadarajulu *et al*[42] (*n* = 148) to evaluate complications in patients undergoing EUS-guided PFC drainage, authors reported low rates of complications; perforation (*n* = 2) bleeding (*n* = 1) infection (*n* = 4) and stent migration (*n* = 1). Both cases of perforation occurred in pseudocysts in uncinate process. Most of the patients could be managed conservatively, 2 with perforation and 2 with infection required surgery. They concluded that most of the complications during EUS drainage can be managed successfully, and EUS guided drainage should be the first option in places with expertise.

Seewald *et al*[44] in a retrospective analysis of 80 patients with symptomatic PFC (mean diameter: 11.7 cm, range 3-20 cm; pseudocysts: 24/80, abscess: 20/80, infected WOPN: 36/80) observed clinical success in 83% initial for PFC drainage. The long-term clinical success over 21 mo followup was 72.5%. There was recurrence in 9 patients due to failure of endoscopic treatment of pancreatic duct abnormalities. They concluded that EUS drainage is safe and effective. They emphasized that EUS guidance is important for reduced bleeding related complications, and surgical or endoscopic treatment of pancreatic ductal lesion is extremely important for complete resolution of PFCs.

We had studied the role of combined EUS-guided drainage (with placement of double pigtail stents) and nasocystic drainage in a series of 40 patients who had non bulging pancreatic pseudocysts, 32 had no evidence of infection and 8 had infection. All 32 patients without infection and 7 out of 8 patients with infection had complete drainage. One patient had to undergo surgery due to bleeding in the pseudocyst[50]. Siddiqui *et al*[51] reported drainage of pseudocysts with viscous solid debris by combination of stents and nasocystic tubes (*n* = 63) *vs* stents alone (*n* = 24). They found three times higher short-term success rate for combined group with both stents and nasocystic tube (*P* = 0.03). After 1 year of follow up, they found that with nasocystic drain there was higher occurrence of complete resolution (79% *vs* 58%, *P* = 0.59), lower occurrence of stent occlusion (13% *vs* 33%, *P* = 0.03)[51]. Authors recommended combining both nasocystic drain and transmural stents in EUS guided drainage of pseudocysts with viscous debris-laden fluid.

Lin *et al*[52] in a retrospective study to define the number of stents required for successful drainage of PFCs evaluated 93 patients [acute pseudocyst (*n* = 67), chronic pseudocyst (*n* = 9), and WOPN (*n* = 17)]. There was no difference in the outcome based on the type of collection. Clinical success for single-stent drainage was 93.9% (46/49) *vs* 97.4% (37/38) for multiple stent drainage (*P* = 0.799). The occurrence of secondary infection for single-stent drainage was 18.4% (9/49) *vs* 5.3% (2/38) for multiple-stent drainage (*P* = 0.134). Secondary infection for stent diameter less than or equal to 8.5 F was 3.4% (1/29). It was 17.2% (10/58) for stent diameter larger than or equal to 10 F (*P* = 0.138). The authors concluded that during EUS-guided transmural drainage of PFCs, single-stent transmural drainage of PFCs is sufficient, and the number of stents or its size does not seem to influence clinical success or occurrence of secondary infection. In a similar study Bang *et al*[53] retrospectively studied 122 patients; 45 (36.9%) had 10Fr stents of which 30 patients (66.7%) had more than one stent, 77 (63.1%) patients had 7 Fr stents of which 56 (72.7%) had more than one stent. The overall treatment success was 94.3%**.** On multiple logistic regression analysis, the stent size (OR = 1.54; 95%CI: 0.23-10.4) and number of stents inserted (OR = 1.15; 95%CI: 0.25-5.25) were not associated with the number of interventions required for treatment success. Authors concluded that the number of interventions required and stent characteristics in patients undergoing endoscopic transmural drainage of uncomplicated pancreatic pseudocysts does not influence the clinical outcome[53].

Panamonta *et al*[54] reported a meta-analysis of (2 randomized-controlled trials and two prospective studies, 229 patients) comparing conventional transmural drainage and EUS guided drainage They found that the technical success rate was significantly higher for EUS group than for conventional drainage group (RR = 12.38, 95%CI: 1.39-110.22). A crossover to EUS drainage with failure of conventional drainage of non-bulging lesions (*n* = 18) was successful in all 16 cases. All patients with portal hypertension and bleeding tendency underwent EUS guided drainage to avoid severe complications. The authors found that the outcome of EUS drainage was comparable to conventional drainage in terms of short-term success (RR = 1.03, 95%CI: 0.95-1.11), long-term success (RR = 0.98, 95%CI: 0.76-1.25) and occurrence of complications (RR = 0.98, 95%CI: 0.52-1.86). They concluded that, either EUS drainage or conventional drainage are equally good for bulging pseudocysts and EUS guided drainage should be preferred for those with non-bulging pseudocysts, portal hypertension, or

coagulopathy.

The promising results of these studies on EUS drainage has increased the application of EUS guided PFC drainage world over. Yusuf *et al*[55] reported the results of a web-based survey of United States and International members of the American Society for Gastrointestinal Endoscopy. Of the 266 replies they received 198 performed pseudocyst drainage. A baseline CT scan was performed by 95% of responders. Endoscopic ultrasound was used before drainage by 70% of United States endoscopists and 59% of International endoscopists and EUS guided drainage was used by 56% and 43% of endoscopists respectively. The most common access route was transgastric (65%), and 1 to 5 stents were placed for drain.

USE OF COVERED SELF-EXPANDING METAL STENTS

Most of the studies reported the use of plastic double pigtail stents of varying size and nasocystic drains[35,56]. There are a few studies that have reported the use of metal stents for drainage of PFC. They are wide bore stents and tend to stabilize the pseudocyst wall at the site of insertion by applying radial expansive force. Talreja *et al*[57] reported drainage of PFC (n = 18) with covered self-expandable metal stents (covered SEMS; VIABIL; Conmed, Utica, NY, United States). Seventeen patients had a successful response, and 14 achieved complete resolution of their fluid collection (median number of sessions, n = 1, range 1-4). There were only a few complications in the form of superinfection (5), bleeding (2), and inner migration (1). There was no group with plastic stents for comparing the results.

Fabbri *et al*[45] reported 22 patients with infected PFC (mean size, 13.2 cm) of which 20 underwent EUS guided transmural drainage with covered SEMS. Early complications (superinfection, n = 1 and stent migration, n = 1) were seen in 2 patients. In the remaining 18 patients, stents could be removed easily in 17 patients (after a median of 26 d). In one patient stent had to be removed surgically due to inflammatory tissue in growth. Resolution of PFC was achieved in 17 patients (mean follow-up of 610 d) with only one symptomatic recurrence. Penn *et al*[48] reported use of combining double pigtail stent with covered SEMS (n = 20) to prevent migration of the latter. Partial migration occurred in 2 patients and the double pigtail prevented complete migration of covered SEMS. Initial success was reported in 17/20patients (1 patient had complete migration), with recurrence of PFC in three patients after stent removal. Weilert *et al*[27] in another study of 18 patients reported a success rate of 14 (78%) with the use of fully covered SEMS and only 1 patient required repeat stent placement. There are no randomized controlled trials that have shown the superiority of these stents over plastic stents.

NEW DEVELOPMENTS IN ACCESS DEVICES STENTS AND TECHNIQUES

One limitation of EUS guided drainage in many settings is dependence on fluroscopy and anesthesia. Schneider *et al*[58] evaluated the short and long-term outcomes of PFC drainage with endoscopic ultrasound guidance without fluoroscopy or anesthesia support**.** They studied 80 consecutive patients with symptomatic fluid collections ($\leqslant$ 6 cm in size and located < 2 cm from the gastrointestinal wall). PFCs were approached through gastric or duodenal wall, and those with estimated > 40% debris were excluded unless the features of sepsis. EUS was performed under conscious sedation with midazolam (2.5-10 mg) and fentanyl (100-300 μg). Procedural success was achieved in 74/80 (93%) with re-interventions in 16/74 (22%) cases and complications in only 11% (2 severe bleeding, 4 free perforations, 1 stent-related pressure ulcer, 1 minor bleed, 1 stent migration).

NAVIX access device is a multifunction, exchange-free system. It has a 3.5 mm switch blade to provide easy access across through the luminal wall. It has an 8 mm anchor balloon to maintain the catheter position in the pseudocyst, a 10-mm dilating balloon, and 2 guide-wire ports[27]. It was described for successful placement of fully covered SEMS (n = 18 patients) for drainage of PFC[27]. Gornals *et al*[28] used NAVIX system and reported a shorter median procedure duration (22 min; range, 10-30) compared to exchange devices (40 min; range, 25-55)[25,28].

Anchoring covered SEMSs have been recently introduced for improved drainage of PFCs. Itoi *et al*[46] first reported the use of Xlumena Mountain view CA (AXIOS) stent; a lumen-apposing fully covered, 10-mm diameter, nitinol, braided stent. The cyst wall and luminal wall are held together by anchoring flanges. This study involved 15 patients with symptomatic pancreatic pseudocysts who underwent 12 transgastric and three transduodenal pseudocyst drainage procedures. They showed that the AXIOS stents were successful in all cases with just one case of migration into stomach without any complications (median follow-up time of 11.4 mo). NAGI stent, a novel covered self-expanding metallic stent (Taewoong-Medical Co, Seoul, South Korea, with a 10 mm diameter in the center and 20 mm ends, for an endoscopic cystogastric anastomosis) prevents stent migration and ensures safe and effective of PFCs. It can be deployed in a single step procedure and a larger fistula diameter in the endoscopic cystogastric anastomosis. Téllez-Ávila *et al*[59] reported the use of NAGI stent in successful drainage of PFC and reported complete resolution of the PFC at 6 mo follow up. In another study AXIOS stent was compared with plastic double pigtail stents and found similar technical and clinical success rates[28]. But with multiple plastic stents, they noted increased number of adverse events, use of increased

number of stents and increased mean procedure duration. One patient however developed a tension pneumothorax secondary to trans-esophageal AXIOS placement. AXIOS stent placement in esophagus is technically challenging due to its large size. These new stents provide stent stability, minimize the risk of migration due to the anchoring effect, and maintain the larger SEMS lumen which helps in easy passage of echoendoscope into the cavity of PFC.

The different studies described so far followed single transluminal gateway drainage using transmural stenting (single or multiple plastic stents or SEMSs). It is usually successful in complete resolution of unilocular or uncomplicated PFCs. In the presence of multilocular or huge infected PFCs, particularly WOPN, a new approach by multiple transluminal gateway drainage has been described[60,61]. In this technique, the caudal part of the WOPN is first drained initially with two 7Fr stents. For WOPN between 6-12 cm only one transluminal tract and those between 12 and 15 cm atleast 2 transmural tract and those more than 15 cm multiple tracts (3-6) are made. An 18 Fr nasogastric tube is placed in cranial part of collection to help irrigation[62]. Combination of transluminal and percutaneous drainage techniques can help in accessing all the subcavities in certain cases. Patients who fail to respond clinically to these drainage methods require endoscopic necrosectomy or surgery. Dhingra *et al*[63] has recently described percutaneous endoscopic necrosectomy (PEN) in patients with infected pancreatic necrosis who had failed to percutaneous catheter drainage. In their study 14 of 15 patients improved (mean of 5 sessions) after single or multiport PEN, with only minor side effects in two patients (self-limiting bleeding and pancreatic fistula in 1 patient each) and death in one patient.

CONCLUSION

The use of EUS in drainage of pancreatic fluid collections has increased over the last few years. Many new techniques and stent designs have increased the applicability of this method. Compared to conventional transmural drainage there are some clear advantages for EUS-guided drainage over as in accessing non-bulging cysts and in patients with portal hypertension and bleeding tendency. Covered SEMS and anchoring covered SEMS are shown to drain PFCs successfully. Prospective randomized trials are required to establish the exact role of covered SEMS as compared to the plastic stents. Further experience will enable us to utilize EUS guided techniques for more successful drainage of PFCs with fewer complications.

REFERENCES

1 **Tenner S**, Baillie J, DeWitt J, Vege SS. American College of Gastroenterology guideline: management of acute pancreatitis. *Am J Gastroenterol* 2013; **108**: 1400-1415; 1416 [PMID: 23896955]

2 **Sarr MG**. 2012 revision of the Atlanta classification of acute pancreatitis. *Pol Arch Med Wewn* 2013; **123**: 118-124 [PMID: 23396317]

3 **Baillie J**. Pancreatic pseudocysts (Part I). *Gastrointest Endosc* 2004; **59**: 873-879 [PMID: 15173808 DOI: 10.1016/S0016-5107(04)00354-2]

4 **Yeo CJ**, Cameron JL, Sohn TA, Lillemoe KD, Pitt HA, Talamini MA, Hruban RH, Ord SE, Sauter PK, Coleman J, Zahurak ML, Grochow LB, Abrams RA. Six hundred fifty consecutive pancreaticoduodenectomies in the 1990s: pathology, complications, and outcomes. *Ann Surg* 1997; **226**: 248-257; discussion 257-260 [PMID: 9339931 DOI: 10.1097/00000658-199709000-00004]

5 **Arvanitakis M**, Delhaye M, Chamlou R, Matos C, Closset J, Medhi A, Baize M, Le Moine O, Deviere J. Endoscopic therapy for main pancreatic-duct rupture after Silastic-ring vertical gastroplasty. *Gastrointest Endosc* 2005; **62**: 143-151 [PMID: 15990839 DOI: 10.1016/S0016-5107(05)01627-5]

6 **Klöppel G**. Pseudocysts and other non-neoplastic cysts of the pancreas. *Semin Diagn Pathol* 2000; **17**: 7-15 [PMID: 10721803]

7 **Baron TH**, Harewood GC, Morgan DE, Yates MR. Outcome differences after endoscopic drainage of pancreatic necrosis, acute pancreatic pseudocysts, and chronic pancreatic pseudocysts. *Gastrointest Endosc* 2002; **56**: 7-17 [PMID: 12085029 DOI: 10.1067/mge.2002.125106]

8 **Fabbri C**, Luigiano C, Maimone A, Polifemo AM, Tarantino I, Cennamo V. Endoscopic ultrasound-guided drainage of pancreatic fluid collections. *World J Gastrointest Endosc* 2012; **4**: 479-488 [PMID: 23189219 DOI: 10.4253/wjge.v4.i11.479]

9 **Jacobson BC**, Baron TH, Adler DG, Davila RE, Egan J, Hirota WK, Leighton JA, Qureshi W, Rajan E, Zuckerman MJ, Fanelli R, Wheeler-Harbaugh J, Faigel DO. ASGE guideline: The role of endoscopy in the diagnosis and the management of cystic lesions and inflammatory fluid collections of the pancreas. *Gastrointest Endosc* 2005; **61**: 363-370 [PMID: 15758904 DOI: 10.1016/S0016-5107(04)02779-8]

10 **Kawakami H**, Itoi T, Sakamoto N. Endoscopic ultrasound-guided transluminal drainage for peripancreatic fluid collections: where are we now? *Gut Liver* 2014; **8**: 341-355 [PMID: 25071899 DOI: 10.5009/gnl.2014.8.4.341]

11 **Hirota WK**, Petersen K, Baron TH, Goldstein JL, Jacobson BC, Leighton JA, Mallery JS, Waring JP, Fanelli RD, Wheeler-Harbough J, Faigel DO. Guidelines for antibiotic prophylaxis for GI endoscopy. *Gastrointest Endosc* 2003; **58**: 475-482 [PMID: 14520276 DOI: 10.1067/S0016-5107(03)01883-2]

12 **Akshintala VS**, Saxena P, Zaheer A, Rana U, Hutfless SM, Lennon AM, Canto MI, Kalloo AN, Khashab MA, Singh VK. A comparative evaluation of outcomes of endoscopic versus percutaneous drainage for symptomatic pancreatic pseudocysts. *Gastrointest Endosc* 2014; **79**: 921-928; quiz 983.e2, 983.e5 [PMID: 24315454 DOI: 10.1016/j.gie.2013.10.032]

13 **Varadarajulu S**, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology* 2013; **145**: 583-590.e1 [PMID: 23732774]

14 **Boerma D**, van Gulik TM, Obertop H, Gouma DJ. Internal drainage of infected pancreatic pseudocysts: safe or sorry? *Dig Surg* 1999; **16**: 501-505 [PMID: 10805550 DOI: 10.1159/000018776]

15 **vanSonnenberg E**, Wittich GR, Casola G, Brannigan TC, Karnel F, Stabile BE, Varney RR, Christensen RR. Percutaneous drainage of infected and noninfected pancreatic pseudocysts: experience in 101 cases. *Radiology* 1989; **170**: 757-761 [PMID: 2644662 DOI: 10.1148/radiology.170.3.2644662]

16 **Baron TH**. Endoscopic drainage of pancreatic pseudocysts. *J Gastrointest Surg* 2008; **12**: 369-372 [PMID: 17906903 DOI: 10.1007/s11605-007-0334-5]

17 **Giovannini M**. EUS-guided pancreatic pseudocyst drainage. *Tech Gastrointest Endosc* 2007; **9**: 32-38 [DOI: 10.1016/j.tgie.2006.11.013]

18 **Howell DA**, Holbrook RF, Bosco JJ, Muggia RA, Biber BP. Endoscopic needle localization of pancreatic pseudocysts before transmural drainage. *Gastrointest Endosc* 1993; **39**: 693-698 [PMID: 8224695 DOI: 10.1016/S0016-5107(93)70225-4]

19 **Antillon MR**, Shah RJ, Stiegmann G, Chen YK. Single-step EUS-guided transmural drainage of simple and complicated pancreatic pseudocysts. *Gastrointest Endosc* 2006; **63**: 797-803 [PMID: 16650541 DOI: 10.1016/j.gie.2005.10.025]

20 **Sanchez Cortes E**, Maalak A, Le Moine O, Baize M, Delhaye M, Matos C, Devière J. Endoscopic cystenterostomy of nonbulging pancreatic fluid collections. *Gastrointest Endosc* 2002; **56**: 380-386 [PMID: 12196776 DOI: 10.1016/S0016-5107(02)70042-4]

21 **Binmoeller KF**, Seifert H, Walter A, Soehendra N. Transpapillary and transmural drainage of pancreatic pseudocysts. *Gastrointest Endosc* 1995; **42**: 219-224 [PMID: 7498686 DOI: 10.1016/S0016-5107(95)70095-1]

22 **Hookey LC**, Debroux S, Delhaye M, Arvanitakis M, Le Moine O, Devière J. Endoscopic drainage of pancreatic-fluid collections in 116 patients: a comparison of etiologies, drainage techniques, and outcomes. *Gastrointest Endosc* 2006; **63**: 635-643 [PMID: 16564865 DOI: 10.1016/j.gie.2005.06.028]

23 **Arvanitakis M**, Delhaye M, Bali MA, Matos C, De Maertelaer V, Le Moine O, Devière J. Pancreatic-fluid collections: a randomized controlled trial regarding stent removal after endoscopic transmural drainage. *Gastrointest Endosc* 2007; **65**: 609-619 [PMID: 17324413 DOI: 10.1016/j.gie.2006.06.083]

24 **Varadarajulu S**, Bang JY, Phadnis MA, Christein JD, Wilcox CM. Endoscopic transmural drainage of peripancreatic fluid collections: outcomes and predictors of treatment success in 211 consecutive patients. *J Gastrointest Surg* 2011; **15**: 2080-2088 [PMID: 21786063]

25 **Singhal S**, Rotman SR, Gaidhane M, Kahaleh M. Pancreatic fluid collection drainage by endoscopic ultrasound: an update. *Clin Endosc* 2013; **46**: 506-514 [PMID: 24143313 DOI: 10.5946/ce.2013.46.5.506]

26 **Seifert H**, Faust D, Schmitt T, Dietrich C, Caspary W, Wehrmann T. Transmural drainage of cystic peripancreatic lesions with a new large-channel echo endoscope. *Endoscopy* 2001; **33**: 1022-1026 [PMID: 11740644 DOI: 10.1055/s-2001-18927]

27 **Weilert F**, Binmoeller KF, Shah JN, Bhat YM, Kane S. Endoscopic ultrasound-guided drainage of pancreatic fluid collections with indeterminate adherence using temporary covered metal stents. *Endoscopy* 2012; **44**: 780-783 [PMID: 22791588 DOI: 10.1055/s-0032-1309839]

28 **Gornals JB**, De la Serna-Higuera C, Sánchez-Yague A, Loras C, Sánchez-Cantos AM, Pérez-Miranda M. Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent. *Surg Endosc* 2013; **27**: 1428-1434 [PMID: 23232994 DOI: 10.1007/s00464-012-2591-y]

29 **Giovannini M**, Bernardini D, Seitz JF. Cystogastrotomy entirely performed under endosonography guidance for pancreatic pseudocyst: results in six patients. *Gastrointest Endosc* 1998; **48**: 200-203 [PMID: 9717789 DOI: 10.1016/S0016-5107(98)70165-8]

30 **Baron TH**. Endoscopic drainage of pancreatic pseudocysts, abscesses and organized (walled-off) necrosis. In: Baron TH, Kozarek RA, Carr- Locke DL, editors. ERCP. Philadelphia: Saunders/Elsevier, 2008: 475-491

31 **Grimm H**, Binmoeller KF, Soehendra N. Endosonography-guided drainage of a pancreatic pseudocyst. *Gastrointest Endosc* 1992; **38**: 170-171 [PMID: 1568613 DOI: 10.1016/S0016-5107(92)70384-8]

32 **Giovannini M**, Pesenti C, Rolland AL, Moutardier V, Delpero JR. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts or pancreatic abscesses using a therapeutic echo endoscope. *Endoscopy* 2001; **33**: 473-477 [PMID: 11437038 DOI: 10.1055/s-2001-14967]

33 **Azar RR**, Oh YS, Janec EM, Early DS, Jonnalagadda SS, Edmundowicz SA. Wire-guided pancreatic pseudocyst drainage by using a modified needle knife and therapeutic echoendoscope. *Gastrointest Endosc* 2006; **63**: 688-692 [PMID: 16564874 DOI: 10.1016/j.gie.2005.10.032]

34 **Krüger M**, Schneider AS, Manns MP, Meier PN. Endoscopic management of pancreatic pseudocysts or abscesses after an EUS-guided 1-step procedure for initial access. *Gastrointest Endosc* 2006; **63**: 409-416 [PMID: 16500388 DOI: 10.1016/j.gie.2005.11.047]

35 **Kahaleh M**, Shami VM, Conaway MR, Tokar J, Rockoff T, De La Rue SA, de Lange E, Bassignani M, Gay S, Adams RB, Yeaton P. Endoscopic ultrasound drainage of pancreatic pseudocyst: a prospective comparison with conventional endoscopic drainage. *Endoscopy* 2006; **38**: 355-359 [PMID: 16680634 DOI: 10.1055/s-2006-925249]

36 **Lopes CV**, Pesenti C, Bories E, Caillol F, Giovannini M. Endoscopic-ultrasound-guided endoscopic transmural drainage of pancreatic pseudocysts and abscesses. *Scand J Gastroenterol* 2007; **42**: 524-529 [PMID: 17454865 DOI: 10.1080/00365520601065093]

37 **Varadarajulu S**, Wilcox CM, Tamhane A, Eloubeidi MA, Blakely J, Canon CL. Role of EUS in drainage of peripancreatic fluid collections not amenable for endoscopic transmural drainage. *Gastrointest Endosc* 2007; **66**: 1107-1119 [PMID: 17892874 DOI: 10.1016/j.gie.2007.03.1027]

38 **Barthet M**, Lamblin G, Gasmi M, Vitton V, Desjeux A, Grimaud JC. Clinical usefulness of a treatment algorithm for pancreatic pseudocysts. *Gastrointest Endosc* 2008; **67**: 245-252 [PMID: 18226686 DOI: 10.1016/j.gie.2007.06.014]

39 **Varadarajulu S**, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2008; **68**: 1102-1111 [PMID: 18640677 DOI: 10.1016/j.gie.2008.04.028]

40 **Park DH**, Lee SS, Moon SH, Choi SY, Jung SW, Seo DW, Lee SK, Kim MH. Endoscopic ultrasound-guided versus conventional transmural drainage for pancreatic pseudocysts: a prospective randomized trial. *Endoscopy* 2009; **41**: 842-848 [PMID: 19798610 DOI: 10.1055/s-0029-1215133]

41 **Zheng M**, Qin M. Endoscopic ultrasound guided transgastric stenting for the treatment of traumatic pancreatic pseudocyst. *Hepatogastroenterology* 2011; **58**: 1106-1109 [PMID: 21937358 DOI: 10.5754/hge11059]

42 **Varadarajulu S**, Christein JD, Wilcox CM. Frequency of complications during EUS-guided drainage of pancreatic fluid collections in 148 consecutive patients. *J Gastroenterol Hepatol* 2011; **26**: 1504-1508 [PMID: 21575060 DOI: 10.1111/j.1440-1746.2011.06771.x]

43 **Bakker OJ**, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, van Eijck CH, Fockens P, Hazebroek EJ, Nijmeijer RM, Poley JW, van Ramshorst B, Vleggaar FP, Boermeester MA, Gooszen HG, Weusten BL, Timmer R. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012; **307**: 1053-1061 [PMID: 22416101 DOI: 10.1001/jama.2012.276]

44 **Seewald S**, Ang TL, Richter H, Teng KY, Zhong Y, Groth S, Omar S, Soehendra N. Long-term results after endoscopic drainage and necrosectomy of symptomatic pancreatic fluid collections. *Dig Endosc* 2012; **24**: 36-41 [PMID: 22211410 DOI: 10.1111/j.1443-1661.2011.01162.x]

45 **Fabbri C**, Luigiano C, Cennamo V, Polifemo AM, Barresi L, Jovine E, Traina M, D'Imperio N, Tarantino I. Endoscopic ultrasound-guided transmural drainage of infected pancreatic fluid collections with placement of covered self-expanding metal stents: a case series. *Endoscopy* 2012; **44**: 429-433 [PMID: 22382852 DOI: 10.1055/s-0031-1291624]

46 **Itoi T**, Binmoeller KF, Shah J, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Moriyasu F. Clinical evaluation of a novel lumen-apposing metal stent for endosonography-guided pancreatic pseudocyst and gallbladder drainage (with videos). *Gastrointest Endosc* 2012; **75**: 870-876 [PMID: 22301347 DOI: 10.1016/j.gie.2011.10.020]

47 **Berzosa M**, Maheshwari S, Patel KK, Shaib YH. Single-step endoscopic ultrasonography-guided drainage of peripancreatic fluid collections with a single self-expandable metal stent and standard linear echoendoscope. *Endoscopy* 2012; **44**: 543-547 [PMID: 22407382 DOI: 10.1055/s-0031-1291710]

48 **Penn DE**, Draganov PV, Wagh MS, Forsmark CE, Gupte AR, Chauhan SS. Prospective evaluation of the use of fully covered self-expanding metal stents for EUS-guided transmural drainage

of pancreatic pseudocysts. *Gastrointest Endosc* 2012; **76**: 679-684 [PMID: 22732874 DOI: 10.1016/j.gie.2012.04.457]

49 **Mangiavillano B**, Arcidiacono PG, Masci E, Mariani A, Petrone MC, Carrara S, Testoni S, Testoni PA. Single-step versus two-step endo-ultrasonography-guided drainage of pancreatic pseudocyst. *J Dig Dis* 2012; **13**: 47-53 [PMID: 22188916 DOI: 10.1111/j.1751-2980.2011.00547.x]

50 **Puri R**, Mishra SR, Thandassery RB, Sud R, Eloubeidi MA. Outcome and complications of endoscopic ultrasound guided pancreatic pseudocyst drainage using combined endoprosthesis and naso-cystic drain. *J Gastroenterol Hepatol* 2012; **27**: 722-727 [PMID: 22313377 DOI: 10.1111/j.1440-1746.2012.07089.x]

51 **Siddiqui AA**, Dewitt JM, Strongin A, Singh H, Jordan S, Loren DE, Kowalski T, Eloubeidi MA. Outcomes of EUS-guided drainage of debris-containing pancreatic pseudocysts by using combined endoprosthesis and a nasocystic drain. *Gastrointest Endosc* 2013; **78**: 589-595

52 **Lin H**, Zhan XB, Sun SY, Yang XJ, Jin ZD, Zou DW, Li ZS. Stent selection for endoscopic ultrasound-guided drainage of pancreatic fluid collections: a multicenter study in china. *Gastroenterol Res Pract* 2014; **2014**: 193562 [PMID: 25018767 DOI: 10.1155/2014/193562]

53 **Bang JY**, Wilcox CM, Trevino JM, Ramesh J, Hasan M, Hawes RH, Varadarajulu S. Relationship between stent characteristics and treatment outcomes in endoscopic transmural drainage of uncomplicated pancreatic pseudocysts. *Surg Endosc* 2014; **28**: 2877-2883 [PMID: 24789132 DOI: 10.1007/s00464-014-3541-7]

54 **Panamonta N**, Ngamruengphong S, Kijsirichareanchai K, Nugent K, Rakvit A. Endoscopic ultrasound-guided versus conventional transmural techniques have comparable treatment outcomes in draining pancreatic pseudocysts. *Eur J Gastroenterol Hepatol* 2012; **24**: 1355-1362 [PMID: 23114741 DOI: 10.1097/MEG.0b013e32835871eb]

55 **Yusuf TE**, Baron TH. Endoscopic transmural drainage of pancreatic pseudocysts: results of a national and an international survey of ASGE members. *Gastrointest Endosc* 2006; **63**: 223-227 [PMID: 16427925 DOI: 10.1016/j.gie.2005.09.034]

56 **Cahen D**, Rauws E, Fockens P, Weverling G, Huibregtse K, Bruno M. Endoscopic drainage of pancreatic pseudocysts: long-term outcome and procedural factors associated with safe and successful treatment. *Endoscopy* 2005; **37**: 977-983 [PMID: 16189770 DOI: 10.1055/s-2005-870336]

57 **Talreja JP**, Shami VM, Ku J, Morris TD, Ellen K, Kahaleh M. Transenteric drainage of pancreatic-fluid collections with fully covered self-expanding metallic stents (with video). *Gastrointest Endosc* 2008; **68**: 1199-1203 [PMID: 19028232 DOI: 10.1016/j.gie.2008.06.015]

58 **Schneider CP**, Paquin SC, Sahai A. Feasability, safety, short and long-term outcomes of EUS-guided drainage of pancreatic fluid collections without fluoroscopy or anesthesia support. *Gastrointest Endosc* 2014; **79** (Suppl): AB414 [DOI: 10.1016/j.gie.2014.02.553]

59 **Téllez-Ávila FI**, Villalobos-Garita A, Ramírez-Luna MÁ. Use of a novel covered self-expandable metal stent with an anti-migration system for endoscopic ultrasound-guided drainage of a pseudocyst. *World J Gastrointest Endosc* 2013; **5**: 297-299 [PMID: 23772268 DOI: 10.4253/wjge.v5.i6.297]

60 **Varadarajulu S**, Phadnis MA, Christein JD, Wilcox CM. Multiple transluminal gateway technique for EUS-guided drainage of symptomatic walled-off pancreatic necrosis. *Gastrointest Endosc* 2011; **74**: 74-80 [PMID: 21612778 DOI: 10.1016/j.gie.2011.03.1122]

61 **Mukai S**, Itoi T, Sofuni A, Itokawa F, Kurihara T, Tsuchiya T, Ishii K, Tsuji S, Ikeuchi N, Tanaka R, Umeda J, Tonozuka R, Honjo M, Moriyasu F. Novel single transluminal gateway transcystic multiple drainages after EUS-guided drainage for complicated multilocular walled-off necrosis (with videos). *Gastrointest Endosc* 2014; **79**: 531-535 [PMID: 24287280 DOI: 10.1016/j.gie.2013.10.004]

62 **Bang JY**, Wilcox CM, Trevino J, Ramesh J, Peter S, Hasan M, Hawes RH, Varadarajulu S. Factors impacting treatment outcomes in the endoscopic management of walled-off pancreatic necrosis. *J Gastroenterol Hepatol* 2013; **28**: 1725-1732 [PMID: 23829423 DOI: 10.1111/jgh.12328]

63 **Dhingra R**, Srivastava S, Behra S, Vadiraj PK, Venuthurimilli A, Shalimar NR, Madhusudhan KS, Gamanagatti SR, Garg PK. Single or multiport percutaneous endoscopic necrosectomy performed with the patient under conscious sedation is a safe and effective treatment for infected pancreatic necrosis (with video). *Gastrointest Endosc* 2015; **81**: 351-359 [PMID: 25293824 DOI: 10.1016/j.gie.2014.07.060]

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MINIREVIEWS

Palliative percutaneous endoscopic gastrostomy placement for gastrointestinal cancer: Roles, goals, and complications

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Abstract

Percutaneous endoscopic gastrostomy tube placement is an invaluable tool in clinical practice that has an important role in the palliative care of patients with gastrointestinal cancer. While there is no extensive data regarding the use of this procedure in patients with gastrointestinal malignancy, inferences can be made from the available information derived from studies of similar or mixed populations. Percutaneous endoscopic gastrostomy tubes can be used to provide enteral nutrition for terminal malignancies of the upper gastrointestinal tract as well as for decompression of malignant obstructions. The rates of successful placement for cancer patients with either of these indications are high, similar to those in mixed populations. There is no conclusive evidence that the procedure will help patients reach nutritional goals for those needing alimental supplementation. However, it is effective at relieving symptoms caused by malignant obstruction. A high American Society of Anesthesiologist physical status score and an advanced tumor stage have been shown to be independent predictors of poor outcomes following placement in cancer patients. This suggests the potential for similar outcomes in the palliative care of patients with advanced stage gastrointestinal cancer who may be in relatively poor physiologic condition. However, this potential should not preclude its use in patients with terminal gastrointestinal cancer considering the high rate of successful tube placement, the possible benefits and the ultimate goal of comfort in palliative care.

Key words: Percutaneous endoscopic gastrostomy tube; Palliative care; gastrointestinal cancer; Nutritional supplementation; Gastrointestinal decompression

Core tip: Percutaneous endoscopic gastrostomy tube placement may be used in the palliative care of patients with gastrointestinal cancer for supplemental nutrition or to decompress distal obstructions. There is a high rate of successful placement in cancer patients. It has been shown to relieve symptoms of malignant obstruction and has the potential to help patients reach nutritional goals. While poor physiologic condition and advanced tumor stage have been associated with a higher risk of worse outcomes, this should not preclude its use in these patients considering the high rate of successful placement, potential benefits and the goal of comfort in palliative care.

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INTRODUCTION

The use of gastrostomy tubes to gain enteral access has been implemented since the late 19th century. The Witzel or Stamm techniques, either open or laparoscopic, have been the standard of care for surgical gastrostomy through the 1970s[1]. In 1980, Gauderer *et al*[2] first described the percutaneous endoscopic gastrostomy (PEG) method for enteral access in children with swallowing disorders[2]. Since that time, the use of PEG has been extended broadly to patients with dysphagia, either physiologic or obstructive, for the provision of enteral nutrition. PEG tube placement can be performed quickly at the bedside and requires only local anesthesia and minimal sedation resulting in substantial time and cost savings compared to surgical gastrostomy[3]. Additionally, it has been successfully used to decompress the stomach and/or proximal gastrointestinal tract in the setting of malignant obstructions distal to the pylorus[4]. PEG placement has become an important and frequent procedure performed by surgeons and gastroenterologists. In a review 20 years following its initial description there were estimated to be greater than 216000 PEG procedures performed annually in the United States[5].

This endoscopic procedure has also been utilized with a palliative intent as a means to provide enteral nutrition or relieve intestinal obstructions. The World Health Organization characterizes "palliative care" as "an approach that improves the quality of life of patients and their families facing the problem associated with life-threatening illness[6]". More concisely, "palliative care" provides "care alleviating symptoms without curing the underlying disease"[7]. It was a surgeon, Balfour Mount, who originally coined the term "palliative care" in 1975[8]. Since that time, as the elderly population and the prominence of chronic disease have increased, the need for palliative care has increased in kind[9]. Palliative medicine is an essential component to the care of patients with gastrointestinal cancer, encompassing any malignancy from the mouth to the anus, and PEG tube placement is an invaluable tool in the field. In the palliative care of patients with terminal gastrointestinal cancer, PEG may be used either as a method to provide enteral nutrition in patients with an obstructing upper gastrointestinal cancer or as a means to decompress the upper gastrointestinal tract in patients with malignant bowel obstructions.

The purpose of this review is to better understand roles (uses) and goals (outcomes) of palliative PEG tube placement in patients with gastrointestinal cancer. Unfortunately, the use of this type of palliative PEG for patients with terminal gastrointestinal cancer has not been extensively studied. There are no clear guidelines regarding the role of PEG placement in the palliative care of these patients. However, an understanding of the use, broad outcomes and complication incidence of PEGs placed in all cancer patients for nutritional support or bowel decompression may provide insight into its roles and goals in the palliative care of patients with gastrointestinal cancer. While the need to decompress a gastrointestinal obstruction is a clear indication for intervention, PEG tube placement for nutritional purposes in the setting of palliative care raises multiple ethical issues. This review will focus on better understanding the risks and benefits of the procedure in these situations in order to properly guide the patient towards an informed decision.

ROLES

Enteral nutrition

The most common indication for PEG tube placement is provision of enteral nutrition for patients with neurologic disorders, head/neck cancer and trauma[10,11]. With respect to gastrointestinal cancer, PEG tube placement in patients with obstructing oropharyngeal, esophageal or stomach cancer is designed to provide enteral nutrition. In a recent retrospective review of all patients within a cancer institution who underwent PEG, roughly half of the patients had head/neck cancer; 22% of the patients had a different gastrointestinal cancer. The most common indication for PEG was nutritional supplementation[12]. Similarly, another retrospective study of all cancer patients found that 73% of the patients received a PEG tube for enteral access and nutritional supplementation while the remaining 27% had it placed for bowel decompression[13].

Decompressive PEG

Malignant bowel obstruction is an important consideration in patients with gastrointestinal cancer. It is particularly relevant to palliative care as its occurrence often serves as a harbinger of worsening disease or recurrence[14]. Though the rates of obstruction vary in the literature, the incidence of malignant obstruction for colorectal cancer has been reported to be between 10% and 28.4%[15]. In the setting of metastatic disease its identification is particularly ominous and often signals the need for end-stage palliation[16].

Obstruction of the gastrointestinal tract by a malignancy leads to a complex pathophysiologic process that involves aggregation of bowel gas and secretions, impaired motility, decreased absorption and inflammation[17]. The result is malnutrition and debilitating nausea, vomiting and abdominal pain. PEG tube placement is a method to decompress the stomach and proximal bowel to alleviate these symptoms[18].

For patients ineligible for definitive surgical treatment, other management strategies for malignant bowel obstruction include medical therapy, nasogastric tube decompression, stent placement in colorectal cancer and surgical resection. Medical treatment is targeted both at resolution of obstruction and symptom management. In addition to their antiemetic effect, a Cochrane review showed that corticosteroids have the potential to aide in the resolution of intestinal obstruction[19]. The medical armamentarium also includes other antiemetics, anti-cholinergics, somatostatin analogues and opiates, all of which may be of limited benefit[16,20,21]. The initial management of malignant obstruction usually involves nasogastric tube decompression. However, long-term use of nasogastric tubes is not feasible considering patient discomfort and the potential erosion of the nasal pathways[14,17]. For patients with colorectal cancer, stents have been used to relieve obstruction. A systematic review of self-expanding metal stents found a median clinical success rate of 92% however complication rates of stent migration and re-obstruction were both > 10%[22]. Given the mixed success and complication rates of these strategies, the role of decompressive PEG tube placement should be considered.

In a retrospective review of all PEG tubes placed at a medical center, 6% were performed for decompressing a malignant obstruction[16]. When limited to cancer patients excluding those with head/neck and thoracic malignancies, Keung *et al*[13] found that 27% of PEGs were performed for gastric decompression/management of obstructive symptoms. This procedure has the ability to both alleviate obstructive symptoms and permit patients to participate in the culturally important act of eating, albeit non-nutritive, that can dramatically improve the quality of life of patients undergoing palliative care. The success and complication rates of both decompressive PEG and those placed for nutritional supplementation in patients with gastrointestinal malignancy is considered below.

GOALS

Outcomes

In patients with head and neck cancer, PEGs placed for enteral alimentation is well studied and has clearly been shown to improve both nutritional status and quality of life[12,23-25]. Similarly, the use of decompressive PEG in patients with malignant bowel obstruction secondary to advanced gynecologic cancer has been shown to effectively ameliorate obstructive symptoms[18,26,27]. While the use of PEG in these scenarios has been well studied, there has been relatively little data regarding the outcomes of PEG in patients with primary gastrointestinal malignancy outside of the oropharynx. As mentioned above, several recent studies have looked at PEG placement in all cancer patients who may benefit from PEG as a palliative measure either for nutritional support or decompressing malignant obstructions[12].

There is a high rate of success for PEG placement in patients with cancer. Three retrospective studies analyzing PEG in cancer patients reported success rates > 95%[13,28,29]. One of these studies found a 98.9% success rate despite 51.9% of their patients having had prior abdominal surgery[13]. The success rate for PEG placement in cancer patients is similar to that of the overall population. This suggests that cancer is not necessarily a physiologic or technical limitation. For cancer patients who had successful PEG placement, studies have found varied median survival times. A 2013 retrospective study of 218 cancer patients who underwent PEG found a median survival time of 10.2 mo (8 d-5.7 years); the 30-d mortality rate was 13%[12]. This is comparable to a 14% 30-d mortality rate reported by Zera *et al*[28] in a similar patient population[28]. Interestingly, a study that excluded patients with head/neck and thoracic cancer found a slightly higher 30-d mortality rate of 18.5%[13]. It is important to note that Keung *et al*[13] additionally assessed the achievement of nutritional goals following PEG. Among all cancer patients (those who received PEG for nutritional support and those who received decompressive PEG) 73.5% were able to tolerate some degree of tube feeding following the procedure. However, among those who had the procedure for nutritional support and received total parental nutrition (TPN) prior, only about half became independent of TPN following the PEG[13].

Several smaller retrospective studies have looked at the outcomes of decompressive PEG placement for malignant obstruction alone and have reported similar outcomes[16,26,27,30-35]. The largest and most recent of which, performed by Kawata *et al*[30] in 2013 with 76 patients, reported a success rate of 93%, obstructive symptom relief in 95% and a median survival of 63 d (range of 8-444 d). Notably, 96% of patients in the study who required nasogastric decompression prior to the procedure no longer required it following PEG placement[30]. These data suggest that patients with malignant obstruction secondary to a GI malignancy would benefit from a PEG with a high probability of success and obstructive symptom relief.

Complications

PEG complications are differentiated as major and minor. While minor complications include pain, formation of granulation tissue, cellulitis, *etc.*, major complications are more immediately life-threatening such as pneumonia, peritonitis, perforation, and deep venous thrombosis/pulmonary embolism (DVT/PE)[12,36-40]. In mixed patient populations, the incidence of major PEG complications has been reported at 1%-3% to as high as 9%; the incidence of minor complications is more widely varied ranging from 16% to 50%[41,42]. A large systematic review of patients with head/neck cancer found a 7.4% incidence of major complications and a 28.9% incidence of minor complications[37].

Table 1 American Society of Anesthesiologists Physical Status Classification

Class	Description
1	Patient is a completely health fit patient
2	Patient has mild systemic disease
3	Patient has severe systemic disease that is not incapacitating
4	Patient has incapacitating disease that is a constant threat to life
5	A moribund patient who is not expected to live 24 h with or without surgery

E. Emergency surgery, E is placed after the Roman numeral.

In all cancer patients, many who receive PEG for palliative reasons, several studies have assessed the incidence of complications and their predictors[12,13,28]. Richards et al. studied the incidence of PEG complications in all cancer patients, 22% had gastrointestinal cancer, and found a major and minor complication incidence of 8.7% and 37%, respectively; 30-d mortality was 13% while overall mortality was 72%[12]. Only the overall mortality was inconsistent with mixed populations as would be expected in cancer patients[42]. The only significant predictor of major complications on multivariate analysis was an American Society of Anesthesiologist (ASA) score of 4/4E/5E (HR = 4.9, p = 0.0394); packed red blood cell transfusion was nearly significant (HR = 4.6, *P* = 0.0543). Table 1 describes the ASA physical status classification[43]. With respect to 30-d mortality, an ASA score 4/4E/5E (HR = 4.66, *P* = 0.0292), advanced tumor stage (HR = 8.22, *P* = 0.0362) and elevated WBC count (HR = 1.17, *P* = 0.0060) were found to be independent predictors. Interestingly, the indication of decompressing a malignant obstruction was an independent predictor of overall mortality (HR = 1.74, *P* = 0.031)[12]. As may be expected, this data suggests that patients in worse physiologic condition (*e.g.*, higher ASA scores) or with more terminal stages of cancer (*e.g.*, advanced tumor stage), such as patients receiving a PEG for palliative reasons, would potentially have a higher incidence of major complications and 30-d mortality.

Several studies have also evaluated complication rates for only decompressive PEGs in cancer patients. In the recent study performed by Kawata *et al*[30] assessing palliative PEG in patients with malignant bowel obstruction deemed ineligible for surgical intervention, 15 of 71 patients (21%) experienced complications, only one of which would be considered a major complication[30]. This incidence of complications is consistent with previous studies that evaluated decompressive PEGs[16,26,27,31-35]. In these studies only 1 case of PEG-related death was reported, secondary to peritonitis[27]. These complication incidences for decompressive PEG with malignant obstruction are comparable with mixed populations. Therefore, while this indication may be a predictor of worse outcomes, likely a reflection of the terminal status of the illness, the procedure itself does not seem to put the patient with malignant bowel obstruction at undue risk.

CONCLUSION

PEG tube placement may be used in the palliative care of patients with terminal gastrointestinal cancer either as a means to provide enteral nutrition in cases of proximal obstruction or to decompress the upper gastrointestinal tract in cases of distal bowel obstruction. The evidence suggests that PEG can be performed in these patients with a high level of success[12]. With respect to goal achievement, it is not clear that terminal cancer patients receiving PEG for enteral alimentation will meet their nutritional goals and become independent of TPN. Additionally, considering the goal of palliative care is to provide comfort, it is unclear if PEG placement for nutritional supplementation is consistent with this objective. While nutritional supplementation may help ameliorate suffering involved with starvation and comfort family members faced with this difficult situation, PEG placement for this purpose does not ensure achievement of nutritional goals, may lead to further patient discomfort and could unduly prolong suffering. The decision to place a PEG tube for nutritional supplementation in patients with terminal gastrointestinal cancer involves careful discussion of the potential risks and benefits in addition to understanding the patient's wishes. Patients receiving PEG for decompression of a malignant obstruction, however, clearly have improvement of their obstructive symptoms. Given both the association of major complications with high ASA scores and the association of 30-d mortality with both high ASA scores and advanced tumor stage, it would not be surprising if palliative patients with advanced stage gastrointestinal cancer, who may be in relatively poor physiologic condition, would have a higher incidence of these bad outcomes. However, these poor outcome rates would need to be viewed through the lens of the palliative care ethos whereby the ultimate goal is patient comfort. Undoubtedly, more objective data is needed to determine evidence-based guidelines for palliative PEG placement in patients with gastrointestinal cancer.

REFERENCES

1 **Spelsberg FW**, Hoffmann RT, Lang RA, Winter H, Weidenhagen R, Reiser M, Jauch KW, Trumm C. CT fluoroscopy guided percutaneous gastrostomy or jejunostomy without (CT-PG/PJ) or with simultaneous endoscopy (CT-PEG/PEJ) in otherwise untreatable patients. *Surg Endosc* 2013; **27**: 1186-1195 [PMID: 23232989 DOI: 10.1007/s00464-012-2574-z]

2 **Gauderer MW**, Ponsky JL, Izant RJ. Gastrostomy without laparotomy: a percutaneous endoscopic technique. *J Pediatr Surg* 1980; **15**: 872-875 [PMID: 6780678]

3 **Dwyer KM**, Watts DD, Thurber JS, Benoit RS, Fakhry SM. Percutaneous endoscopic gastrostomy: the preferred method of elective feeding tube placement in trauma patients. *J Trauma* 2002; **52**: 26-32 [PMID: 11791048]

4 **McClave SA**, Ritchie CS. The role of endoscopically placed feeding or decompression tubes. *Gastroenterol Clin North Am* 2006;

35: 83-100 [PMID: 16530112 DOI: 10.1016/j.gtc.2005.12.003]
5 **Gauderer MW**. Percutaneous endoscopic gastrostomy-20 years later: a historical perspective. *J Pediatr Surg* 2001; **36**: 217-219 [PMID: 11150469]
6 **WHO**. WHO Definition of Palliative Care 2014. The World Health Organization Definition of Palliative Care. Available from: URL: http://www.who.int/cancer/palliative/definition/en/
7 Stedman' Medical Dictionary. 25th ed. Baltimore: Williams & Wilkins, 1990
8 **Fahy BN**. Palliative care for the surgical oncologist: embracing the palliativist within. *Surgery* 2013; **153**: 1-3 [PMID: 22910488 DOI: 10.1016/j.surg.2012.06.002]
9 **Teitelbaum HS**, Travis LD, Heilig DL, Neslund SE, Menze AK, Baker CD, Gragossian A, Mays C, Risner EK. The epidemiology of hospice and palliative care. *Dis Mon* 2013; **59**: 309-324 [PMID: 23973414 DOI: 10.1016/j.disamonth.2013.05.002]
10 **Rosenberger LH**, Newhook T, Schirmer B, Sawyer RG. Late accidental dislodgement of a percutaneous endoscopic gastrostomy tube: an underestimated burden on patients and the health care system. *Surg Endosc* 2011; **25**: 3307-3311 [PMID: 21533968 DOI: 10.1007/s00464-011-1709-y]
11 **Schrag SP**, Sharma R, Jaik NP, Seamon MJ, Lukaszczyk JJ, Martin ND, Hoey BA, Stawicki SP. Complications related to percutaneous endoscopic gastrostomy (PEG) tubes. A comprehensive clinical review. *J Gastrointestin Liver Dis* 2007; **16**: 407-418 [PMID: 18193123]
12 **Richards DM**, Tanikella R, Arora G, Guha S, Dekovich AA. Percutaneous endoscopic gastrostomy in cancer patients: predictors of 30-day complications, 30-day mortality, and overall mortality. *Dig Dis Sci* 2013; **58**: 768-776 [PMID: 23007733 DOI: 10.1007/s10620-012-2397-8]
13 **Keung EZ**, Liu X, Nuzhad A, Rabinowits G, Patel V. In-hospital and long-term outcomes after percutaneous endoscopic gastrostomy in patients with malignancy. *J Am Coll Surg* 2012; **215**: 777-786 [PMID: 22999329 DOI: 10.1016/j.jamcollsurg.2012.08.013]
14 **Dolan EA**. Malignant bowel obstruction: a review of current treatment strategies. *Am J Hosp Palliat Care* 2011; **28**: 576-582 [PMID: 21504999 DOI: 10.1177/1049909111406706]
15 **Ripamonti C**, De Conno F, Ventafridda V, Rossi B, Baines MJ. Management of bowel obstruction in advanced and terminal cancer patients. *Ann Oncol* 1993; **4**: 15-21 [PMID: 8435356]
16 **Teriaky A**, Gregor J, Chande N. Percutaneous endoscopic gastrostomy tube placement for end-stage palliation of malignant gastrointestinal obstructions. *Saudi J Gastroenterol* 2012; **18**: 95-98 [PMID: 22421713 DOI: 10.4103/1319-3767.93808]
17 **Roeland E**, von Gunten CF. Current concepts in malignant bowel obstruction management. *Curr Oncol Rep* 2009; **11**: 298-303 [PMID: 19508835]
18 **Brooksbank MA**, Game PA, Ashby MA. Palliative venting gastrostomy in malignant intestinal obstruction. *Palliat Med* 2002; **16**: 520-526 [PMID: 12465700]
19 **Feuer DJ**, Broadley KE. Corticosteroids for the resolution of malignant bowel obstruction in advanced gynaecological and gastrointestinal cancer. *Cochrane Database Syst Rev* 2000; **(2)**: CD001219 [PMID: 10796761 DOI: 10.1002/14651858.cd001219]
20 **Mercadante S**, Casuccio A, Mangione S. Medical treatment for inoperable malignant bowel obstruction: a qualitative systematic review. *J Pain Symptom Manage* 2007; **33**: 217-223 [PMID: 17280927 DOI: 10.1016/j.jpainsymman.2006.06.014]
21 **Ang SK**, Shoemaker LK, Davis MP. Nausea and vomiting in advanced cancer. *Am J Hosp Palliat Care* 2010; **27**: 219-225 [PMID: 20197557 DOI: 10.1177/1049909110361228]
22 **Watt AM**, Faragher IG, Griffin TT, Rieger NA, Maddern GJ. Self-expanding metallic stents for relieving malignant colorectal obstruction: a systematic review. *Ann Surg* 2007; **246**: 24-30 [PMID: 17592286 DOI: 10.1097/01.sla.0000261124.72687.72]
23 **Nguyen NP**, North D, Smith HJ, Dutta S, Alfieri A, Karlsson U, Lee H, Martinez T, Lemanski C, Nguyen LM, Ludin A, Sallah S. Safety and effectiveness of prophylactic gastrostomy tubes for head and neck cancer patients undergoing chemoradiation. *Surg Oncol* 2006; **15**: 199-203 [PMID: 17280829 DOI: 10.1016/j.suronc.2006.12.002]
24 **Corry J**, Poon W, McPhee N, Milner AD, Cruickshank D, Porceddu SV, Rischin D, Peters LJ. Prospective study of percutaneous endoscopic gastrostomy tubes versus nasogastric tubes for enteral feeding in patients with head and neck cancer undergoing (chemo)radiation. *Head Neck* 2009; **31**: 867-876 [PMID: 19296528 DOI: 10.1002/hed.21044]
25 **Morton RP**, Crowder VL, Mawdsley R, Ong E, Izzard M. Elective gastrostomy, nutritional status and quality of life in advanced head and neck cancer patients receiving chemoradiotherapy. *ANZ J Surg* 2009; **79**: 713-718 [PMID: 19878166 DOI: 10.1111/j.1445-2197.2009.05056.x]
26 **Campagnutta E**, Cannizzaro R, Gallo A, Zarrelli A, Valentini M, De Cicco M, Scarabelli C. Palliative treatment of upper intestinal obstruction by gynecological malignancy: the usefulness of percutaneous endoscopic gastrostomy. *Gynecol Oncol* 1996; **62**: 103-105 [PMID: 8690280 DOI: 10.1006/gyno.1996.0197]
27 **Herman LL**, Hoskins WJ, Shike M. Percutaneous endoscopic gastrostomy for decompression of the stomach and small bowel. *Gastrointest Endosc* 1992; **38**: 314-318 [PMID: 1607082]
28 **Zera RT**, Nava HR, Fischer JI. Percutaneous endoscopic gastrostomy (PEG) in cancer patients. *Surg Endosc* 1993; **7**: 304-307 [PMID: 8351601]
29 **Shastri YM**, Shirodkar M, Mallath MK. Endoscopic feeding tube placement in patients with cancer: a prospective clinical audit of 2055 procedures in 1866 patients. *Aliment Pharmacol Ther* 2008; **27**: 649-658 [PMID: 18221411 DOI: 10.1111/j.1365-2036.2008.03621.x]
30 **Kawata N**, Kakushima N, Tanaka M, Sawai H, Imai K, Hagiwara T, Takao T, Hotta K, Yamaguchi Y, Takizawa K, Matsubayashi H, Ono H. Percutaneous endoscopic gastrostomy for decompression of malignant bowel obstruction. *Dig Endosc* 2014; **26**: 208-213 [PMID: 23772988 DOI: 10.1111/den.12139]
31 **Stellato TA**, Gauderer MW. Percutaneous endoscopic gastrostomy for gastrointestinal decompression. *Ann Surg* 1987; **205**: 119-122 [PMID: 3813684]
32 **Cannizzaro R**, Bortoluzzi F, Valentini M, Scarabelli C, Campagnutta E, Sozzi M, Fornasarig M, Poletti M. Percutaneous endoscopic gastrostomy as a decompressive technique in bowel obstruction due to abdominal carcinomatosis. *Endoscopy* 1995; **27**: 317-320 [PMID: 7555938 DOI: 10.1055/s-2007-1005700]
33 **Scheidbach H**, Horbach T, Groitl H, Hohenberger W. Percutaneous endoscopic gastrostomy/jejunostomy (PEG/PEJ) for decompression in the upper gastrointestinal tract. Initial experience with palliative treatment of gastrointestinal obstruction in terminally ill patients with advanced carcinomas. *Surg Endosc* 1999; **13**: 1103-1105 [PMID: 10556447]
34 **Felsher J**, Chand B, Ponsky J. Decompressive percutaneous endoscopic gastrostomy in nonmalignant disease. *Am J Surg* 2004; **187**: 254-256 [PMID: 14769314 DOI: 10.1016/j.amjsurg.2003.11.002]
35 **Vashi PG**, Dahlk S, Vashi RP, Gupta D. Percutaneous endoscopic gastrostomy tube occlusion in malignant peritoneal carcinomatosis-induced bowel obstruction. *Eur J Gastroenterol Hepatol* 2011; **23**: 1069-1073 [PMID: 21975697]
36 **Larson DE**, Burton DD, Schroeder KW, DiMagno EP. Percutaneous endoscopic gastrostomy. Indications, success, complications, and mortality in 314 consecutive patients. *Gastroenterology* 1987; **93**: 48-52 [PMID: 3108063]
37 **Grant DG**, Bradley PT, Pothier DD, Bailey D, Caldera S, Baldwin DL, Birchall MA. Complications following gastrostomy tube insertion in patients with head and neck cancer: a prospective multi-institution study, systematic review and meta-analysis. *Clin Otolaryngol* 2009; **34**: 103-112 [PMID: 19413607 DOI: 10.1111/j.1749-4486.2009.01889.x]
38 **Ehrsson YT**, Langius-Eklöf A, Bark T, Laurell G. Percutaneous endoscopic gastrostomy (PEG) - a long-term follow-up study in head and neck cancer patients. *Clin Otolaryngol Allied Sci* 2004; **29**: 740-746 [PMID: 15533171 DOI: 10.1111/j.1365-2273.2004.00897.x]
39 **Pruthi D**, Duerksen DR, Singh H. The practice of gastrostomy tube placement across a Canadian regional health authority. *Am*

J Gastroenterol 2010; **105**: 1541-1550 [PMID: 20104220 DOI: 10.1038/ajg.2009.756]

40 **Rustom IK**, Jebreel A, Tayyab M, England RJ, Stafford ND. Percutaneous endoscopic, radiological and surgical gastrostomy tubes: a comparison study in head and neck cancer patients. *J Laryngol Otol* 2006; **120**: 463-466 [PMID: 16772054 DOI: 10.1017/s0022215106000661]

41 **Kwon RS**, Banerjee S, Desilets D, Diehl DL, Farraye FA, Kaul V, Mamula P, Pedrosa MC, Rodriguez SA, Varadarajulu S, Song LM, Tierney WM. Enteral nutrition access devices. *Gastrointest Endosc* 2010; **72**: 236-248 [PMID: 20541746 DOI: 10.1016/j.gie.2010.02.008]

42 **Sheehan JJ**, Hill AD, Fanning NP, Healy C, McDermott EW, O'Donoghue DP, O'Higgins NJ. Percutaneous endoscopic gastrostomy: 5 years of clinical experience on 238 patients. *Ir Med J* 2003; **96**: 265-267 [PMID: 14753579]

43 **Dripps R**. New classification of physical status. *Anesthesiology* 1963; 24

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MINIREVIEWS

Multiband mucosectomy for advanced dysplastic lesions in the upper digestive tract

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Abstract

Endoscopic resection (ER) is at present an accepted treatment for superficial gastrointestinal neoplasia. ER provides similar efficacy to surgery; however, it is minimally invasive and less expensive. Endoscopic mucosal resection (EMR) is superior to biopsy for diagnosing advanced dysplasia and can change the diagnostic grade and the management. Several EMR techniques have been described that are alternatively used dependent upon the endoscopist personal experience, the anatomic conditions and the endoscopic appearance of the lesion to be resected. The literature suggests that EMR offers comparable outcomes to surgery for selected indications. EMR techniques using a cap fitted endoscope and EMR using a ligation device [multiband mucosectomy (MBM)] are the most frequently use. MBM technique does not require submucosal injection as with the endoscopic resection-cap technique, multiple resections can be performed with the same snare, pre-looping the endoscopic resection-snare in the ridge of the cap is not necessary, MBM does not require withdrawal of the endoscope between resections and up to six consecutive resections can be performed. This reduces the time and cost required for the procedure, while also reducing patient discomfort. Despite the increasing popularity of MBM, data on the safety and efficacy of this technique in upper gastrointestinal lesions with advanced dysplasia, defined as those lesions that have high-grade dysplasia or early cancer, is limited.

Key words: Endoscopic mucosal resection; Barrett's esophagus; Esophageal cancer; Early gastric cancer; Stepwise radical endoscopic resection; Multiband mucosectomy; Endoscopic submucosal dissection

Core tip: Early detection of upper gastrointestinal lesions with advanced dysplasia is especially important in the management of the patients. These changes may indicate an increased risk of cancer or may detect cancer at an earlier stage, when it can be more effectively treated. Multiband mucosectomy (MBM) is an easy endoscopic mucosal resection technique allowing a definitive histologic diagnosis and potentially being curative. The available evidence suggests that MBM for these conditions, has an initial success rate comparable

to surgical treatment, but with fewer complications.

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INTRODUCTION

Most commonly, the treatment of high-grade dysplasia (HGD) and mucosal cancer has been surgical. However, it does carry procedure-related morbidity and mortality[1-4]. In addition, a notable proportion of these patients have significant comorbidities, which medically preclude them from undergoing surgery. These high rates of morbidity and mortality have filed attention in other types of less invasive treatment. Endoscopic mucosal resection (EMR) is an endoscopic therapeutic proposal in which the dysplastic epithelium is removed, thus making it possible for a definitive histologic diagnosis and treatment[5-9]. EMR is possible due to the existence of a loose adhesion between the submucosa and the muscular layer in the gastrointestinal tract's wall because of a different embryologic origin. This anatomic characteristic allows, for example, the saline injection between the two layers, thus transforming a flat or depressed lesion into an elevated one. This permits the safe resection of mucosal lesions without causing damage of the deeper muscle layer, and reduces the risk of perforation. EMR has been used not only for Barrett's esophagus with HGD but also for early cancer in which the risk of hematogenous dissemination or lymph node involvement is low[10-12]. EMR is effective and safe for total resection of superficial lesions. Furthermore, EMR does not compromise subsequent ablative therapy. Ablative techniques do not supply specimen for histopathologic evaluation and are mainly use as an adjunct therapy to EMR[13]. Several different EMR techniques have been described[14]: (1) strip biopsy; (2) endoscopic double snare polypectomy; (3) EMR using a transparent cap fitted endoscope; and (4) EMR using a ligation device [multiband mucosectomy (MBM)]. EMR is a technique that requires skill, both to resect lesions in a safe and effective manner and to manage complications. EMR should only be carried out by experienced endoscopists in advanced therapeutic endoscopy. Despite the increasing popularity of MBM, limited data on the safety and efficacy of this technique in lesions with advanced dysplasia (LAD), are available.

This article reviews the current evidence and gaps in knowledge in the understanding of management of LAD of the upper gastrointestinal tract with MBM. "Advanced dysplasia" was defined as those lesions that have HGD or early cancer (EC).

MBM DEVICE

MBM (Duette; Cook Medical) uses a modified variceal band ligator that includes a transparent cap with 6 bands and a handle that allows the passage of a snare through the accessory channel (Figure 1). The target mucosa is sucked into the cap and a pseudopolyp is created. The pseudopolyp can then be removed (Figure 2). MBM has several advantages: (1) no lifting is need because the esophageal muscle layer will immediately retract when captured within a band; (2) several resections can be performed by repetitive suck-band-snare sequences; (3) pre-looping the endoscopic resection-snare in the ridge of the cap is not required; (4) MBM does not need withdrawal of the endoscope between resections, and sequential 6 bands resections can be carried out; (5) MBM yields tissue specimen for hystology and staging[7]; (6) MBM is minimally invasive and carries lower morbidity and mortality compared to surgical treatment; and (7) surgery can be performed if advanced neoplasia is confirmed on histologic evaluation of the MBM specimen. By contrast, MBM has some disadvantages: (1) MBM demands advanced endoscopic skills; (2) larger lesions can only be resected by piecemeal technique which might preclude complete histological evaluation; and (3) there are no randomized trials directly comparing MBM with surgery.

MBM TECHNIQUE

MBM is generally performed with the patient under unconscious sedation with titrated intravenous propofol. After, the endoscope is introduced without the ligator and the lesion for resection is recognized. The lesion is outlined by using argon plasma coagulation. Marks are placed 2-5 mm outside the margins of the lesion (Figure 3). Then, the endoscope is withdrawn and the ligator assembled on the endoscope. The wires are placed in line with the working channel to provide the best endoscopic view (Figure 4). The endoscope is then reintroduced with the ligator, the dysplastic mucosa is sucked into the cap, and a rubber band is deployed. The rubber band forms a pseudopolyp which is then immediately resected by using pure coagulating current (Figure 5). It does not matter whether the snare is placed above or below the band. In most of the cases, however, the snare will lie below the rubber band. The second ligation is performed by suctioning the adjacent mucosa with a small overlap to ensure that no dysplastic mucosa remnant remains[15-18]. After each resection, the specimen is pushed into the stomach by using the tip of the snare's catheter. Resected specimens are retrieved from the stomach with a polypectomy snare or retrieval net. If cancer diagnosis is made, the histological report should include these characteristics: tumor infiltration depth, tumor differentiation grade, existence of lymphatic or vascular infiltration and the radicality of

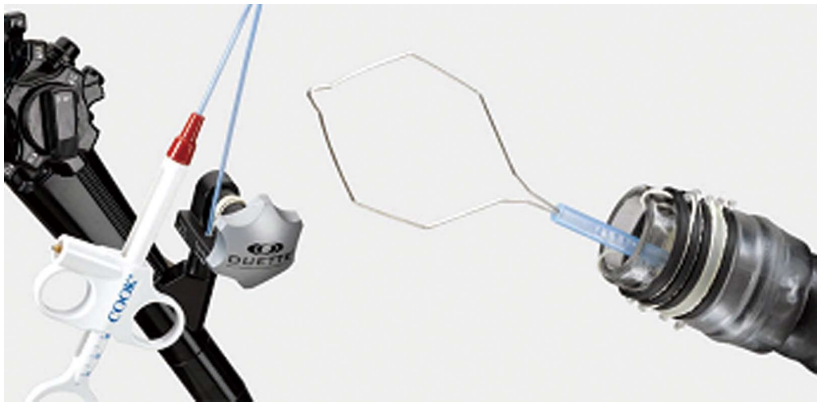

Figure 1 Multiband device (Duette). A variceal ligation device is used to suck the lesion into the ligation cap, allowing it to be captured with a rubber band and resected with a hexagonal snare (Courtesy of Cook®).

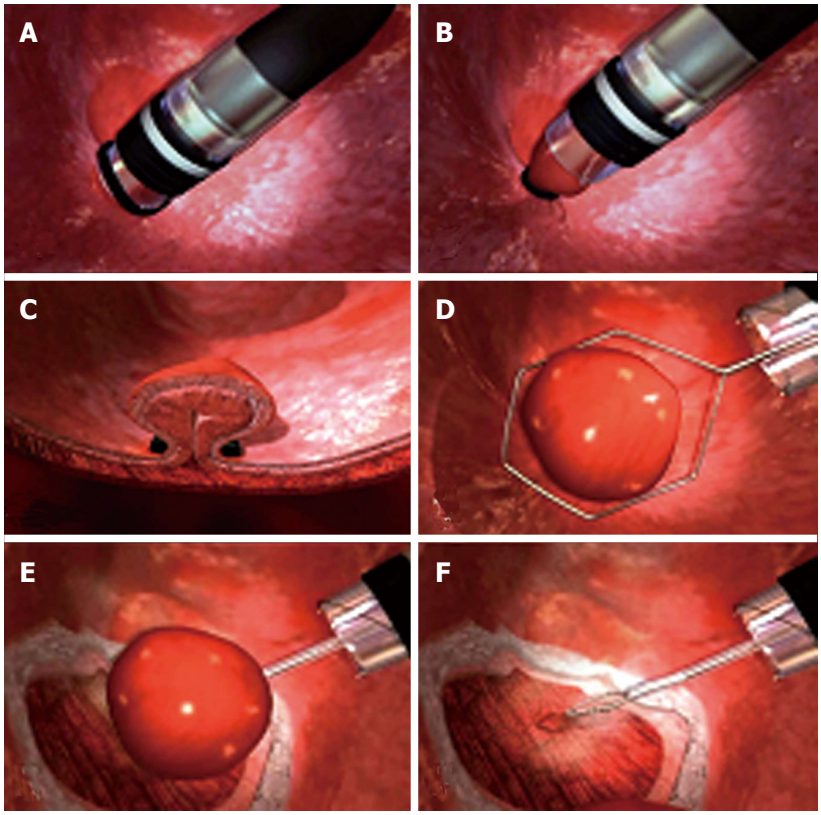

Figure 2 Multiband mucosectomy technical sequence (A to F) (Courtesy of Cook®). A-C: Pseudopolyp that is created by suctioning the mucosa into the ligation cap and releasing a rubber band; D-F: Pseudopolyp resection by hexagonal snare.

the lateral margins. After MBM, patients are put on a proton pump inhibitor and sucralfate suspension. A pureed diet is recommended. In patients without comorbidities, MBM can be performed on an outpatient basis. However, we prefer that patients are discharged after 24 h of observation. Primary endoscopic follow-up is performed 4 wk later on an outpatient basis.

INDICATIONS FOR MULTIBAND MUCOSECTOMY

The most common indication for EMR in the upper gastrointestinal tract is the staging and treatment of early neoplasia in Barrett's esophagus (BE). MBM has been applied not only to mucosal lesions with HGD but also to early cancer in which the risk of lymph node involvement or hematogenous dissemination is low enough to justify a relatively conservative approach compared with surgery[15-31].

Nondysplastic BE

At present, there are no randomized controlled trials reviewing the role of endoscopic treatment compared with surveillance alone in nondyspastic BE. Probably, the number needed to treat to prevent one cancer is high and the risk of endoscopic treatment outweighs the benefits of this procedure**.** Thus, the current American Gastroenterological Association (AGA) guidelines do not recomend endoscopic eradication therapy (EET) in patients with nondysplastic BE[32].

Low-grade dysplasia in BE

The natural history of low-grade dysplasia (LGD) in BE is unclear with variability in the rates of development to esophageal adenocarcinoma (EAC), poor interobserver concordance, unclear risk stratification, and lack of

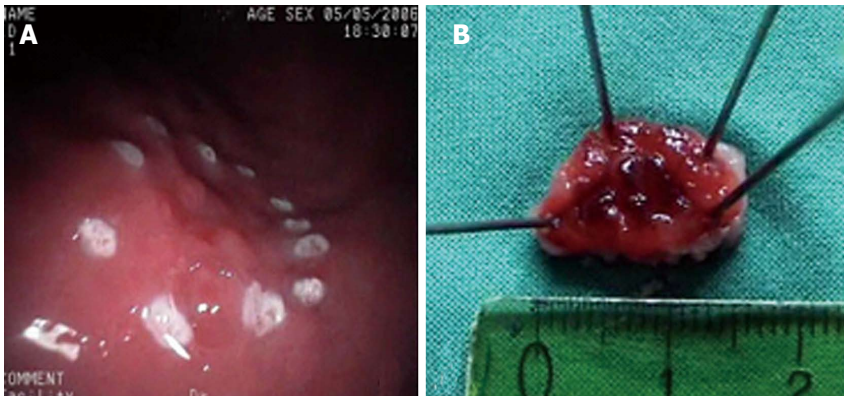

Figure 3 Early gastric cancer treated with multiband mucosectomy. A: Argon plasma coagulation marks are placed 2-5 mm outside the margins of the lesion; B: Specimen resected (15 mm).

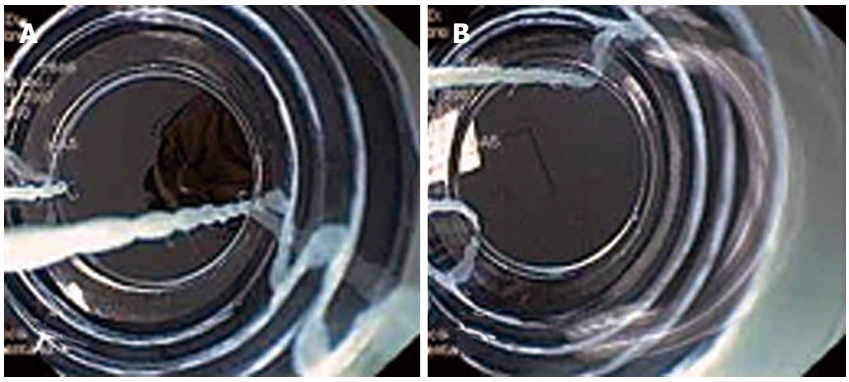

Figure 4 Best endoscopic views. A: Wires positioned incorrectly; B: Wires positioned correctly (in line with the working cannel).

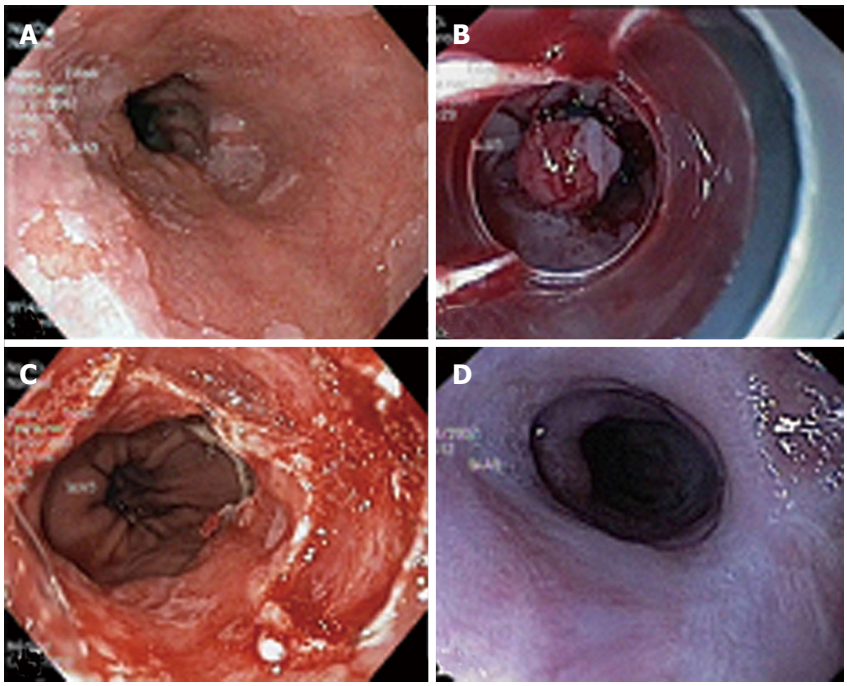

Figure 5 Stepwise radical multiband endoscopic resection of Barrett's esophagus with high-grade dysplasia (A to D). A: A 3-cm long Barrett's mucosa; B: Rubber band applied for resection; C: Circumferential resection; D: Complete neosquamous re-epithelization.

established benefit of eradication[33-35]. Therefore, systematic EET of patients with LGD is not currently advised. Now, AGA guidelines suggest the use of RFA as an alternative for the treatment of verified LGD but, this decision should be individualize with agreement between the patient and the physician[32].

HGD or early adenocarcinoma in BE

At the present, AGA guidelines recommend EET in the management of patients with HGD[32]. Current evidence suggests that EMR of HGD and early cancer EC has similar success rates as surgical treatment[6,36]. The indications for EMR in the setting of Barrett's neoplasia include the following: flat mucosal lesions, tumor size between 20-30 mm, and good to moderate differentiation on histology[6]. Furthermore, EMR has better diagnostic reproducibility compared to mucosal biopsies alone, suggesting a possible role in BE

surveillance[37].

Esophageal squamous cell carcinoma

Usually, EMR is indicated for superficial well- or moderately differentiated squamous cell carcinoma without venous or lymphatic involvement that is limited to the lamina propria[38].

Early gastric cancer

Candidates for MBM must meet the following criteria: well- or moderately differentiated adenocarcinoma, confined to the mucosa, < 20 mm for elevated lesions, < 10 mm for flat or depressed lesions, with no evidence of ulceration, lymphatic or venous involvement[39].

MULTIBAND MUCOSECTOMY AS STAGING PROCEDURE

Accurate T-staging is critical in making therapeutic decisions in patients with dysplastic Barrett's esophagus. The distinction between different categories of dysplastic lesions can be difficult since it depends in part upon the size, location, depth, and number of biopsies. The Seattle biopsy protocol is recommended for mapping Barrett's esophagus with HGD[40]. Targeted biopsies are acquired from all visible abnormalities and random four-quadrant biopsies are taken every 1 cm starting from the top of the gastric folds up to the most proximal extent of the BE (squamocolumnar junction). Another concern with the diagnosis of dysplastic lesions is the interobserver reliability among pathologists. Therefore, it is recommended that a second, experienced pathologist should confirm the diagnosis of HGD. Studies comparing routine biopsies of visible lesions with EMR report a 30% to 48% rate in change in diagnosis after obtaining an EMR[26,28]. Furthermore, in a study comparing preoperative EMR with histologic examination on esophagectomy specimens, there was perfect agreement between the two[41]. We consider MBM may represent not only a reasonable treatment option but also the final step of the diagnostic work-up for patients with dysplastic lesions[37]. Assessment of the depth of infiltration and estimation of local nodal metastasis can be achieved by endoscopic resection of these areas within a lesion which look suspicious[42,43]. Among patients diagnosed with dysplastic lesions, other imaging techniques could be taken into account to evaluate tumor infiltration depth, local lymph node status and metastatic spread. Endoscopic ultrasonography (EUS) and computerized tomography (CT) scan are the most widely used techniques. Although the role of EUS has been established in the accurate T and N staging of invasive EAC, recent studies have shown only a modest accuracy in delineating T-staging in patients with HGD and intramucosal EAC[44-47]. Recent studies report that the overall accuracy of EUS in establishing T-stage (depth of invasion), using EMR/surgical pathology as the gold standard, was 65%-72%. Based on this information, EUS has a limited role in the evaluation of patients with early neoplasia[44,48]. Other techniques, such as magnetic resonance imaging and positron emission tomography scanning, do not have a role in the evaluation of patients with these lesions.

MULTIBAND MUCOSECTOMY AS THERAPEUTIC PROCEDURE

The first objective of endoscopic therapy is to prevent the development of invasive EAC by treating the dysplastic lesion. The available evidence suggests that endoscopic resection (ER) for these conditions has an initial success rate comparable to surgical treatment, but with fewer complications[6,8,26,28,36]. The rate of complete remission ranges from 59% to 99% in different studies[6,8,26,28,36,49,50]. Higher degrees of success are seen in patients with lower risk lesions. In a systematic review, complete eradication of HGD or EC was achieved in 95% of patients, and complete eradication of all Barrett's mucosa was achieved in 89%[51]. ER is best performed on patients with small (< 20 mm diameter), solitary, flat type lesion that is limited to the mucosa. Histopathologic differentiation is less important, since the great majority of these early lesions will be classified as HGD or well differentiated cancers[7]. However, patients who develop dysplasia are at higher risk of recurrence of neoplasia and metachronous lesions from the remaining segment of BE, which occurs in up to 30% of patients undergoing EET[6,8,28,36,52-54]. Factors associated with recurrence in BE are larger diameter, long segment, piecemeal resection, lack of adjunctive ablative therapy, presence of multifocal neoplasia, an elapsed time of more than 10 mo prior to achieving complete remission and the presence of residual dysplasia[8,36]. In most patients, recurrences can be successfully treated endoscopically[54]. Recurrence is a possible limitation after EMR. Patients therefore require regular follow up with endoscopy (every three months during the first year and annually thereafter) and treatment of any residual Barrett's mucosa. Endoscopic ablative therapy with radiofrequency ablation or photodynamic therapy allows treatment of the whole Barrett's segment in a few sessions. Complete ER of the whole Barrett's segment may also be used as endoscopic treatment [stepwise radical endoscopic resection (SRER)][21-23,49] (Figure 5). Most experts believe that EMR resection of the entire Barrett segment can be performed in patients with Barrett segment length of less than or equal to 5 cm. This technique has several advantages over ablative therapy: it allows complete removal of the whole mucosa at risk for malignant progression and provides tissue samples for histological diagnosis. Furthermore, the feasibility and safety of ER of the entire Barrett's segment has been demonstrated on several series[21-23,49]. However, the role of the stepwise

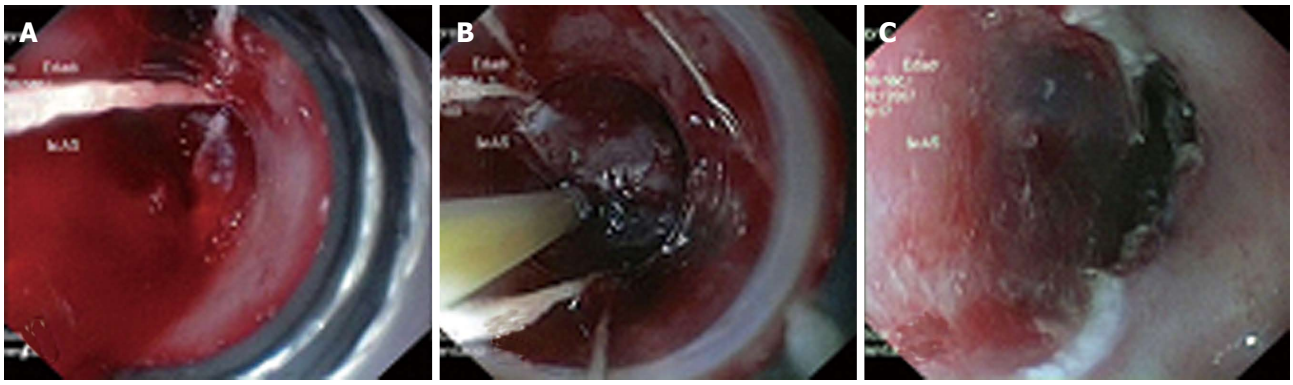

Figure 6 Active bleeding post-multiband mucosectomy in Barrett's esophagus, effectively treated by adrenaline injection (A to C). A: Active pumping bleeding; B: Adrenaline injection by needle; C: Cessation of bleeding.

radical endoscopic resection technique seems restricted to selected patients in the treatment of HGD or EC in Barrett's esophagus. Although the SRER technique is equally effective and has several advantages over ablative treatment, it is related to a much higher rate of strictures than ER plus RFA. Currently, it is advised for complete eradication of intestinal metaplasia, that patients with HGD and early esophageal adenocarcinoma(EAC) undergo EMR of a visible lesion followed by RFA to the remaining Barrett segment, or to use the SRER procedure only for patients with more extensive lesions in BE up to 5 cm[30].

MULTIBAND MUCOSECTOMY COMPLICATIONS

The three major EMR-complications include: (1) bleeding; (2) perforation; and (3) strictures[20,29,55-58]. Bleeding is apparent in 0% to 46% of cases and can be managed with endoscopic treatment**.** Immediate bleeding can be considered as a complication if there are clinical signs. Perforation has been described in less than 5%. The risk is higher in piecemeal resection. Strictures have been described in 2% to 88% of patients undergoing EMR for dysplastic Barrett's esophagus. The size/length of the mucosal defect and the circumferential involvement by the BE predicts stenosis formation. Stenosis are more frequent if the BE involves more than 75% of the esophageal circumference. Stenosis can be successfully treated with endoscopic dilation**.** Chest pain occurs in about 30% of patients undergoing EMR.

Several studies demonstrated that the MBM is safe and effective[15,17,18,29] (Table 1). In these studies, acute complications were observed in 3% and no perforations occurred[15,17,26]. MBM does not appear to be associated with more complications than endoscopic resection-cap, despite lack of submucosal lifting. Perforations occur in approximately 1% of the endoscopic resections performed with the widely used cap technique in Barrett's esophagus[59,60], compared to MBM where the probability of perforation seems to be very low, with perforation rates reported in the range of 0% to 1.2%[16-31]. Most acute bleedings with MBM resolve spontaneously or can effectively be treated by adrenaline injection or coagulation techniques (Figure 6). Several studies have reported stenosis rates of 26%-70% after radical resection with MBM of the whole Barrett's segment[16,23,25,26]. A larger study evidenced stricture requiring dilatation in 48% of the patients who underwent the MBM procedure as part of the (stepwise) radical resection protocol. Stenosis rates increase with the extent of the resected area in the esophagus, especially if the resection is more than 3 cm in length and comprises more than 75% of the circumference[61]. Suitable data comparing stenosis rate with MBM and cap technique, is not available.

MULTIBAND MUCOSECTOMY *VS* CAP-ASSISTED EMR

Multiband mucosectomy and cap-assisted EMR are new minimally invasive therapies alternatives for LAD. A randomized controlled trial comparing these two techniques demonstrated that there is no difference in the thickness of the specimen and submucosal resection; however, the multiband mucosectomy had a shorter procedure time and produced smaller EMR specimens. The clinical relevance of these findings may be questioned, since there was no significant difference in the depth of resection between the two techniques[18]. In addition, costs for disposables were significantly lower for MBM procedures. Rates of complete endoscopic resection were similar for MBM (91% of delineated focal lesions, 86% of delineated areas in Barrett's esophagus, and 100% of the escape treatments) and the cap technique (88% success rate for complete endoscopic resection)[60]. Both techniques are very effective in this respect[18,60,62,63]. MBM can fail if there is significant fibrosis which impeded suctioning of the mucosa into the cap and subsequent rubber band ligation[17]. Similarly, both techniques seem equally safe and the lack of submucosal lifting with MBM does not increase the risk of perforation compared with that of the cap technique. A disadvantage for MBM may be decreased visibility due to

Table 1 Results of multiband mucosectomy procedures from different studies

Ref.	Number and procedures	Complete eradication	Recurrence rate	Complications	Follow-up (mo)
Soehendra *et al*[16]	10 MBM	90%	N/A	Stricture (SRER 70%)	N/A
Ell *et al*[62]	100 MBM (%N/A) Cap	99%	11%	0%	33
Peters *et al*[31]	40 MBM	N/A	N/A	Bleeding (6%)	N/A
Chennat *et al*[26]	49 MBM (4%) Cap FH	65%	2.50%	Stricture (SRER 36.7%)	23
Espinel *et al*[15]	8 MBM	100%	0%	Stricture (SRER 25%)	32
Moss *et al*[28]	75 MBM (%N/A) Cap	94%	0%	Stricture (SRER 8%)	31
Pouw *et al*[27]	169 MBM (%N/A) Cap FH	95.30%	1.80%	Bleeding (1.8%) Perforation (2.4%) Stricture (SRER 50%)	32
Brahmania *et al*[63]	22 MBM	82%	18%	Stricture (SRER 13%)	24
Pouw *et al*[18]	42 MBM	100%	N/A	Perforation (2%)	N/A
Alvarez Herrero *et al*[17]	243 MBM	91%	0%	Bleeding (3%) Stricture (SRER 48%)	3
Van Vilsteren *et al*[30]	25 MBM (48%) Cap FH	100%	4%	Perforation (4%) Stricture (SRER 88%)	25
Gerke *et al*[29]	41 MBM (76%) Cap	78%	9%	Perforation (4.9%) Stricture (SRER 44%)	25
Tomizawa *et al*[56]	681 MBM (18%) Cap	N/A	N/A	Bleeding (1.2%) Stricture (1%)	63

MBM: Multiband mucosectomy; Cap: Cap technique; FH: Free hand technique; N/A: No data available; SRER: Stepwise radical endoscopic resection.

the effect of the black rubber bands. Therefore, it is desirable to have previously correctly delineated the target area by placement of markers, in order to maximize complete endoscopic resection. The learning curve for MBM is shorter compared with that of cap-assisted EMR, because it combines the techniques of variceal band ligation and polypectomy.

MULTIBAND MUCOSECTOMY *VS* ENDOSCOPIC SUBMUCOSAL DISSECTION

Endoscopic submucosal dissection (ESD) was initially introduced for the endoscopic treatment of early gastric cancer in Japan[64,65]. It was developed for the *en-bloc* resection of large lesions and enables precise histological assessment of specimens. The comparison between ESD and EMR in the treatment of early esophageal carcinoma is debatable. EMR and ESD have been suggested as alternatives to esophagectomy in the treatment of these lesions, without lymph node metastasis. A meta-analysis has compared the efficacy and safety of EMR and ESD for the treatment of early esophageal carcinoma[66]. Five retrospective trials were identified and a total of 710 patients and 795 lesions were included. The results confirmed substantial advantages of ESD over EMR for early esophageal carcinoma regarding en bloc resection rate, histologically complete resection rate and local recurrence even for small lesions, without increasing the complication rate. A previous meta-analysis by Cao *et al*[67] compared clinical outcomes of ESD with EMR in the treatment of tumors of the gastrointestinal tract, and they found that ESD showed better en bloc and curative resection rates and local recurrence, but was more time-consuming and had higher rates of bleeding and perforation complications.

A recent review on the safety and efficacy of MBM compared with ESD for the treatment of early neoplasia in Barrett's or neoplasias at the esophagogastric junction (EGJ), showed that the recurrence rate was slightly higher in the EMR group (2.8%) compared with the ESD group (0.3%), but the difference did not reach statistical significance (P = 0.06)[68]. All recurrences in the EMR group were managed by additional endoscopic resections. Complete eradication rate in the EMR group was 95.5%. Curative resection rate in the ESD group was 75.5%. The risk of delayed bleeding and perforation rates in both groups was similar (EMR group 1.2%; ESD group 2.1%, P = 0.26). The perforation rate in the EMR group (1.2%) was similar to that in the ESD group (1.5%), and the difference was not statistically significant. The stricture rate was similar in both groups when comparing resection of the neoplastic lesion alone. Stricture rates increased rapidly in the SRER group when the complete Barrett's mucosa was resected. The procedure time was less time-consuming in the EMR group (mean time: 36.7 min, 95%CI: 34.5-38.9) compared with the ESD group (mean time: 83.3 min, 95%CI: 57.4-109.2). The authors concluded that the MBM technique appears as effective as ESD when comparing important outcome parameters on the eradication of early Barrett's or EGJ neoplasia. There

are no differences in the outcome when comparing strictures, bleedings and perforation rates for both EMR and ESD in experienced hands. The MBM technique has considerable advantages in being both easier to master and less time-consuming.

MULTIBAND MUCOSECTOMY AND EARLY GASTRIC CANCER

The endoscopic treatment of early gastric cancer (EGC) with mucosectomy has increasingly proven to be an effective modality for local treatment, especially if the tumor is limited to the mucosa, of a size no greater than 2 cm, with neither histologic ulceration nor lymphatic vessel invasion and a cancer-negative resection line. Mucosectomy has also demonstrated to be useful in the resection of precancerous lesions such as adenomas[69-71]. European experience in EMR for early gastric cancer is still relatively low, since early stomach cancer is diagnosed at a much lower rate in Europe than in Japan and generally, operable patients are referred to surgery for radical resection. With EMR, complete resection rates have been reported in 74%-97% and survival rates between 95%-100%[14,72]. The most frequent complication is bleeding (1%-20%)[73] and recurrence rates were observed to be between 2%-13%[74]. EMR appears to have a better post-procedure quality of life compared with surgical gastrectomy[75]. Data on the use of MBM in the management of patients with EGC is small. Our experience is very limited but, highly positive, in selected patients[15]. Three patients diagnosed by biopsy of EGC (type Ⅱa) and 1 patient with HGD were treated by MBM (Figure 3). The length of lesions ranged between 10 mm and 20 mm. MBM was accomplished in 1 session in each patient. The histological analysis of MBM specimens confirmed mucinous adenocarcinoma with submucosal infiltration (1 patient who was referred for surgery), EGC (2 patients), and HGD (1 patient). Minor bleeding without clinical consequences occurred in 1 patient and was controlled by local adrenaline injection. Endoscopic surveillance was recommended for all our patients and *Helicobacter pylori* was eradicated. Regular follow-up did not detect any recurrent lesions. MBM in EGC may have also diagnostic and therapeutic implications. Further studies are needed in this field to determine the clinical impact of this therapeutic approach.

CONCLUSION

MBM is an exciting EMR technique that provides heightened levels of diagnostic accuracy and minimally invasive therapy for the management of upper gastrointestinal tract lesions with advanced dysplasia. This minimally invasive technique is safe and effective for complete resection of superficial lesions with high-grade dyspasia or early cancer.

REFERENCES

1 **van Lanschot JJ**, Hulscher JB, Buskens CJ, Tilanus HW, ten Kate FJ, Obertop H. Hospital volume and hospital mortality for esophagectomy. *Cancer* 2001; **91**: 1574-1578 [PMID: 11301408]

2 **Enzinger PC**, Mayer RJ. Esophageal cancer. *N Engl J Med* 2003; **349**: 2241-2252 [PMID: 14657432 DOI: 10.1056/NEJMra035010]

3 **Birkmeyer JD**, Stukel TA, Siewers AE, Goodney PP, Wennberg DE, Lucas FL. Surgeon volume and operative mortality in the United States. *N Engl J Med* 2003; **349**: 2117-2127 [PMID: 14645640 DOI: 10.1056/NEJMsa035205]

4 **Swisher SG**, Deford L, Merriman KW, Walsh GL, Smythe R, Vaporicyan A, Ajani JA, Brown T, Komaki R, Roth JA, Putnam JB. Effect of operative volume on morbidity, mortality, and hospital use after esophagectomy for cancer. *J Thorac Cardiovasc Surg* 2000; **119**: 1126-1132 [PMID: 10838528 DOI: 10.1067/mtc.2000.105644]

5 **Nijhawan PK**, Wang KK. Endoscopic mucosal resection for lesions with endoscopic features suggestive of malignancy and high-grade dysplasia within Barrett's esophagus. *Gastrointest Endosc* 2000; **52**: 328-332 [PMID: 10968845 DOI: 10.1067/mge.2000.105777]

6 **Ell C**, May A, Gossner L, Pech O, Günter E, Mayer G, Henrich R, Vieth M, Müller H, Seitz G, Stolte M. Endoscopic mucosal resection of early cancer and high-grade dysplasia in Barrett's esophagus. *Gastroenterology* 2000; **118**: 670-677 [PMID: 10734018 DOI: 10.1016/S0016-5085(00)70136-3]

7 **Vieth M**, Ell C, Gossner L, May A, Stolte M. Histological analysis of endoscopic resection specimens from 326 patients with Barrett' s esophagus and early neoplasia. *Endoscopy* 2004; **36**: 776-781 [PMID: 15326572 DOI: 10.1055/s-2004-825802]

8 **Pech O**, Behrens A, May A, Nachbar L, Gossner L, Rabenstein T, Manner H, Guenter E, Huijsmans J, Vieth M, Stolte M, Ell C. Long-term results and risk factor analysis for recurrence after curative endoscopic therapy in 349 patients with high-grade intraepithelial neoplasia and mucosal adenocarcinoma in Barrett's oesophagus. *Gut* 2008; **57**: 1200-1206 [PMID: 18460553 DOI: 10.1136/gut.2007.142539]

9 **Ahmadi A**, Draganov P. Endoscopic mucosal resection in the upper gastrointestinal tract. *World J Gastroenterol* 2008; **14**: 1984-1989 [PMID: 18395896 DOI: 10.3748/wjg.14.1984]

10 **Nigro JJ**, Hagen JA, DeMeester TR, DeMeester SR, Theisen J, Peters JH, Kiyabu M. Occult esophageal adenocarcinoma: extent of disease and implications for effective therapy. *Ann Surg* 1999; **230**: 433-448; discussion 438-440 [PMID: 10493489 DOI: 10.1097/00000658-199909000-00015]

11 **Stein HJ**, Feith M, Mueller J, Werner M, Siewert JR. Limited resection for early adenocarcinoma in Barrett's esophagus. *Ann Surg* 2000; **232**: 733-742 [PMID: 11088068 DOI: 10.1097/00000658-200012000-00002]

12 **Crumley AB**, Going JJ, McEwan K, McKernan M, Abela JE, Shearer CJ, Stanley AJ, Stuart RC. Endoscopic mucosal resection for gastroesophageal cancer in a U.K. population. Long-term follow-up of a consecutive series. *Surg Endosc* 2011; **25**: 543-548 [PMID: 20623237 DOI: 10.1007/s00464-010-1213-9]

13 **Bennett C**, Vakil N, Bergman J, Harrison R, Odze R, Vieth M, Sanders S, Gay L, Pech O, Longcroft-Wheaton G, Romero Y, Inadomi J, Tack J, Corley DA, Manner H, Green S, Al Dulaimi D, Ali H, Allum B, Anderson M, Curtis H, Falk G, Fennerty MB, Fullarton G, Krishnadath K, Meltzer SJ, Armstrong D, Ganz R, Cengia G, Going JJ, Goldblum J, Gordon C, Grabsch H, Haigh C, Hongo M, Johnston D, Forbes-Young R, Kay E, Kaye P, Lerut T, Lovat LB, Lundell L, Mairs P, Shimoda T, Spechler S, Sontag S, Malfertheiner P, Murray I, Nanji M, Poller D, Ragunath K, Regula J, Cestari R, Shepherd N, Singh R, Stein HJ, Talley NJ, Galmiche JP, Tham TC, Watson P, Yerian L, Rugge M, Rice TW, Hart J, Gittens S, Hewin D, Hochberger J, Kahrilas P, Preston S, Sampliner R, Sharma P, Stuart R, Wang K, Waxman I, Abley C, Loft D, Penman I, Shaheen NJ, Chak A, Davies G, Dunn L, Falck-Ytter Y, Decaestecker J, Bhandari P, Ell C, Griffin SM, Attwood S, Barr H, Allen J, Ferguson MK, Moayyedi P, Jankowski JA. Consensus statements for management of Barrett's dysplasia and

early-stage esophageal adenocarcinoma, based on a Delphi process. *Gastroenterology* 2012; **143**: 336-346 [PMID: 22537613 DOI: 10.1053/j.gastro.2012.04.032]
14 **Marc G**, Lopes CV. Endoscopic resection of superficial gastrointestinal tumors. *World J Gastroenterol* 2008; **14**: 4600-4606 [PMID: 18698673 DOI: 10.3748/wjg.14.4600]
15 **Espinel J**, Pinedo E, Rascarachi G. Endoscopic mucosal resection with a multiband ligator for the treatment of Barrett s high-grade dysplasia and early gastric cancer. *Rev Esp Enferm Dig* 2009; **101**: 403-407 [PMID: 19630463 DOI: 10.4321/S1130-01082009000600005]
16 **Soehendra N**, Seewald S, Groth S, Omar S, Seitz U, Zhong Y, de Weerth A, Thonke F, Schroeder S. Use of modified multiband ligator facilitates circumferential EMR in Barrett's esophagus (with video). *Gastrointest Endosc* 2006; **63**: 847-852 [PMID: 16650552 DOI: 10.1016/j.gie.2005.06.052]
17 **Alvarez Herrero L**, Pouw RE, van Vilsteren FG, ten Kate FJ, Visser M, Seldenrijk CA, van Berge Henegouwen MI, Weusten BL, Bergman JJ. Safety and efficacy of multiband mucosectomy in 1060 resections in Barrett's esophagus. *Endoscopy* 2011; **43**: 177-183 [PMID: 21365511 DOI: 10.1055/s-0030-1256095]
18 **Pouw RE**, van Vilsteren FG, Peters FP, Alvarez Herrero L, Ten Kate FJ, Visser M, Schenk BE, Schoon EJ, Peters FT, Houben M, Bisschops R, Weusten BL, Bergman JJ. Randomized trial on endoscopic resection-cap versus multiband mucosectomy for piecemeal endoscopic resection of early Barrett's neoplasia. *Gastrointest Endosc* 2011; **74**: 35-43 [PMID: 21704807 DOI: 10.1016/j.gie.2011.03.1243]
19 **Gerke H**, Siddiqui J, Parekh KR, Vanderheyden AD, Mitros FA. Esophageal perforation complicating band ligator-assisted mucosal resection. *Gastrointest Endosc* 2009; **69**: 153-154; discussion 154 [PMID: 18951128 DOI: 10.1016/j.gie.2008.06.020]
20 **van Vilsteren FG**, Pouw RE, Herrero LA, Peters FP, Bisschops R, Houben M, Peters FT, Schenk BE, Weusten BL, Visser M, Ten Kate FJ, Fockens P, Schoon EJ, Bergman JJ. Learning to perform endoscopic resection of esophageal neoplasia is associated with significant complications even within a structured training program. *Endoscopy* 2012; **44**: 4-12 [PMID: 22109651 DOI: 10.1055/s-0031-1291384]
21 **Seewald S**, Akaraviputh T, Seitz U, Brand B, Groth S, Mendoza G, He X, Thonke F, Stolte M, Schroeder S, Soehendra N. Circumferential EMR and complete removal of Barrett's epithelium: a new approach to management of Barrett's esophagus containing high-grade intraepithelial neoplasia and intramucosal carcinoma. *Gastrointest Endosc* 2003; **57**: 854-859 [PMID: 12776032 DOI: 10.1016/S0016-5107(03)70020-0]
22 **Giovannini M**, Bories E, Pesenti C, Moutardier V, Monges G, Danisi C, Lelong B, Delpero JR. Circumferential endoscopic mucosal resection in Barrett's esophagus with high-grade intraepithelial neoplasia or mucosal cancer. Preliminary results in 21 patients. *Endoscopy* 2004; **36**: 782-787 [PMID: 15326573 DOI: 10.1055/s-2004-825813]
23 **Peters FP**, Kara MA, Rosmolen WD, ten Kate FJ, Krishnadath KK, van Lanschot JJ, Fockens P, Bergman JJ. Stepwise radical endoscopic resection is effective for complete removal of Barrett' s esophagus with early neoplasia: a prospective study. *Am J Gastroenterol* 2006; **101**: 1449-1457 [PMID: 16863545 DOI: 10.1111/j.1572-0241.2006.00635.x]
24 **Larghi A**, Lightdale CJ, Ross AS, Fedi P, Hart J, Rotterdam H, Noffsinger A, Memeo L, Bhagat G, Waxman I. Long-term follow-up of complete Barrett's eradication endoscopic mucosal resection (CBE-EMR) for the treatment of high grade dysplasia and intramucosal carcinoma. *Endoscopy* 2007; **39**: 1086-1091 [PMID: 17701854 DOI: 10.1055/s-2007-966788]
25 **Pouw RE**, Peters FP, Sempoux C, Piessevaux H, Deprez PH. Stepwise radical endoscopic resection for Barrett's esophagus with early neoplasia: report on a Brussels' cohort. *Endoscopy* 2008; **40**: 892-898 [PMID: 19009481 DOI: 10.1055/s-2008-1077675]
26 **Chennat J**, Konda VJ, Ross AS, de Tejada AH, Noffsinger A, Hart J, Lin S, Ferguson MK, Posner MC, Waxman I. Complete Barrett' s eradication endoscopic mucosal resection: an effective treatment modality for high-grade dysplasia and intramucosal carcinoma--an American single-center experience. *Am J Gastroenterol* 2009; **104**: 2684-2692 [PMID: 19690526 DOI: 10.1038/ajg.2009.465]
27 **Pouw RE**, Seewald S, Gondrie JJ, Deprez PH, Piessevaux H, Pohl H, Rösch T, Soehendra N, Bergman JJ. Stepwise radical endoscopic resection for eradication of Barrett's oesophagus with early neoplasia in a cohort of 169 patients. *Gut* 2010; **59**: 1169-1177 [PMID: 20525701 DOI: 10.1136/gut.2010.210229]
28 **Moss A**, Bourke MJ, Hourigan LF, Gupta S, Williams SJ, Tran K, Swan MP, Hopper AD, Kwan V, Bailey AA. Endoscopic resection for Barrett's high-grade dysplasia and early esophageal adenocarcinoma: an essential staging procedure with long-term therapeutic benefit. *Am J Gastroenterol* 2010; **105**: 1276-1283 [PMID: 20179694 DOI: 10.1038/ajg.2010.1]
29 **Gerke H**, Siddiqui J, Nasr I, Van Handel DM, Jensen CS. Efficacy and safety of EMR to completely remove Barrett's esophagus: experience in 41 patients. *Gastrointest Endosc* 2011; **74**: 761-771 [PMID: 21824611 DOI: 10.1016/j.gie.2011.06.009]
30 **van Vilsteren FG**, Pouw RE, Seewald S, Alvarez Herrero L, Sondermeijer CM, Visser M, Ten Kate FJ, Yu Kim Teng KC, Soehendra N, Rösch T, Weusten BL, Bergman JJ. Stepwise radical endoscopic resection versus radiofrequency ablation for Barrett's oesophagus with high-grade dysplasia or early cancer: a multicentre randomised trial. *Gut* 2011; **60**: 765-773 [PMID: 21209124 DOI: 10.1136/gut.2010.229310]
31 **Peters FP**, Kara MA, Curvers WL, Rosmolen WD, Fockens P, Krishnadath KK, Ten Kate FJ, Bergman JJ. Multiband mucosectomy for endoscopic resection of Barrett's esophagus: feasibility study with matched historical controls. *Eur J Gastroenterol Hepatol* 2007; **19**: 311-315 [PMID: 17353695 DOI: 10.1097/MEG.0b013e328080ca90]
32 **Spechler SJ**, Sharma P, Souza RF, Inadomi JM, Shaheen NJ. American Gastroenterological Association medical position statement on the management of Barrett's esophagus. *Gastroenterology* 2011; **140**: 1084-1091 [PMID: 21376940 DOI: 10.1053/j.gastro.2011.01.030]
33 **Wani S**, Falk GW, Post J, Yerian L, Hall M, Wang A, Gupta N, Gaddam S, Singh M, Singh V, Chuang KY, Boolchand V, Gavini H, Kuczynski J, Sud P, Bansal A, Rastogi A, Mathur SC, Young P, Cash B, Goldblum J, Lieberman DA, Sampliner RE, Sharma P. Risk factors for progression of low-grade dysplasia in patients with Barrett's esophagus. *Gastroenterology* 2011; **141**: 1179-1186, 1186.e1 [PMID: 21723218 DOI: 10.1053/j.gastro.2011.06.055]
34 **Wani S**. Management of low-grade dysplasia in Barrett's esophagus. *Curr Opin Gastroenterol* 2012; **28**: 370-376 [PMID: 22508323 DOI: 10.1097/MOG.0b013e328353af02]
35 **Curvers WL**, ten Kate FJ, Krishnadath KK, Visser M, Elzer B, Baak LC, Bohmer C, Mallant-Hent RC, van Oijen A, Naber AH, Scholten P, Busch OR, Blaauwgeers HG, Meijer GA, Bergman JJ. Low-grade dysplasia in Barrett's esophagus: overdiagnosed and underestimated. *Am J Gastroenterol* 2010; **105**: 1523-1530 [PMID: 20461069 DOI: 10.1038/ajg.2010.171]
36 **Esaki M**, Matsumoto T, Hirakawa K, Nakamura S, Umeno J, Koga H, Yao T, Iida M. Risk factors for local recurrence of superficial esophageal cancer after treatment by endoscopic mucosal resection. *Endoscopy* 2007; **39**: 41-45 [PMID: 17252459 DOI: 10.1055/s-2006-945143]
37 **Mino-Kenudson M**, Hull MJ, Brown I, Muzikansky A, Srivastava A, Glickman J, Park DY, Zuckerberg L, Misdraji J, Odze RD, Lauwers GY. EMR for Barrett's esophagus-related superficial neoplasms offers better diagnostic reproducibility than mucosal biopsy. *Gastrointest Endosc* 2007; **66**: 660-676; quiz 767, 769 [PMID: 17905005 DOI: 10.1016/j.gie.2007.02.063]
38 **Seewald S**, Ang TL, Omar S, Groth S, Dy F, Zhong Y, Seitz U, Thonke F, Yekebas E, Izbicki J, Soehendra N. Endoscopic mucosal resection of early esophageal squamous cell cancer using the Duette mucosectomy kit. *Endoscopy* 2006; **38**: 1029-1031 [PMID: 17058169 DOI: 10.1055/s-2006-944527]
39 **Tsujitani S**, Oka S, Saito H, Kondo A, Ikeguchi M, Maeta M,

Kaibara N. Less invasive surgery for early gastric cancer based on the low probability of lymph node metastasis. *Surgery* 1999; **125**: 148-154 [PMID: 10026747 DOI: 10.1016/S0039-6060(99)70258-8]
40 **Reid BJ**, Blount PL, Feng Z, Levine DS. Optimizing endoscopic biopsy detection of early cancers in Barrett's high-grade dysplasia. *Am J Gastroenterol* 2000; **95**: 3089-3096 [PMID: 11095322 DOI: 10.1111/j.1572-0241.2000.03182.x]
41 **Prasad GA**, Buttar NS, Wongkeesong LM, Lewis JT, Sanderson SO, Lutzke LS, Borkenhagen LS, Wang KK. Significance of neoplastic involvement of margins obtained by endoscopic mucosal resection in Barrett's esophagus. *Am J Gastroenterol* 2007; **102**: 2380-2386 [PMID: 17640326 DOI: 10.1111/j.1572-0241.2007.01419.x]
42 **Buskens CJ**, Westerterp M, Lagarde SM, Bergman JJ, ten Kate FJ, van Lanschot JJ. Prediction of appropriateness of local endoscopic treatment for high-grade dysplasia and early adenocarcinoma by EUS and histopathologic features. *Gastrointest Endosc* 2004; **60**: 703-710 [PMID: 15557945 DOI: 10.1016/S0016-5107(04)02017-6]
43 **Peters FP**, Brakenhoff KP, Curvers WL, Rosmolen WD, Fockens P, ten Kate FJ, Krishnadath KK, Bergman JJ. Histologic evaluation of resection specimens obtained at 293 endoscopic resections in Barrett's esophagus. *Gastrointest Endosc* 2008; **67**: 604-609 [PMID: 18155214 DOI: 10.1016/j.gie.2007.08.039]
44 **Young PE**, Gentry AB, Acosta RD, Greenwald BD, Riddle M. Endoscopic ultrasound does not accurately stage early adenocarcinoma or high-grade dysplasia of the esophagus. *Clin Gastroenterol Hepatol* 2010; **8**: 1037-1041 [PMID: 20831900 DOI: 10.1016/j.cgh.2010.08.020]
45 **Pouw RE**, Heldoorn N, Alvarez Herrero L, ten Kate FJ, Visser M, Busch OR, van Berge Henegouwen MI, Krishnadath KK, Weusten BL, Fockens P, Bergman JJ. Do we still need EUS in the workup of patients with early esophageal neoplasia? A retrospective analysis of 131 cases. *Gastrointest Endosc* 2011; **73**: 662-668 [PMID: 21272876 DOI: 10.1016/j.gie.2010.10.046]
46 **Pech O**, Günter E, Dusemund F, Origer J, Lorenz D, Ell C. Accuracy of endoscopic ultrasound in preoperative staging of esophageal cancer: results from a referral center for early esophageal cancer. *Endoscopy* 2010; **42**: 456-461 [PMID: 20306385 DOI: 10.1055/s-0029-1244022]
47 **May A**, Günter E, Roth F, Gossner L, Stolte M, Vieth M, Ell C. Accuracy of staging in early oesophageal cancer using high resolution endoscopy and high resolution endosonography: a comparative, prospective, and blinded trial. *Gut* 2004; **53**: 634-640 [PMID: 15082579 DOI: 10.1136/gut.2003.029421]
48 **Wani SB**, Edmundowicz SA, Abrams JA, Gupta N, Green D, Hovis CE, Gaddam S, Higbee AD, Bansal A, Early DS, Rastogi A, Lightdale CJ, Prateek Sharma P. Accuracy of Endoscopic Ultrasonography (EUS) in Staging Early Neoplasia in Barrett's Esophagus (BE): Results From a Large Multicenter Cohort Study. *Gastrointest Endosc* 2011; **73** Suppl 4: AB166–AB167 [DOI: 10.1016/j.gie.2011.03.161]
49 **Chung A**, Bourke MJ, Hourigan LF, Lim G, Moss A, Williams SJ, McLeod D, Fanning S, Kariyawasam V, Byth K. Complete Barrett's excision by stepwise endoscopic resection in short-segment disease: long term outcomes and predictors of stricture. *Endoscopy* 2011; **43**: 1025-1032 [PMID: 22068701 DOI: 10.1055/s-0030-1257049]
50 **Wu J**, Pan YM, Wang TT, Gao DJ, Hu B. Endotherapy versus surgery for early neoplasia in Barrett's esophagus: a meta-analysis. *Gastrointest Endosc* 2014; **79**: 233-241.e2 [PMID: 24079410 DOI: 10.1016/j.gie.2013.08.005]
51 **Chadwick G**, Groene O, Markar SR, Hoare J, Cromwell D, Hanna GB. Systematic review comparing radiofrequency ablation and complete endoscopic resection in treating dysplastic Barrett's esophagus: a critical assessment of histologic outcomes and adverse events. *Gastrointest Endosc* 2014; **79**: 718-731.e3 [PMID: 24462170 DOI: 10.1016/j.gie.2013.11.030]
52 **Pech O**, Bollschweiler E, Manner H, Leers J, Ell C, Hölscher AH. Comparison between endoscopic and surgical resection of mucosal esophageal adenocarcinoma in Barrett's esophagus at two high-volume centers. *Ann Surg* 2011; **254**: 67-72 [PMID: 21532466 DOI: 10.1097/SLA.0b013e31821d4bf6]
53 **Yamada M**, Oda I, Nonaka S, Suzuki H, Yoshinaga S, Taniguchi H, Sekine S, Kushima R, Saito Y, Gotoda T. Long-term outcome of endoscopic resection of superficial adenocarcinoma of the esophagogastric junction. *Endoscopy* 2013; **45**: 992-996 [PMID: 24288219 DOI: 10.1055/s-0033-1344862]
54 **Pech O**, May A, Manner H, Behrens A, Pohl J, Weferling M, Hartmann U, Manner N, Huijsmans J, Gossner L, Rabenstein T, Vieth M, Stolte M, Ell C. Long-term efficacy and safety of endoscopic resection for patients with mucosal adenocarcinoma of the esophagus. *Gastroenterology* 2014; **146**: 652-660.e1 [PMID: 24269290 DOI: 10.1053/j.gastro.2013.11.006]
55 **Qumseya B**, Panossian AM, Rizk C, Cangemi D, Wolfsen C, Raimondo M, Woodward T, Wallace MB, Wolfsen H. Predictors of esophageal stricture formation post endoscopic mucosal resection. *Clin Endosc* 2014; **47**: 155-161 [PMID: 24765598 DOI: 10.5946/ce.2014.47.2.155]
56 **Tomizawa Y**, Iyer PG, Wong Kee Song LM, Buttar NS, Lutzke LS, Wang KK. Safety of endoscopic mucosal resection for Barrett's esophagus. *Am J Gastroenterol* 2013; **108**: 1440-1447; quiz 1448 [PMID: 23857478 DOI: 10.1038/ajg.2013.187]
57 **Konda VJ**, Gonzalez Haba Ruiz M, Koons A, Hart J, Xiao SY, Siddiqui UD, Ferguson MK, Posner M, Patti MG, Waxman I. Complete endoscopic mucosal resection is effective and durable treatment for Barrett's-associated neoplasia. *Clin Gastroenterol Hepatol* 2014; **12**: 2002-10.e1-2 [PMID: 24732285 DOI: 10.1016/j.cgh.2014.04.010]
58 **Masci E**, Viale E, Notaristefano C, Mangiavillano B, Fiori G, Crosta C, Dinelli M, Maino M, Viaggi P, Della Giustina F, Teruzzi V, Grasso G, Manes G, Zambelli S, Testoni PA. Endoscopic mucosal resection in high- and low-volume centers: a prospective multicentric study. *Surg Endosc* 2013; **27**: 3799-3805 [PMID: 23708711 DOI: 10.1007/s00464-013-2977-5]
59 **Peters FP**, Brakenhoff KP, Curvers WL, Rosmolen WD, ten Kate FJ, Krishnadath KK, Fockens P, Bergman JJ. Endoscopic cap resection for treatment of early Barrett's neoplasia is safe: a prospective analysis of acute and early complications in 216 procedures. *Dis Esophagus* 2007; **20**: 510-515 [PMID: 17958727 DOI: 10.1111/j.1442-2050.2007.00727.x]
60 **May A**, Gossner L, Behrens A, Kohnen R, Vieth M, Stolte M, Ell C. A prospective randomized trial of two different endoscopic resection techniques for early stage cancer of the esophagus. *Gastrointest Endosc* 2003; **58**: 167-175 [PMID: 12872081 DOI: 10.1067/mge.2003.339]
61 **Katada C**, Muto M, Manabe T, Boku N, Ohtsu A, Yoshida S. Esophageal stenosis after endoscopic mucosal resection of superficial esophageal lesions. *Gastrointest Endosc* 2003; **57**: 165-169 [PMID: 12556777 DOI: 10.1067/mge.2003.73]
62 **Ell C**, May A, Pech O, Gossner L, Guenter E, Behrens A, Nachbar L, Huijsmans J, Vieth M, Stolte M. Curative endoscopic resection of early esophageal adenocarcinomas (Barrett's cancer). *Gastrointest Endosc* 2007; **65**: 3-10 [PMID: 17185072 DOI: 10.1016/j.gie.2006.04.033]
63 **Brahmania M**, Lam E, Telford J, Enns R. Endoscopic mucosal resection: early experience in British Columbia. *Can J Gastroenterol* 2010; **24**: 239-244 [PMID: 20431812]
64 **Hirao M**, Masuda K, Asanuma T, Naka H, Noda K, Matsuura K, Yamaguchi O, Ueda N. Endoscopic resection of early gastric cancer and other tumors with local injection of hypertonic saline-epinephrine. *Gastrointest Endosc* 1988; **34**: 264-269 [PMID: 3391382 DOI: 10.1016/S0016-5107(88)71327-9]
65 **Kodashima S**, Fujishiro M, Yahagi N, Kakushima N, Omata M. Endoscopic submucosal dissection using flexknife. *J Clin Gastroenterol* 2006; **40**: 378-384 [PMID: 16721217 DOI: 10.1097/00004836-200605000-00004]
66 **Wang J**, Ge J, Zhang XH, Liu JY, Yang CM, Zhao SL. Endoscopic submucosal dissection versus endoscopic mucosal resection for the treatment of early esophageal carcinoma: a meta-analysis. *Asian Pac J Cancer Prev* 2014; **15**: 1803-1806 [PMID: 24641412 DOI: 10.7314/APJCP.2014.15.4.1803]
67 **Cao Y**, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of

endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009; **41**: 751-757 [PMID: 19693750 DOI: 10.1055/s-0029-1215053]

68 **Komeda Y**, Bruno M, Koch A. EMR is not inferior to ESD for early Barrett's and EGJ neoplasia: An extensive review on outcome, recurrence and complication rates. *Endoscopy International Open* 2014; **2**: E58-E64 [DOI: 10.1055/s-0034-1365528]

69 **Barreda B F**, Sánchez L J. Endoscopic treatment of early gastric cancer andprecancerous gastric lesions with mucosectomy. *Rev Gastroenterol Peru* 1998; **18**: 214-226 [PMID: 12209217]

70 **Tanabe S**, Koizumi W, Mitomi H, Nakai H, Murakami S, Nagaba S, Kida M, Oida M, Saigenji K. Clinical outcome of endoscopic aspiration mucosectomy for early stage gastric cancer. *Gastrointest Endosc* 2002; **56**: 708-713 [PMID: 12397280 DOI: 10.1016/S0016-5107(02)70121-1]

71 **Tada M**, Tanaka Y, Matsuo N, Shimamura T, Yamaguchi K. Mucosectomy for gastric cancer: current status in Japan. *J Gastroenterol Hepatol* 2000; **15** Suppl: D98-102 [PMID: 10759227 DOI: 10.1046/j.1440-1746.2000.02137.x]

72 **Park JC**, Lee SK, Seo JH, Kim YJ, Chung H, Shin SK, Lee YC. Predictive factors for local recurrence after endoscopic resection for early gastric cancer: long-term clinical outcome in a single-center experience. *Surg Endosc* 2010; **24**: 2842-2849 [PMID: 20428894 DOI: 10.1007/s00464-010-1060-8]

73 **Min BH**, Lee JH, Kim JJ, Shim SG, Chang DK, Kim YH, Rhee PL, Kim KM, Park CK, Rhee JC. Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: comparison with endoscopic mucosal resection after circumferential precutting (EMR-P). *Dig Liver Dis* 2009; **41**: 201-209 [PMID: 18571998 DOI: 10.1016/j.dld.2008.05.006]

74 **Ono H**, Hasuike N, Inui T, Takizawa K, Ikehara H, Yamaguchi Y, Otake Y, Matsubayashi H. Usefulness of a novel electrosurgical knife, the insulation-tipped diathermic knife-2, for endoscopic submucosal dissection of early gastric cancer. *Gastric Cancer* 2008; **11**: 47-52 [PMID: 18373177 DOI: 10.1007/s10120-008-0452-0]

75 **Ohyama T**, Kobayashi Y, Mori K, Kano K, Sakurai Y, Sato Y. Factors affecting complete resection of gastric tumors by the endoscopic mucosal resection procedure. *J Gastroenterol Hepatol* 2002; **17**: 844-848 [PMID: 12164959 DOI: 10.1046/j.1440-1746.2002.02814.x]

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Advances in the endoscopic management of pancreatic collections

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Abstract

Treatment of pancreatic collections has experienced great progress in recent years with the emergence of alternative minimally invasive techniques comparing to the classic surgical treatment. Such techniques have been shown to improve outcomes of morbidity *vs* surgical treatment. The recent emergence of endoscopic drainage is noteworthy. The advent of endoscopic ultrasonography has been crucial for treatment of these specific lesions. They can be characterized, their relationships with neighboring structures can be evaluated and the drainage guided by this technique has been clearly improved compared with the conventional endoscopic drainage. Computed tomography is the technique of choice to characterize the recently published new classification of pancreatic collections. For this reason, the radiologist's role establishing and classifying in a rigorously manner the collections according to the new nomenclature is essential to making therapeutic decisions. Ideal scenario for comprehensive treatment of these collections would be those centers with endoscopic ultrasound and interventional radiology expertise together with hepatobiliopancreatic surgery. This review describes the different types of pancreatic collections: acute peripancreatic fluid collection, pancreatic pseudocysts, acute necrotic collection and walled-off necrosis; the indications and the contraindications for endoscopic drainage, the drainage technique and their outcomes. The integrated management of pancreatic collections according to their type and evolution time is discussed.

Key words: Pancreatic collection; Endosonography; Drainage; Pancreatic duct; Endoscopic retrograde cholangiopancreatografic

Core tip: The interventional endoscopic ultrasonography (EUS) development has become in recent years as the first therapeutic alternative for the management of pancreatic collections. The great advantage of EUS is the possibility to in see in real-time image with ultrasound guidance all the material previously introduced into the working channel. The new classification of Atlanta 2012 defines two different evolved pancreatic collections (⩾ 4 wk) such as pseudocysts and necrotic encapsulated collections. If both types of collections are symptomatic, they would be subsidiaries of treatment. Given their morphological differences, the technique is similar but the stents used and the results generated differ.

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INTRODUCTION

Acute pancreatitis (AP) is a potentially life-threatening disease with a wide spectrum of severity, representing an acute inflammation of the pancreas that may be triggered by a variety of etiologies. After the initial etiologic insult, the activation of pancreatic enzymes occurs in the gland itself, triggering a process of the pancreas self-digestion accompanied by inflammation. This phenomenon leads a repairing and healing process or, less commonly, a systemic inflammatory response that can cause disease in other systems (circulatory, respiratory or renal) promoting the development of organ failure and even death of patient[1]. AP prevalence is increasing, leading to a significant consumption of medical resources[2].

In Atlanta symposium in 1992 a global consensus and a classification system universally applicable for AP was discussed[3]. However, some of these definitions have proved somewhat confusing, and the better understanding of the pathophysiology of organ failure and the development of pancreatic necrosis and the better progress in diagnostics imaging methods have forced a revision of the original classification of Atlanta[4].

An important and illuminating compilation of the terminology of local complications of AP has been established. Four types of collections based on content and time evolution have been defined. These collections are called acute peripancreatic fluid collection, pancreatic pseudocyst, acute necrotic collection and encapsulated necrosis or walled-off necrosis. This new classification represents a breakthrough and facilitates therapeutic decisions in these patients.

The aim of this review is to perform an update of endoscopic management of each of these collections, evaluating the endoscopic treatment role in their comprehensive management.

CLASSIFICATION OF ATLANTA 2012

According to the new classification of Atlanta 2012, pancreatic collections can be classified depending to their content, purely liquid or with associate necrosis, and its evolution time, greater or less than 4 wk. Therefore, four types of pancreatic collections can be found.

Acute peripancreatic fluid collection (Figure 1A): is developed in the first phase of AP and characterized by flowing purely liquid homogeneous collections on CT, with no wall defined. It is confined to normal retroperitoneal fascial planes and can be multiple. Most of these collections resolve spontaneously in the first weeks after the AP. In addition to its spontaneous resolution usually it remain sterile[5].

Pancreatic pseudocysts (Figure 1C): it develops when acute pancreatic fluid collection persists more than 4 wk. A well-defined wall is usually generated and they rename pancreatic pseudocyst, presenting high liquid content in amylase and other pancreatic enzymes. The pancreatic pseudocyst is considered to be formed by obstruction or disruption of the main duct or secondary branches, which facilitates its chronicity. The development of pancreatic pseudocyst in the setting of AP on healthy pancreas is rare, most frequently it develops within chronic pancreatitis. In a recent prospective observational study that included 302 patients with AP, acute peripancreatic fluid collection was developed in 129 (42.7%). Among them, pancreatic pseudocyst was developed only in 19 (14.7%). In 90 patients (69.8%) there was spontaneous resolution of acute peripancreatic fluid collection and the other 20 patients (15.5%) failed to complete the follow-up. Regarding to the 19 patients with pancreatic pseudocyst, spontaneous resolution occurred during follow-up in 5 patients (26.3%), a decrease in size in 11 (57.9%) and finally in another patient the monitoring could not be completed. Two patients developed infection with pancreatic pseudocyst requiring percutaneous treatment in one case, and endoscopic drainage on the other[6]. Thus, the percentage of pseudocysts requiring treatment is small.

Acute necrotic collection (ANC) (Figure 1B): it is developed during the first 4 wk of AP evolution and it can contain varying amounts of fluid and necrotic tissue. It may be difficult to distinguish from acute peripancreatic fluid collection during the first week of evolution, but then the distinction between the two is clearer. Like pancreatic pseudocyst, acute necrotic collection may be associated with disruption or obstruction of the pancreatic duct.

Walled-off necrosis (WON) (Figure 1D): consisting of a variable number of necrotic tissue encapsulated within a reactive tissue wall, derived from acute necrotic collection encapsulation past 4 wk. A well-defined wall around the collection can be observed in the imaging, whose complete formation typically occurs within 4 wk of AP origin. The percentage of spontaneous resolution of acute necrotic collections and encapsulated necrosis is unknown, so the knowledge of the natural history of all pancreatic collections is not complete[7].

The presence of necrosis in a pancreatic collection is considered an important prognostic marker, the mortality in patients with necrotizing pancreatitis can reach 15% and even 30% in patients with infected necrosis. This infection typically occurs from the second week after the onset of pancreatitis, but can occur at any time during the clinical course[8]. Through

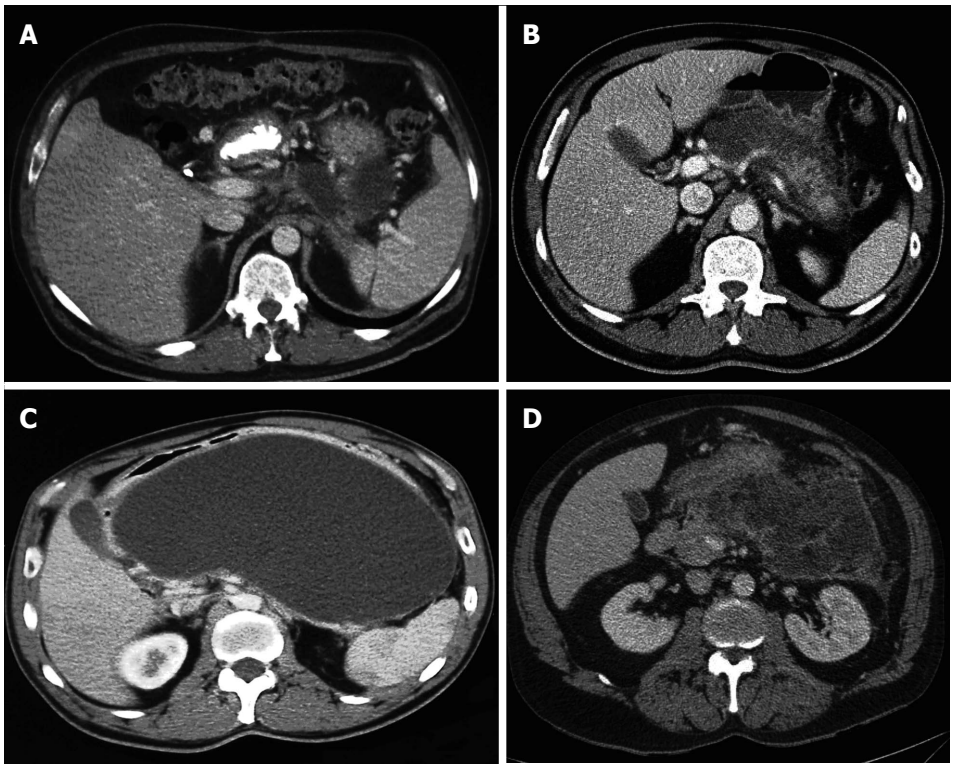

Figure 1 Acute peripancreatic fluid collection (A), acute necrotic collection (B), pancreatic pseudocyst (C), and walled-of necrosis (D).

Gram staining or culture from material aspirated by percutaneous or endoscopic puncture, the infection can be tested, but also the presence of gas within the acute necrotic collection or encapsulated necrosis by computed tomography can be a good infection diagnostic indicator.

INDICATIONS AND CONTRAINDICATIONS FOR ENDOSCOPIC DRAINAGE OF PANCREATIC COLLECTIONS

Pancreatic pseudocysts and WON are considered the most often treated collections, having the characteristics and evolution time required for such treatment.

The transmural approach is the most commonly used. Conducting a transpapillary or combined approach will depend on the collection size, its relationship with the pancreatic duct, its location, and underlying disease.

Usually, pigtail stents are used for pseudocysts drainage while for WON covered self-expandable metallic stents are more commonly employed, associated to an inner coaxial pig-tail stent. Futhermore, the use of flushing nasocystic catheter in WON has been reported in several studies with good results[9,10].

To perform an endoscopic treatment of pancreatic collections is accepted in those cases of symptomatic collections, complicated collections with infections and those producing obstructive symptoms in neighboring viscera, such as stomach, duodenum or bile duct obstruction. It is also accepted the prophylactic treatment in collections which produce vascular compression[11].

Endoscopic drainage is contraindicated in unencapsulated collections, those away from gastroduodenal tract (> 1 cm) and collections with vascular pseudoaneurysm, which should be treated by interventional radiology prior to endoscopic drainage. The presence of neovascularization by portal hypertension is considered a relative contraindication[12].

RESULT OF ENDOSCOPIC DRAINAGE OF PANCREATIC COLLECTIONS

The therapeutic success of endoscopic drainage of pancreatic collections differ in the case of a pseudocyst or an encapsulated necrotic collection.

Conventional endoscopy has been deprecated for drainage of pancreatic collections, being overtaken by the therapeutic endoscopic ultrasonography (EUS) being reflected in numerous studies[13]. The use of EUS allows a better study of collections and may change management in 5%-9% of cases, either by making an alternative diagnosis or by checking the resolution of pancreatic pseudocyst (Figure 2)[14]. Endoscopic drainage of pancreatic pseudocysts is simpler and more resolutive than WON drainage[15].

In a recent study involving 117 patients with pancreatic pseudocyst drained endoscopically, pancreatic pseudocyst resolution was achieved in 98.3% of

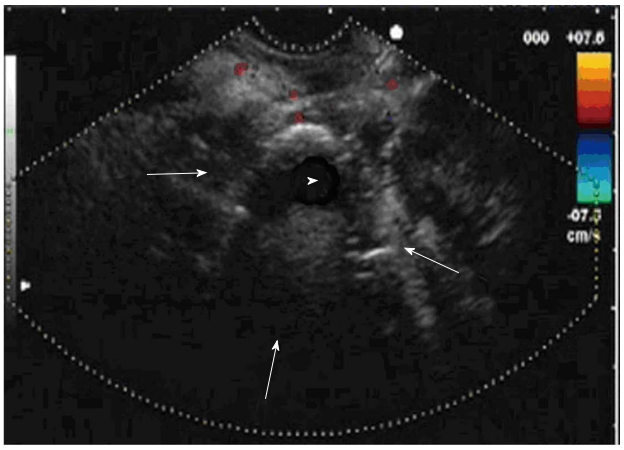

Figure 2 Endoscopic ultrasonography image of walled-off necrosis collection. The limits of the walled-off necrosis are signalled by the arrows. The necrotic content is marked with arrowhead.

cases. In 87.2% of patients the pancreatic pseudocyst was resolved with only an endoscopic procedure, with no significant differences in treatment success depending on the size (7 or 10 F) or number of stents placed (Figure 3A, B and C)[16].

The recurrence of pancreatic pseudocyst after endoscopic drainage is less than 1%, with series with 0% recurrence at two years when ductal pathology associated is treated by transpapillary stent and transmural stents are maintained indefinitely if there is a ductal disconnection syndrome[17].

By contrast, the result of endoscopic drainage of WON is less effective, demonstrating in different series treatment success rates significantly lower[18]. Therapeutic success described in a multicenter Japanese study (JENIPaN) including 57 patients with WON treated with endoscopic necrosectomy was 75% with a median of 5 endoscopic sessions per patient[19]. In 14 patients in whom endoscopic treatment was ineffective, 8 received other percutaneous or surgical treatment, while 6 patients died during the treatment period without achieving WON resolution. In another similar study from Germany involving 93 patients the WON resolution was achieved in 80% of patients[20]. The median of endoscopic sessions to successfully complete the endoscopic treatment in these patients is between 3 and 6 in the different studies.

In a recently published meta-analysis study that included the results of 12 studies with 481 patients presenting infected necrosis treated only with conservative measures, including percutaneous or endoscopic drainage, treatment success was achieved without any necrosectomy in 59% of patients[21].

Currently, it is very difficult to predict which are the WON collections that can be efficiently and safely managed without necrosectomy. In cases of large and anfractuous collections with a large amount of necrosis, necrosectomy is usually required, either by means of retroperitoneal or endoscopic access. Necrosectomy is usually performed when the initial endoscopic drainage has not been effective. Several studies have shown that the therapeutic success of endoscopic treatment depends largely on the amount of necrosis[22,23].

In this regard, a new lumen-apposing metallic stent (AXIOS®, Xlumena, Mountain View, Ca) has been designed recently for draining pancreatic collections proving good effectiveness in different studies. These stents are completely covered and offer a maximum size of 15 mm so endoscopic necrosectomy is allowed in repeated sessions without the need for replacement of the stents[24].

Assessment of pancreatic ductal pathology in all patients with pancreatic pseudocyst or WON is vital, as if the transmural resolution of the collection is not accompanied by a correct diagnosis and treatment of the underlying ductal pathology, the risk of recurrence is high[25]. In this sense, ductal disruption or stenosis should be ruled out. Currently, the least invasive technique for assessing the integrity of the pancreatic duct is secretin enhanced pancreatic MRI. Ductal evaluation by means of ERCP is another recommended option prior to removing the transmural stents. Varadarajulu *et al*[17] described the presence of ductal disruption in 10 patients and ductal disconnection syndrome in 4 from 18 patients with pancreatic pseudocyst treated endoscopically[17].

Furthermore ERCP is an endoscopic technique which provides the possibility of transpapillary drainage by placing duct stents in addition to a transmural drainage or as monotherapy, mainly in pseudocysts located in the head or body of the pancreas. This approach is considered less traumatic than the transmural. It is accepted that in patients with underlying chronic pancreatitis with pancreatic pseudocyst under 6 cm communicated with the pancreatic duct, a transpapillary drain as monotherapy can be performed[26].

COMPLICATIONS OF ENDOSCOPIC DRAINAGE OF PANCREATIC COLLECTIONS

Endoscopic drainage of pancreatic collections is not free of complications. The most frequent are bleeding, perforation, post-procedure infection and migration of the stents.

A prospective study aimed to determine the frequency of these complications included 148 patients with pancreatic collections of mean diameter 92.3 mm drained by EUS[27]. These collections were classified as pancreatic pseudocyst in 72 (48.6%), abscess in 38 (25.7%) and necrosis in 38 patients (25.7%). There was a transgastric fistula perforation in two patients (1.3%) with pancreatic pseudocyst located at the level of the uncinate process. These perforations were not suspected during the procedure, which in both cases was uneventful. In pseudocysts localised at uncinate process level drained transduodenally no perforation occurred. The authors attributed this drilling to a lack

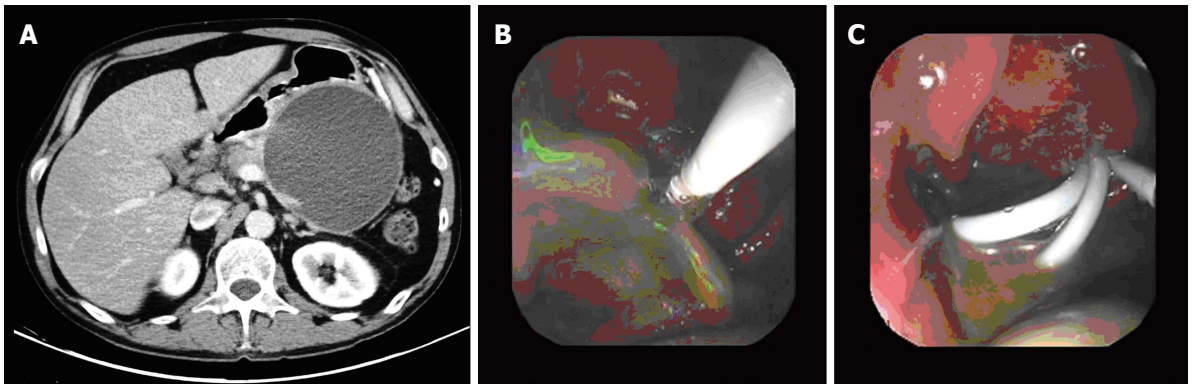

Figure 3 Pancreatic pseudocyst (A), endoscopic dilation of transmural tract (B), and three double-pigtail plastic stents placed (C).

of adhesion of pancreatic pseudocyst to the stomach wall despite being at a distance less than 1 cm. It is postulated that after decompression of pancreatic pseudocysts by the stents, it is separated from the stomach due to be originated in uncinate process and stents were housed in the retroperitoneum. Therefore it is recommended to avoid transgastric drainage of pancreatic pseudocyst localized at uncinate process. Other authors have reported perforations related with the use of electrocautery during drainage procedure[28]. For this reason it is recommended to avoid the use of electrocautery during the creation and expansion of the fistula, making a gradual mechanical dilation. The vast majority of these perforations can be managed by conservative measures with antibiotic treatment and nasogastric suction. The need for surgery in these cases is exceptional[29].

The rate of bleeding after endoscopic drainage has decreased dramatically with EUS. In a prospective randomized study comparing drainage of pancreatic pseudocyst by EUS and conventional endoscopy, severe bleeding occurred in two patients (13.3%) drained by conventional endoscopy. One of them died and no cases of bleeding were observed in the group of patients drained with EUS[30]. The intracystic hemorrhage is inaccessible to endoscopic treatment methods, most of them stop spontaneously or by intracystic washing with serum and diluted epinephrine, sometimes requiring treatment by interventional radiology or surgery. The haemorrhage in the fistula tract is more easily treated by endoscopic methods such as sclerosis or hemoclips placement.

Stent migration is another complication associated with endoscopic drainage of pancreatic collections. Its incidence ranges from less than 1% and 2%[27]. External migration requires only a repetition in the procedure. By contrast, internal migration of stent represents a serious complication and a therapeutic challenge. It is advisable to remove it as early as possible to avoid the fistula closure previously created (Figure 4).

Another complication of endoscopic drainage of pancreatic collections is the infection after endoscopic manipulation, so it is very important the proper drainage. In the series published by Varadarajulu *et al*[27], infection occurred in 4 patients (2.7%) which was resolved by new endoscopic drainage in two patients and by surgery in the other two[27].

Finally, another potentially fatal complication related to endoscopic necrosectomy is air embolism. It has been described in different multicenter series. In the GEPARD study from Germany that included 93 patients, endoscopic necrosectomy was performed and air embolism occurred in two patients[20]. In JENIPaN study from Japan, there was also an air embolism in a series of 57 patients with endoscopic necrosectomy[19]. Although its usefulness has not been proven, it is now recommended the CO_2 distension during necrosectomy to avoid this complication.

Overall, the complication rate is significantly lower with endoscopic drainage of pancreatic pseudocyst drainage compared with WON drainage[31].

In a recent study, Varadarajulu *et al*[17] compared the results of endoscopic drainage of pancreatic pseudocysts by endoscopic *vs* surgical cystogastrostomy with 20 patients in each group observing no complications related to endoscopic treatment[17]. Moreover, in the series of patients undergoing endoscopic necrosectomy previously mentioned, the complication rate was much higher. Thus, in the GEPARD study complications occurred in 26% of patients, with a mortality rate of 7.5% and in the JENIPaN study the complication rate was 33% with an overall mortality of 11%[19,20].

The transpapillary drainage has a complication rate of 16%, especially post-ERCP pancreatitis and infectious complications[32].

INTEGRATED AND MULTIDISCIPLINARY MANAGEMENT OF PANCREATIC COLLECTIONS AND IMPORTANCE OF THEIR CHARACTERIZATION

Endoscopic treatment of pancreatic collections is an alternative therapy that offers a high success rate with a reasonably low morbidity and mortality compared with other available options. For this reason it is

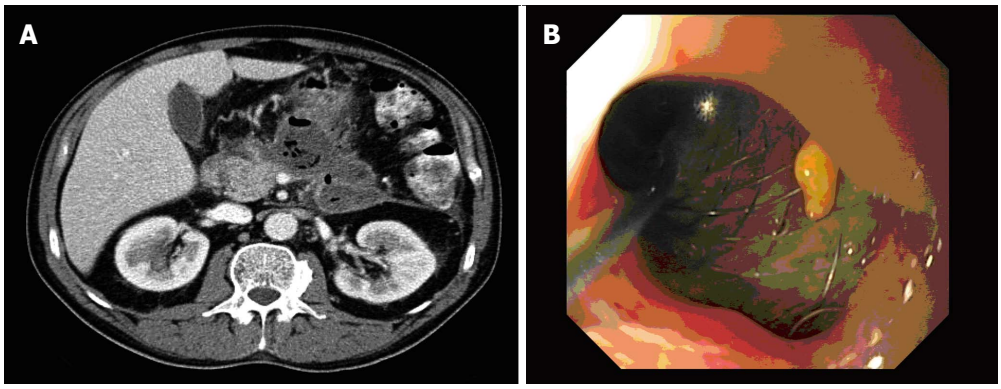

Figure 4 Walled-of necrosis with air content suspicious of fistulization or infection (A) and internal migration of stent (B).

becoming the first-line treatment in many centers. This may vary depending on the experience and resources available so the optimal management of these patients will be in those centers with interventional endoscopist but also interventional radiologist and surgeons specifically devoted to pancreatic surgery. However, endoscopic treatment is not the only therapeutic option in this scenario and is not always the best approach, which will depend on the type of collection and the chronology[33]. Several factors will influence the choice of the initial approach for treatment of pancreatic collections, such as duration of the collection, anatomical factors, previous surgeries, clinical status and integrity of the pancreatic duct.

In the pancreatic pseudocyst treatment, the endoscopic drainage is clearly superior to other therapeutic options, and currently is the therapeutic method of choice[18].

In a recent randomized study, Varadarajulu *et al*[17] compared the endoscopic drainage of pancreatic pseudocysts *vs* surgical drainage and they did not find significant differences regarding treatment success (95% *vs* 100%), complications (0% *vs* 10%), reoperation rate (5% *vs* 5%) or pancreatic pseudocyst recurrence (0% *vs* 5%). However, the median hospital stay (2 *vs* 6) and hospital costs were significantly lower in the endoscopic treatment group[17].

Endoscopic drainage offers advantages over percutaneous or surgical alternatives because it does not require an open incision or placement of an external drainage catheter thereby preventing the onset of complications such as incisional hernia, or fistulae, which can occur in up to 27% of cases[33].

The initial approach of choice in WON collections is less clear because the results are significantly worse with any of the methods used, and sometimes a combination of different techniques is necessary. Traditionally, open surgical necrosectomy has been the treatment of choice in patients with symptomatic or infected pancreatic necrosis. In the past decade minimally invasive therapeutic alternatives have been developed in an attempt to improve the high morbidity (34%-95%) and mortality (11%-39%) of traditional surgical treatment[34].

Currently, it is used the endoscopic transmural approach, percutaneous or a combination of both. It has been also developed less invasive surgical techniques such as video-assisted necrosectomy transretroperitoneal and laparoscopic necrosectomy.

Until recently, there were not enough evidences to confirm that the results obtained with minimally invasive techniques were superior to classical surgery. In 2010, a Dutch multicenter randomized prospective study is published comparing the results obtained by open surgical necrosectomy *vs* a minimally invasive approach. This approach consisted on percutaneous or endoscopic drainage followed by a second similar drain if there was no improvement produced after 72 h or on video-assisted necrosectomy transretroperitoneal alternatively[35].

In this study, 45 patients with infected pancreatic necrosis were included in the surgical group and 43 in the minimally invasive approach group. Percutaneous drainage was initially performed in 40 patients and endoscopic drainage in one patient. 35% of patients in the minimally invasive approach did not require any necrosectomy. The group of surgical necrosectomy presented a percentage significantly higher of severe complications (69% *vs* 40%, $P = 0.006$), there was no difference in mortality rate (16% *vs* 19%, $P = 0.7$) and at six months of follow up the patients who undergone surgical necrosectomy had a higher incidence of incisional hernias (24% *vs* 7%, $P = 0.03$), diabetes mellitus of recent onset (38% *vs* 16%, $P = 0.02$) and need for pancreatic enzyme replacement therapy (33% *vs* 7%, $P = 0.002$). These results were later confirmed in a meta-analysis including 215 patients with infected necrosis treated with minimally invasive approach and 121 treated with surgical necrosectomy[36].

Two years later the Dutch group published a second study that randomly compared the results of minimal invasive surgical necrosectomy (video assisted transretroperitoneal necrosectomy or laparoscopic necrosectomy) *vs* endoscopic transgastric necrosectomy including 10 patients with infected necrosis in each group[37]. The proinflammatory response determined

by IL-6 was significantly lower after endoscopic necrosectomy compared with surgical necrosectomy (P = 0.004). This aspect is relevant because of organ failure in these patients is due to persistent proinflammatory response[38]. In fact, the incidence multiple organ failure after endoscopic treatment was significantly lower (0% *vs* 50%, P = 0.03) while the incidence of pancreatic fistula (10% *vs* 70%, P = 0.02) and the need of pancreatic enzymes (0% *vs* 50%, P = 0.04) were significantly higher after surgical treatment. Median necrosectomy procedures required were significantly higher in the laparoscopic group (3 *vs* 1, P = 0.007).

One of the most determining factors in deciding the initial approach is the time evolution time of the pancreatic collection. Here, reclassification of Atlanta has a crucial importance for the endoscopic treatment, since only endoscopic treatment is recommended in those patients with pancreatic pseudocyst or encapsulated necrosis, *i.e.*, in patients with pancreatic collections of more than 4 wk given the risk of complication, inherent in such treatment in earlier stages[4]. However, it is postulated that patients with pancreatic collections presenting clinical deterioration may undergo endoscopic drainage with relative safety from the third week. Probably management of those patients with progressive clinical deterioration requiring invasive treatment before the third week, should begin by percutaneous retroperitoneal drainage with possibility of subsequently adding video-assisted transretroperitoneal necrosectomy or transgastric endoscopic necrosectomy if there is no clinical improvement. Importantly, maximum delay in necrosectomy (> 4 wk) in patients with infected pancreatic necrosis improves treatment outcomes, if necessary, always using less invasive techniques[39]. This concept was demonstrated in a prospective randomized study comparing early surgical necrosectomy (within the first 48-72 h of admission) *vs* late necrosectomy with conservative management (past 12 d after admission). It was verified that the mortality in the early surgery group reached 56% compared to 27% of the group managed more conservatively with delayed surgery (OR = 3.4). Most of these deaths were due to multiple organ failure and cardiogenic shock[38].

In conclusion, in recent years there have been significant advances in the endoscopic management of pancreatic collections. On the one hand, there are clearer recommendations concerning the most appropriate time to propose an endoscopic treatment of a pancreatic pseudocyst or WON collection. The new classification of Atlanta indicates that endoscopic treatment should wait at least for three or four weeks if imaging tests show maturity of the walls of pancreatic collection. Endoscopic drainage is currently considered as the first treatment of choice for treatment of pancreatic pseudocyst. Furthermore it has been shown that the minimally invasive treatment of the WON offers significant advantages over surgical necrosectomy. In coming years new studies to clarify whether the initial endoscopic approach is better than percutaneous for management of WON and which is the best combination of treatments available for drainage as an alternative rescue.

REFERENCES

1 **Working Group IAP/APA Acute Pancreatitis Guidelines.** IAP/APA evidence-based guidelines for the management of acute pancreatitis. *Pancreatology* 2013; **13**: e1-15 [PMID: 24054878 DOI: 10.1016/j.pan.2013.07.063]

2 **Peery AF**, Dellon ES, Lund J, Crockett SD, McGowan CE, Bulsiewicz WJ, Gangarosa LM, Thiny MT, Stizenberg K, Morgan DR, Ringel Y, Kim HP, Dibonaventura MD, Carroll CF, Allen JK, Cook SF, Sandler RS, Kappelman MD, Shaheen NJ. Burden of gastrointestinal disease in the United States: 2012 update. *Gastroenterology* 2012; **143**: 1179-1187.e1-3 [PMID: 22885331 DOI: 10.1053/j.gastro.2012.08.002]

3 **Bradley EL**. A clinically based classification system for acute pancreatitis. Summary of the International Symposium on Acute Pancreatitis, Atlanta, Ga, September 11 through 13, 1992. *Arch Surg* 1993; **128**: 586-590 [PMID: 8489394]

4 **Banks PA**, Bollen TL, Dervenis C, Gooszen HG, Johnson CD, Sarr MG, Tsiotos GG, Vege SS. Classification of acute pancreatitis--2012: revision of the Atlanta classification and definitions by international consensus. *Gut* 2013; **62**: 102-111 [PMID: 23100216 DOI: 10.1136/gutjnl-2012-302779]

5 **Lenhart DK**, Balthazar EJ. MDCT of acute mild (nonnecrotizing) pancreatitis: abdominal complications and fate of fluid collections. *AJR Am J Roentgenol* 2008; **190**: 643-649 [PMID: 18287434 DOI: 10.2214/AJR.07.2761]

6 **Cui ML**, Kim KH, Kim HG, Han J, Kim H, Cho KB, Jung MK, Cho CM, Kim TN. Incidence, risk factors and clinical course of pancreatic fluid collections in acute pancreatitis. *Dig Dis Sci* 2014; **59**: 1055-1062 [PMID: 24326631 DOI: 10.1007/s10620-013-2967-4]

7 **Bradley EL**. The natural and unnatural history of pancreatic fluid collections associated with acute pancreatitis. *Dig Dis Sci* 2014; **59**: 908-910 [PMID: 24429512 DOI: 10.1007/s10620-013-3012-3]

8 **Freeman ML**, Werner J, van Santvoort HC, Baron TH, Besselink MG, Windsor JA, Horvath KD, vanSonnenberg E, Bollen TL, Vege SS. Interventions for necrotizing pancreatitis: summary of a multidisciplinary consensus conference. *Pancreas* 2012; **41**: 1176-1194 [PMID: 23086243 DOI: 10.1097/MPA.0b013e318269c660]

9 **Puri R**, Mishra SR, Thandassery RB, Sud R, Eloubeidi MA. Outcome and complications of endoscopic ultrasound guided pancreatic pseudocyst drainage using combined endoprosthesis and naso-cystic drain. *J Gastroenterol Hepatol* 2012; **27**: 722-727 [PMID: 22313377 DOI: 10.1111/j.1440-1746.2012.07089.x]

10 **Siddiqui AA**, Dewitt JM, Strongin A, Singh H, Jordan S, Loren DE, Kowalski T, Eloubeidi MA. Outcomes of EUS-guided drainage of debris-containing pancreatic pseudocysts by using combined endoprosthesis and a nasocystic drain. *Gastrointest Endosc* 2013; **78**: 589-595 [PMID: 23660566 DOI: 10.1016/j.gie.2013.03.1337]

11 **Trikudanathan G**, Arain M, Attam R, Freeman ML. Interventions for necrotizing pancreatitis: an overview of current approaches. *Expert Rev Gastroenterol Hepatol* 2013; **7**: 463-475 [PMID: 23899285 DOI: 10.1586/17474124.2013.811055]

12 **de-Madaria E**, Abad-González A, Aparicio JR, Aparisi L, Boadas J, Boix E, de-Las-Heras G, Domínguez-Muñoz E, Farré A, Fernández-Cruz L, Gómez L, Iglesias-García J, García-Malpartida K, Guarner L, Lariño-Noia J, Lluís F, López A, Molero X, Moreno-Pérez O, Navarro S, Palazón JM, Pérez-Mateo M, Sabater L, Sastre Y, Vaquero EC, Martínez J. The Spanish Pancreatic Club' s recommendations for the diagnosis and treatment of chronic pancreatitis: part 2 (treatment). *Pancreatology* 2013; **13**: 18-28 [PMID: 23395565 DOI: 10.1016/j.pan.2012.11.310]

13 **Varadarajulu S**, Christein JD, Tamhane A, Drelichman ER, Wilcox CM. Prospective randomized trial comparing EUS and EGD for transmural drainage of pancreatic pseudocysts (with videos). *Gastrointest Endosc* 2008; **68**: 1102-1111 [PMID: 18640677 DOI: 10.1016/j.gie.2008.04.028]

14 **Fockens P**, Johnson TG, van Dullemen HM, Huibregtse K, Tytgat GN. Endosonographic imaging of pancreatic pseudocysts before endoscopic transmural drainage. *Gastrointest Endosc* 1997; **46**: 412-416 [PMID: 9402114]

15 **Chauhan SS**, Forsmark CE. Evidence-based treatment of pancreatic pseudocysts. *Gastroenterology* 2013; **145**: 511-513 [PMID: 23900106 DOI: 10.1053/j.gastro.2013.07.016]

16 **Bang JY**, Wilcox CM, Trevino JM, Ramesh J, Hasan M, Hawes RH, Varadarajulu S. Relationship between stent characteristics and treatment outcomes in endoscopic transmural drainage of uncomplicated pancreatic pseudocysts. *Surg Endosc* 2014; **28**: 2877-2883 [PMID: 24789132]

17 **Varadarajulu S**, Bang JY, Sutton BS, Trevino JM, Christein JD, Wilcox CM. Equal efficacy of endoscopic and surgical cystogastrostomy for pancreatic pseudocyst drainage in a randomized trial. *Gastroenterology* 2013; **145**: 583-590.e1 [PMID: 23732774 DOI: 10.1053/j.gastro.2013.05.046]

18 **Varadarajulu S**, Wilcox CM, Latif S, Phadnis M, Christein JD. Management of pancreatic fluid collections: a changing of the guard from surgery to endoscopy. *Am Surg* 2011; **77**: 1650-1655 [PMID: 22273224]

19 **Yasuda I**, Nakashima M, Iwai T, Isayama H, Itoi T, Hisai H, Inoue H, Kato H, Kanno A, Kubota K, Irisawa A, Igarashi H, Okabe Y, Kitano M, Kawakami H, Hayashi T, Mukai T, Sata N, Kida M, Shimosegawa T. Japanese multicenter experience of endoscopic necrosectomy for infected walled-off pancreatic necrosis: The JENIPaN study. *Endoscopy* 2013; **45**: 627-634 [PMID: 23807806 DOI: 10.1055/s-0033-1344027,]

20 **Seifert H**, Biermer M, Schmitt W, Jürgensen C, Will U, Gerlach R, Kreitmair C, Meining A, Wehrmann T, Rösch T. Transluminal endoscopic necrosectomy after acute pancreatitis: a multicentre study with long-term follow-up (the GEPARD Study). *Gut* 2009; **58**: 1260-1266 [PMID: 19282306 DOI: 10.1136/gut.2008.163733]

21 **Mouli VP**, Sreenivas V, Garg PK. Efficacy of conservative treatment, without necrosectomy, for infected pancreatic necrosis: a systematic review and meta-analysis. *Gastroenterology* 2013; **144**: 333-340.e2 [PMID: 23063972 DOI: 10.1053/j.gastro.2012.10.004]

22 **Rische S**, Riecken B, Degenkolb J, Kayser T, Caca K. Transmural endoscopic necrosectomy of infected pancreatic necroses and drainage of infected pseudocysts: a tailored approach. *Scand J Gastroenterol* 2013; **48**: 231-240 [PMID: 23268585 DOI: 10.3109/00365521.2012.752029]

23 **Heiss P**, Bruennler T, Salzberger B, Lang S, Langgartner J, Feuerbach S, Schoelmerich J, Hamer OW. Severe acute pancreatitis requiring drainage therapy: findings on computed tomography as predictor of patient outcome. *Pancreatology* 2010; **10**: 726-733 [PMID: 21242714 DOI: 10.1159/000320710]

24 **Gornals JB**, De la Serna-Higuera C, Sánchez-Yague A, Loras C, Sánchez-Cantos AM, Pérez-Miranda M. Endosonography-guided drainage of pancreatic fluid collections with a novel lumen-apposing stent. *Surg Endosc* 2013; **27**: 1428-1434 [PMID: 23232994 DOI: 10.1007/s00464-012-2591-y]

25 **Singhal S**, Rotman SR, Gaidhane M, Kahaleh M. Pancreatic fluid collection drainage by endoscopic ultrasound: an update. *Clin Endosc* 2013; **46**: 506-514 [PMID: 24143313 DOI: 10.5946/ce.2013.46.5.506]

26 **Tandan M**, Nageshwar Reddy D. Endotherapy in chronic pancreatitis. *World J Gastroenterol* 2013; **19**: 6156-6164 [PMID: 24115811 DOI: 10.3748/wjg.v19.i37.6156]

27 **Varadarajulu S**, Christein JD, Wilcox CM. Frequency of complications during EUS-guided drainage of pancreatic fluid collections in 148 consecutive patients. *J Gastroenterol Hepatol* 2011; **26**: 1504-1508 [PMID: 21575060 DOI: 10.1111/j.1440-1746.2011.06771.x]

28 **Giovannini M**, Pesenti C, Rolland AL, Moutardier V, Delpero JR. Endoscopic ultrasound-guided drainage of pancreatic pseudocysts or pancreatic abscesses using a therapeutic echo endoscope. *Endoscopy* 2001; **33**: 473-477 [PMID: 11437038]

29 **Will U**, Wegener C, Graf KI, Wanzar I, Manger T, Meyer F. Differential treatment and early outcome in the interventional endoscopic management of pancreatic pseudocysts in 27 patients. *World J Gastroenterol* 2006; **12**: 4175-4178 [PMID: 16830368]

30 **Varadarajulu S**, Eloubeidi MA. Frequency and significance of acute intracystic hemorrhage during EUS-FNA of cystic lesions of the pancreas. *Gastrointest Endosc* 2004; **60**: 631-635 [PMID: 15472697]

31 **Varadarajulu S**, Wilcox CM, Tamhane A, Eloubeidi MA, Blakely J, Canon CL. Role of EUS in drainage of peripancreatic fluid collections not amenable for endoscopic transmural drainage. *Gastrointest Endosc* 2007; **66**: 1107-1119 [PMID: 17892874]

32 **Lin H**, Zhan XB, Jin ZD, Zou DW, Li ZS. Prognostic factors for successful endoscopic transpapillary drainage of pancreatic pseudocysts. *Dig Dis Sci* 2014; **59**: 459-464 [PMID: 24185684 DOI: 10.1007/s10620-013-2924-2]

33 **Bennett S**, Lorenz JM. The role of imaging-guided percutaneous procedures in the multidisciplinary approach to treatment of pancreatic fluid collections. *Semin Intervent Radiol* 2012; **29**: 314-318 [PMID: 24293805 DOI: 10.1055/s-0032-1330066]

34 **Rodriguez JR**, Razo AO, Targarona J, Thayer SP, Rattner DW, Warshaw AL, Fernández-del Castillo C. Debridement and closed packing for sterile or infected necrotizing pancreatitis: insights into indications and outcomes in 167 patients. *Ann Surg* 2008; **247**: 294-299 [PMID: 18216536 DOI: 10.1097/SLA.0b013e31815b6976]

35 **van Santvoort HC**, Besselink MG, Bakker OJ, Hofker HS, Boermeester MA, Dejong CH, van Goor H, Schaapherder AF, van Eijck CH, Bollen TL, van Ramshorst B, Nieuwenhuijs VB, Timmer R, Laméris JS, Kruyt PM, Manusama ER, van der Harst E, van der Schelling GP, Karsten T, Hesselink EJ, van Laarhoven CJ, Rosman C, Bosscha K, de Wit RJ, Houdijk AP, van Leeuwen MS, Buskens E, Gooszen HG. A step-up approach or open necrosectomy for necrotizing pancreatitis. *N Engl J Med* 2010; **362**: 1491-1502 [PMID: 20410514 DOI: 10.1056/NEJMoa0908821]

36 **Cirocchi R**, Trastulli S, Desiderio J, Boselli C, Parisi A, Noya G, Falconi M. Minimally invasive necrosectomy versus conventional surgery in the treatment of infected pancreatic necrosis: a systematic review and a meta-analysis of comparative studies. *Surg Laparosc Endosc Percutan Tech* 2013; **23**: 8-20 [PMID: 23386143 DOI: 10.1097/SLE.0b013e3182754bca]

37 **Bakker OJ**, van Santvoort HC, van Brunschot S, Geskus RB, Besselink MG, Bollen TL, van Eijck CH, Fockens P, Hazebroek EJ, Nijmeijer RM, Poley JW, van Ramshorst B, Vleggaar FP, Boermeester MA, Gooszen HG, Weusten BL, Timmer R. Endoscopic transgastric vs surgical necrosectomy for infected necrotizing pancreatitis: a randomized trial. *JAMA* 2012; **307**: 1053-1061 [PMID: 22416101 DOI: 10.1001/jama.2012.276]

38 **Mier J**, León EL, Castillo A, Robledo F, Blanco R. Early versus late necrosectomy in severe necrotizing pancreatitis. *Am J Surg* 1997; **173**: 71-75 [PMID: 9074366]

39 **Baron TH**, Kozarek RA. Endotherapy for organized pancreatic necrosis: perspectives after 20 years. *Clin Gastroenterol Hepatol* 2012; **10**: 1202-1207 [PMID: 22835575 DOI: 10.1016/j.cgh.2012.07.009]

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MINIREVIEWS

Future directions of duodenal endoscopic submucosal dissection

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Abstract

Endoscopic therapies for lesions of the duodenum are technically more difficult than those for lesions of the other parts of the gastrointestinal tract due to the anatomical features of the duodenum, and the incidence rate of complications such as perforation and bleeding is also higher. These aforementioned trends were especially noticeable for the case of duodenal endoscopic submucosal dissection (ESD). The indication for ESD of duodenal tumors should be determined by assessment of the histopathology, macroscopic morphology, and diameter of the tumors. The three types of candidate lesions for endoscopic therapy are adenoma, carcinoma, and neuroendocrine tumors. For applying endoscopic therapies to duodenal lesions, accurate preoperative histopathological diagnosis is necessary. The most important technical issue in duodenal ESD is the submucosal dissection process. In duodenal ESD, a short needle-type knife is suitable for the mucosal incision and submucosal dissection processes, and the Small-caliber-tip Transparent hood is an important tool. After endoscopic therapies, the wound should be closed by clipping in order to prevent complications such as secondary hemorrhage and delayed perforation. At present, the criteria for selection between ESD and EMR vary among institutions. The indications for ESD should be carefully considered. Duodenal ESD should have limitations, such as the need for its being performed by experts with abundant experience in performing the procedure.

Key words: Duodenal tumor; Endoscopic submucosal dissection; Cancer; Adenoma; Neuroendocrine tumor; Technical know-how; Complication; Endoscopic mucosal resection

Core tip: Endoscopic therapies for duodenal lesions are technically more difficult than those for lesions of the other parts of the gastrointestinal tract due to the anatomical features of the duodenum, and the incidence rate of complications such as perforation is also higher. These aforementioned trends were especially noticeable for the case of duodenal endoscopic submucosal dissection (ESD). Thus, the indications for ESD should be carefully considered. For applying endoscopic therapies to duodenal lesions, accurate preoperative histopathological diagnosis is necessary. At present, duodenal ESD should have limitations, such as the need for its being performed by experts with abundant

experience in performing the procedure.

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INTRODUCTION

Endoscopic submucosal dissection (ESD) is widely recognized as an effective treatment strategy for early gastric cancer[1,2]. In recent years, the indications for ESD have been expanded to include lesions of the esophagus and the large intestine[3-5]. Although there are several reports of ESD performed for non-ampullary duodenal tumors[6-8], the indication of ESD for the treatment of these tumors remains controversial, because the procedure is technically difficult and associated with a high incidence rate of complications[1]. While ESD may be indicated for non-ampullary duodenal tumors, including adenomas, carcinomas, and neuroendocrine tumors (NET), there is the need to determine whether ESD or endoscopic mucosal resection (EMR) might be optimal. At present, the criteria for selection between ESD and EMR vary among institutions.

In order to determine whether ESD is indicated for duodenal tumors, examination of the site, size, and macroscopic and histological morphology of the tumors is necessary. Development of guidelines for ESD of duodenal lesions (duodenal ESD) is awaited.

DIFFICULTY IN DUODENAL ESD

The duodenum is curved in the shape of a letter C and divided into four portions. The first portion is covered by the peritoneum and is mobile, whereas the second and third portions are dorsally fixed by the peritoneum and located in the retroperitoneum. These portions are immobile. The duodenal wall is thin, which consists of the mucosal, submucosal, proper muscle, and subserosal layers, starting from the lumen inward. At the outermost layer, the anterior aspect of the duodenal wall (peritoneal cavity aspect) is covered by serosa (peritoneum), while the posterior aspect is connected with the retroperitoneum. There are numerous mucosal folds on the internal surface of the duodenum, except in the first portion. The surface of the folds carries many villi which function to absorb nutrients, *etc*. In the duodenal lumen from the second portion downward, a number of circular folds (Kerckring's folds) composed of the mucosa and submucosa are arranged perpendicular to the long axis. Duodenal glands (Brunner's glands), which produce alkaline fluid rich in mucus, are distributed in the submucosa.

In endoscopic therapies for lesions of the duodenum, the maneuverability of the endoscope is poor due to the anatomical features. Moreover, because of the presence of the folds and Brunner's glands, it is more difficult to achieve sufficient bulging by local injection into the submucosa, as compared with the case in other parts of the gastrointestinal tract, and the duration of bulge of the submucosa is also short. Furthermore, because the duodenal wall is thin, the incidence rate of complications such as bleeding and perforation is high. Especially, duodenal ESD is technically difficult, often takes long time to perform, and is associated with a high risk of perforation[6]. Thus, it would seem that duodenal ESD should be performed by operators skilled in safe and reliable techniques for ESD of at least lesions of the stomach, esophagus, and large intestine.

SELECTION OF ENDOSCOPIC THERAPIES FOR LESIONS IN THE DUODENUM

The indication for ESD of duodenal tumors should be determined by assessment of the histopathology, macroscopic morphology, and diameter of the tumors. The three types of candidate lesions for endoscopic therapy are adenoma, carcinoma, and NET.

In the case of duodenal tumors, unlike tumors of the stomach and the large intestine, it is often difficult to differentiate between benign and malignant tumors on the basis of the macroscopic endoscopic findings alone. Thus, histopathological diagnosis is basically essential. However, the high risk of development of fibrosis in the submucosa occurring after biopsy reportedly makes endoscopic therapy difficult[9]. While magnifying endoscopy with narrow-band imaging has frequently been reported to be useful for qualitative diagnosis of early esophageal[10,11], gastric[12,13], and colorectal cancers[14], it is also useful for qualitative diagnosis of superficial non-ampullary duodenal epithelial tumors[15]. For depressed-type lesions, because fibrosis is likely to occur after biopsy, optical biopsy using magnifying endoscopy with narrow-band imaging has been reported to be more effective than tissue biopsy[16].

Endoscopic therapies for duodenal adenomas

Duodenal adenomas have the potential for malignant transformation[17,18]. Especially, those that are 2 cm or more in diameter and adenomas showing high-grade dysplasia on histopathology show a high likelihood of becoming malignant[19-21], and resection is preferable for such lesions. On the other hand, there is a report that low-grade adenomas measuring less than 1 cm in diameter remained low-grade lesions even at 2 years after the first diagnosis[22]. EMR of duodenal tumors has been reported to be safe and useful and to be associated with a favorable long-term prognosis[23-29].

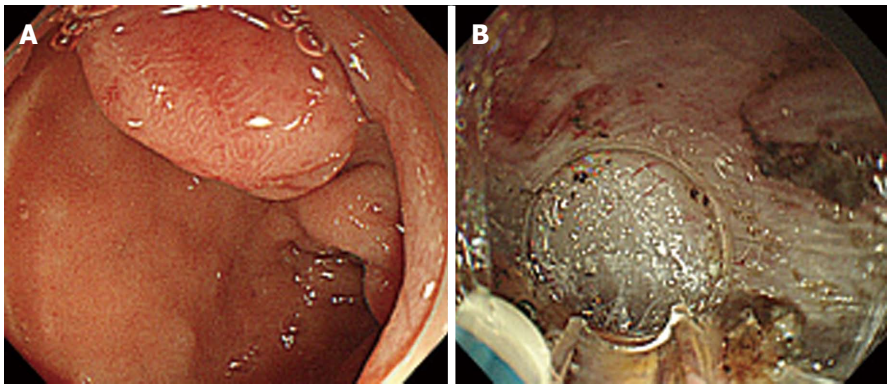

Figure 1 Endoscopic submucosal dissection of a neuroendocrine tumors in the superior duodenal bulb. A: A protruded-type tumor 0.9 cm × 0.9 cm in size was identified; B: We performed a submucosal dissection. The tip of a knife is perpendicularly oriented to the dissection surface.

In addition, piecemeal resection of adenomas is acceptable. Thus, EMR seems to be preferable for the treatment of duodenal tumors. However, a study showed that the preoperative pathological diagnosis was adenoma in 3 of 4 cancer patients who underwent EMR[30], and accurate preoperative diagnosis is necessary. At our institution, endoscopic therapy is not selected for patients with low-grade adenomas measuring less than 1 cm in diameter; instead, such patients are followed up with regular endoscopy. We select endoscopic therapies for adenomas that are at least 1 cm in diameter or show a tendency to grow, those that are histopathologically diagnosed as low-grade adenoma, but appear red and are macroscopically suspected as cancer, *etc.*

Endoscopic therapies for duodenal cancer

In a study of 128 lesions of early duodenal cancer for which surgery or endoscopic polypectomy was performed, it was reported that none of the cases of intramucosal carcinoma showed lymph node metastasis[31]. Thus, endoscopic therapies should be considered for well-differentiated noninvasive carcinomas not showing submucosal invasion. The complete remission rate after EMR for duodenal tumors ranges from 63% to 97%[24-39]. Lesions measuring 2 cm or more in diameter are likely to require piecemeal resection[23,29], and the persistence and recurrence rates are higher after piecemeal resection than after *en bloc* resection[16,29]. Complete (R0) resection is more frequently achieved by ESD than by EMR[16,30]. Furthermore, *en bloc* resection enables accurate histopathological assessment of deep and lateral surgical margins[33]. Thus, it seems preferable to perform EMR for lesions that can be resected *en bloc* by EMR and to perform ESD for lesions in which EMR is expected to result in piecemeal resection.

Endoscopic therapies for duodenal NET

The common sites of NET are the ileum, appendix, and rectum[34], and NET originating from the duodenum accounts for less than 5% of NET[35-38]. While according to one previously reported retrospective study, no recurrence was observed after local excision in any patients with tumors measuring less than 2 cm in diameter[39], another report indicated that lymph node metastasis was observed in 13% of patients with tumors measuring less than 1 cm in diameter[40]. No consensus has been reached on the association between tumor diameter and the likelihood of lymph node metastasis. Burke *et al*[41] reported the following three risk factors as being predictive of metastasis: tumor invasion to the muscle layer, tumor diameter 2 cm or more, and the presence of mitotic figures[41]. Zyromski *et al*[39] also reported that in cases of tumors measuring less than 2 cm in diameter, no metastasis was observed, regardless of the depth of invasion, recommending endoscopic therapies for tumors measuring less than 1 cm in diameter, and open transduodenal local excision for those measuring 1 to 2 cm in diameter[39]. There are reports that endoscopic resection is safe, minimally invasive, and effective for patients with tumors measuring less than 1 cm in diameter that are not identified by EUS as invading the muscle layer[42]. Although EMR may be well applicable in tumors measuring less than 1 cm in diameter invading the superficial layers of the submucosa, especially lesions with polypoid morphology, ESD may be useful for lesions that are difficult to resect *en bloc* by EMR. However, when the lower margin of a tumor lesion is widely attached to the muscle layer, ESD is associated with an extremely high risk of perforation, and the histopathological diagnosis of the deep surgical margin is also slightly uncertain; thus, surgical treatment should be considered for such cases[7].

TECHNICAL KNOW-HOW OF METHODS OF DUODENAL ESD

The most important technical issue in duodenal ESD is the submucosal dissection process, and it is common to encounter difficulties during submucosal dissection, such as when the tip of a knife is perpendicularly oriented to the dissection surface (Figure 1). In

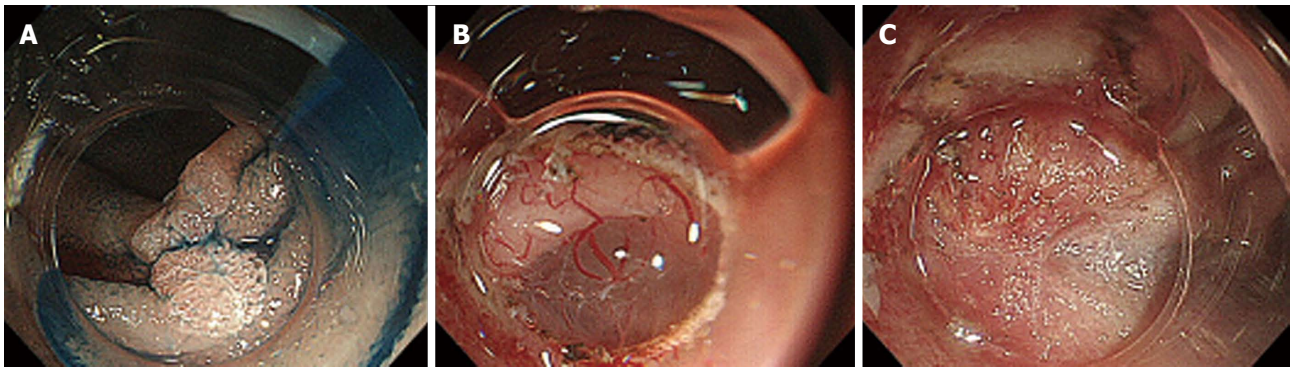

Figure 2 Endoscopic submucosal dissection of an adenoma in the descending part of the duodenum. A: A depressed type tumor 1.2 cm × 1.2 cm in size was identified; B: After incising the oral side of the lesion, we slightly detached it to form a mucosal flap; C: A severe submucosal fibrosis was found.

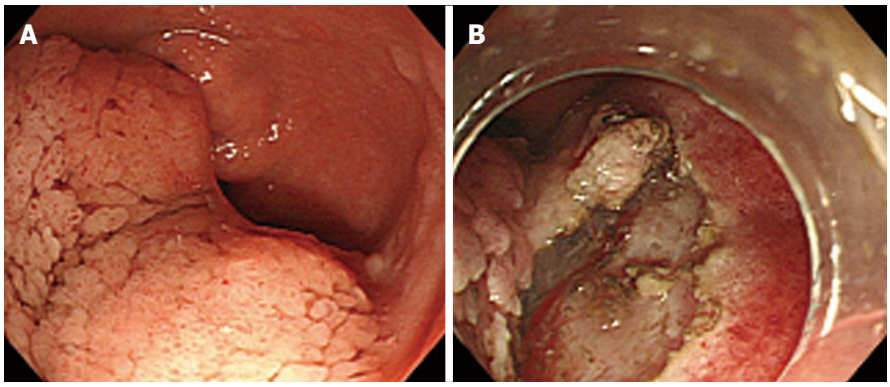

Figure 3 Endoscopic submucosal dissection of an adenoma in the anterior duodenal bulb. A: A flat-elevated type tumor 6.0 cm × 5.0 cm in size was identified; B: We performed submucosal dissection using the ST hood.

duodenal ESD, a short needle-type knife is suitable for the mucosal incision and submucosal dissection processes. The authors use the Dual knife (Olympus, Tokyo, Japan). Moreover, for the submucosal dissection process, the Small-caliber-tip Transparent (ST) hood (Fujifilm, Tokyo, Japan) is an important tool[6]. One of the important aspects of the procedure is to ensure a space for the ST hood to be placed directly under a lesion by incising the oral side of the lesion and slightly detaching it to form a mucosal flap in the early stage (Figure 2). This is the key for the success of the procedure. When a lesion is detached from the anterior wall, the tip of a knife is likely to be perpendicularly oriented to the dissection surface. Under such a situation, the authors make direct visualization of the submucosa easy using the ST hood and apply electrical current while keeping the knife slightly pressed on the lesion (Figure 3) or while the tissue to be detached is hooked and pulled toward the scope by the Hook knife (Olympus, Tokyo, Japan). When the submucosa is detached, it is important to leave as much submucosa on the dissection surface as possible in order not to expose the surface of the muscle layer. Moreover, because there is also a possibility of perforation due to an attachment of the knife such as ST hood, it seems preferable to slightly press the attachment on the dissection surface. The tips for ESD of lesions in the second portion of the duodenum are to push and pull the endoscope and control the intraduodenal air volume. In the third portion of the duodenum, the maneuverability of a scope is poor, and it is essential to check the maneuverability before the operation. If the maneuverability is poor, double-balloon enteroscopy may be useful[43].

Control of bleeding during the procedure is a key to the success of duodenal ESD. It is important to recognize the blood vessels and coagulate them before cutting. Hemostatic forceps should be slightly pulled away from the muscle layer before coagulation to prevent electrical injury of the thin muscle layer[43]. In addition, bipolar coagulation forceps are effective to prevent and restrain hemorrhage.

Because of the high incidence rate of complications caused by duodenal ESD, we have used carbon dioxide insufflation during the ESD. Carbon dioxide insufflation has been reported to be useful for early esophageal[44] and gastric ESD[45]. In addition, a system for ensuring backup by the surgical department may be essential when the procedure is performed. At our institution, in an effort to provide safer treatment, duodenal ESD has been performed under general anesthesia in the operating room since 2010.

Meanwhile, there are also difficult situations encountered during EMR of duodenal lesions. In EMR of lesions in the first portion of the duodenum, the pyloric ring may pose an obstacle to snaring. Moreover, because a lesion relatively often extends over several folds in the second portion, where the space between the folds is small, it may be difficult to ensure snaring in EMR lesions in the second portion of the duodenum.

AFTER DUODENAL ESD

At our institution, intravenous injection of a proton pump inhibitor is started on the day of the ESD, and intravenous cephem antibiotics are administered for approximately 3 d. A blood test is performed on the day after the ESD. If complications such as perforation do not occur, a rice gruel diet is started approximately 3 d after the ESD. Yamamoto suggests taking the fasting period a few days longer in duodenal ESD than other ESDs[43]. During the hospitalization, endoscopy is not performed to check for the formation of ulcers after ESD. If no complications occur, the patients are usually discharged within one week after the operation.

COMPLICATION OF DUODENAL ESD

The most common complication of endoscopic therapies for duodenal lesions is bleeding, which, in general, occurs within 24 h after the operation. The frequency of bleeding after EMR of adenomas ranges from 4% to 33%[23-28]. The frequency of bleeding after ESD ranges from 6.7% to 22.2%[6,30]. The incidence rate of perforation complicating duodenal ESD ranges from 21% to 35.7%[6,46,47], which is extremely high as compared to that of perforation complicating gastric ESD, which ranges from 1.2% to 3.6%[48-50]. Moreover, attention should be paid not only to intraoperative perforation, but also delayed perforation due to exposure to bile or pancreatic juice[6]. As compared to that in patients undergoing EMR, the incidence rate of perforation is significantly higher in those undergoing ESD, and the duration of postoperative hospital stay is also significantly longer[30]. If patients complain of abdominal pain or fever after procedure, they should be checked for their abdominal tenderness and free air in the abdomen by computerized tomography. Thus, the wound should be closed by clipping in order to prevent complications such as secondary hemorrhage and delayed perforation[46,51]. However, in some patients with lesions located in the first portion of the duodenum, closure of the wound by clipping may be difficult, and there is a report of patients in whom perforation occurred after closure of the wound by clipping[52]. In such patients, coverage of the wound with polyglycolic acid sheets (Neoveil; Gunze Ltd., Kyoto, Japan) and fibrin glue (Bolheal; Kaketsuden, Kumamoto, Japan) as a substitute to closure of wound by clipping may be effective for the prevention of delayed perforation[52].

SURGERY FOR NON-AMPULLARY DUODENAL TUMORS

At present, the frequency of complications of duodenal ESD is high, even in institutions with experts in endoscopic therapies. Unlike gastric ESD, it is more difficult to popularize the use of duodenal ESD around the world. Therefore, ESD for duodenal lesions should be performed at limited institutions with abundant experience in performing the procedure. There is also a report that surgery is preferable for lesions exceeding 20 mm in major axis[16]. It is necessary to always keep in mind surgery as one of the treatment options, and endoscopic therapies should not be insisted upon.

Recently, there have been an increasing number of institutions where endoscopists and surgeons cooperatively perform Laparoscopy and Endoscopy Cooperative Surgery (LECS). In a study conducted on 22 patients undergoing LECS for duodenal tumors, the mean tumor diameter was 13.3 mm; the mean diameter of the resected specimens was 28.9 mm; the mean operative time was 133 min; and the duration of postoperative hospital stay was 15.1 d. Complications were observed in 5 patients, 3 (13.6%) of whom had asymptomatic minor leakage. All patients recovered with conservative therapy, and no serious complications were encountered in this study[53].

LONG-TERM PROGNOSIS

In regard to the long-term prognosis, according to one study with a mean follow-up period of 10 mo, no recurrence was observed in any of the 16 patients treated by duodenal ESD, while recurrence was observed in one of the 31 patients undergoing duodenal EMR[30]. Another study also reported that no recurrence was observed with a mean follow-up period of 48 mo in any of the 37 patients treated by ESD for duodenal tumors measuring 20 mm in diameter[54]. Further accumulation of cases may be needed to clarify the long-term prognosis.

REFERENCES

1 **Kim KO**, Kim SJ, Kim TH, Park JJ. Do you have what it takes for challenging endoscopic submucosal dissection cases? *World J Gastroenterol* 2011; **17**: 3580-3584 [PMID: 21987603 DOI: 10.3748/wjg.v17.i31.3580]

2 **Gotoda T**, Yamamoto H, Soetikno RM. Endoscopic submucosal dissection of early gastric cancer. *J Gastroenterol* 2006; **41**: 929-942 [PMID: 17096062]

3 **Fujishiro M**, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Yamamichi N, Tateishi A, Shimizu Y, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Endoscopic submucosal dissection of esophageal squamous cell neoplasms. *Clin Gastroenterol Hepatol* 2006; **4**: 688-694 [PMID: 16713746]

4 **Kakushima N**, Yahagi N, Fujishiro M, Kodashima S, Nakamura M, Omata M. Efficacy and safety of endoscopic submucosal dissection for tumors of the esophagogastric junction. *Endoscopy* 2006; **38**: 170-174 [PMID: 16479425]

5 **Yamamoto H**, Yahagi N, Oyama T. Mucosectomy in the colon with endoscopic submucosal dissection. *Endoscopy* 2005; **37**: 764-768

[PMID: 16032498]
6 **Honda T**, Yamamoto H, Osawa H, Yoshizawa M, Nakano H, Sunada K, Hanatsuka K, Sugano K. Endoscopic submucosal dissection for superficial duodenal neoplasms. *Dig Endosc* 2009; **21**: 270-274 [PMID: 19961529 DOI: 10.1111/j.1443-1661.2009.00908.x]
7 **Matsumoto S**, Miyatani H, Yoshida Y, Nokubi M. Duodenal carcinoid tumors: 5 cases treated by endoscopic submucosal dissection. *Gastrointest Endosc* 2011; **74**: 1152-1156 [PMID: 21944312 DOI: 10.1016/j.gie.2011.07.029]
8 **Suzuki S**, Ishii N, Uemura M, Deshpande GA, Matsuda M, Iizuka Y, Fukuda K, Suzuki K, Fujita Y. Endoscopic submucosal dissection (ESD) for gastrointestinal carcinoid tumors. *Surg Endosc* 2012; **26**: 759-763 [PMID: 21993939 DOI: 10.1007/s00464-011-1948-y]
9 **Bourke MJ**. Endoscopic resection in the duodenum: current limitations and future directions. *Endoscopy* 2013; **45**: 127-132 [PMID: 23364840 DOI: 10.1055/s-0032-1326177]
10 **Goda K**, Tajiri H, Ikegami M, Yoshida Y, Yoshimura N, Kato M, Sumiyama K, Imazu H, Matsuda K, Kaise M, Kato T, Omar S. Magnifying endoscopy with narrow band imaging for predicting the invasion depth of superficial esophageal squamous cell carcinoma. *Dis Esophagus* 2009; **22**: 453-460 [PMID: 19222533 DOI: 10.1111/j.1442-2050.2009.00942.x]
11 **Arima M**, Tada M, Arima H. Evaluation of microvascular pattern of superficial esophageal cancers by magnifying endoscopy. *Esophagus* 2005; **2**: 191-197
12 **Yao K**, Anagnostopoulos GK, Ragunath K. Magnifying endoscopy for diagnosing and delineating early gastric cancer. *Endoscopy* 2009; **41**: 462-467 [PMID: 19418401 DOI: 10.1055/s-0029-1214594]
13 **Nonaka K**, Arai S, Ban S, Kitada H, Namoto M, Nagata K, Ochiai Y, Togawa O, Nakao M, Nishimura M, Ishikawa K, Sasaki Y, Kita H. Prospective study of the evaluation of the usefulness of tumor typing by narrow band imaging for the differential diagnosis of gastric adenoma and well-differentiated adenocarcinoma. *Dig Endosc* 2011; **23**: 146-152 [PMID: 21429020 DOI: 10.1111/j.1443-1661.2010.01070.x]
14 **Hayashi N**, Tanaka S, Hewett DG, Kaltenbach TR, Sano Y, Ponchon T, Saunders BP, Rex DK, Soetikno RM. Endoscopic prediction of deep submucosal invasive carcinoma: validation of the narrow-band imaging international colorectal endoscopic (NICE) classification. *Gastrointest Endosc* 2013; **78**: 625-632 [PMID: 23910062 DOI: 10.1016/j.gie.2013.04.185]
15 **Kikuchi D**, Hoteya S, Iizuka T, Kimura R, Kaise M. Diagnostic algorithm of magnifying endoscopy with narrow band imaging for superficial non-ampullary duodenal epithelial tumors. *Dig Endosc* 2014; **26** Suppl 2: 16-22 [PMID: 24750143 DOI: 10.1111/den.12282]
16 **Yamamoto Y**, Yoshizawa N, Tomida H, Fujisaki J, Igarashi M. Therapeutic outcomes of endoscopic resection for superficial non-ampullary duodenal tumor. *Dig Endosc* 2014; **26** Suppl 2: 50-56 [PMID: 24750149 DOI: 10.1111/den.12273]
17 **Galandiuk S**, Hermann RE, Jagelman DG, Fazio VW, Sivak MV. Villous tumors of the duodenum. *Ann Surg* 1988; **207**: 234-239 [PMID: 3345110]
18 **Miller JH**, Gisvold JJ, Weiland LH, McIlrath DC. Upper gastrointestinal tract: villous tumors. *AJR Am J Roentgenol* 1980; **134**: 933-936 [PMID: 6768268]
19 **Rosen M**, Zuccaro G, Brody F. Laparoscopic resection of a periampullary villous adenoma. *Surg Endosc* 2003; **17**: 1322-1323 [PMID: 12799897]
20 **Lépilliez V**, Napoléon B, Ponchon T, Saurin JC. [Duodenal adenomas: diagnostic and treatment]. *Gastroenterol Clin Biol* 2009; **33**: 240-246 [PMID: 19307075 DOI: 10.1016/j.gcb.2009.02.002]
21 **Okada K**, Fujisaki J, Kasuga A, Omae M, Kubota M, Hirasawa T, Ishiyama A, Inamori M, Chino A, Yamamoto Y, Tsuchida T, Nakajima A, Hoshino E, Igarashi M. Sporadic nonampullary duodenal adenoma in the natural history of duodenal cancer: a study of follow-up surveillance. *Am J Gastroenterol* 2011; **106**: 357-364 [PMID: 21139577 DOI: 10.1038/ajg.2010.422]
22 **Kakushima N**, Ono H, Takao T, Kanemoto H, Sasaki K. Method and timing of resection of superficial non-ampullary duodenal epithelial tumors. *Dig Endosc* 2014; **26** Suppl 2: 35-40 [PMID: 24750146 DOI: 10.1111/den.12259]
23 **Kim HK**, Chung WC, Lee BI, Cho YS. Efficacy and long-term outcome of endoscopic treatment of sporadic nonampullary duodenal adenoma. *Gut Liver* 2010; **4**: 373-377 [PMID: 20981216 DOI: 10.5009/gnl.2010.4.3.373]
24 **Apel D**, Jakobs R, Spiethoff A, Riemann JF. Follow-up after endoscopic snare resection of duodenal adenomas. *Endoscopy* 2005; **37**: 444-448 [PMID: 15844023]
25 **Hirasawa R**, Iishi H, Tatsuta M, Ishiguro S. Clinicopathologic features and endoscopic resection of duodenal adenocarcinomas and adenomas with the submucosal saline injection technique. *Gastrointest Endosc* 1997; **46**: 507-513 [PMID: 9434217]
26 **Ahmad NA**, Kochman ML, Long WB, Furth EE, Ginsberg GG. Efficacy, safety, and clinical outcomes of endoscopic mucosal resection: a study of 101 cases. *Gastrointest Endosc* 2002; **55**: 390-396 [PMID: 11868015]
27 **Oka S**, Tanaka S, Nagata S, Hiyama T, Ito M, Kitadai Y, Yoshihara M, Haruma K, Chayama K. Clinicopathologic features and endoscopic resection of early primary nonampullary duodenal carcinoma. *J Clin Gastroenterol* 2003; **37**: 381-386 [PMID: 14564184]
28 **Lépilliez V**, Chemaly M, Ponchon T, Napoleon B, Saurin JC. Endoscopic resection of sporadic duodenal adenomas: an efficient technique with a substantial risk of delayed bleeding. *Endoscopy* 2008; **40**: 806-810 [PMID: 18828076 DOI: 10.1055/s-2008-1077619]
29 **Alexander S**, Bourke MJ, Williams SJ, Bailey A, Co J. EMR of large, sessile, sporadic nonampullary duodenal adenomas: technical aspects and long-term outcome (with videos). *Gastrointest Endosc* 2009; **69**: 66-73 [PMID: 18725157 DOI: 10.1016/j.gie.2008.04.061]
30 **Matsumoto S**, Yoshida Y. Selection of appropriate endoscopic therapies for duodenal tumors: an open-label study, single-center experience. *World J Gastroenterol* 2014; **20**: 8624-8630 [PMID: 25024618 DOI: 10.3748/wjg.v20.i26.8624]
31 **Nagatani K**, Takekoshi T, Baba Y, Kaku S, Koizumi K, Fujii A, Ogata E, Ohta H, Nishi M, Kato Y, Yanagisawa A. Indications for endoscopic treatment of early duodenal cancer: based on cases reported in the literature (in Japanese with English abstract). *Endosc Dig* 1993; **7**: 969-976
32 **Abbass R**, Rigaux J, Al-Kawas FH. Nonampullary duodenal polyps: characteristics and endoscopic management. *Gastrointest Endosc* 2010; **71**: 754-759 [PMID: 20363416 DOI: 10.1016/j.gie.2009.11.043]
33 **Sohn JW**, Jeon SW, Cho CM, Jung MK, Kim SK, Lee DS, Son HS, Chung IK. Endoscopic resection of duodenal neoplasms: a single-center study. *Surg Endosc* 2010; **24**: 3195-3200 [PMID: 20490557]
34 **Maggard MA**, O'Connell JB, Ko CY. Updated population-based review of carcinoid tumors. *Ann Surg* 2004; **240**: 117-122 [PMID: 15213627]
35 **Modlin IM**, Lye KD, Kidd M. A 5-decade analysis of 13,715 carcinoid tumors. *Cancer* 2003; **97**: 934-959 [PMID: 12569593]
36 **Godwin JD**. Carcinoid tumors. An analysis of 2,837 cases. *Cancer* 1975; **36**: 560-569 [PMID: 1157019]
37 **Modlin IM**, Sandor A. An analysis of 8305 cases of carcinoid tumors. *Cancer* 1997; **79**: 813-829 [PMID: 9024720]
38 **Neugut AI**, Jacobson JS, Suh S, Mukherjee R, Arber N. The epidemiology of cancer of the small bowel. *Cancer Epidemiol Biomarkers Prev* 1998; **7**: 243-251 [PMID: 9521441]
39 **Zyromski NJ**, Kendrick ML, Nagorney DM, Grant CS, Donohue JH, Farnell MB, Thompson GB, Farley DR, Sarr MG. Duodenal carcinoid tumors: how aggressive should we be? *J Gastrointest Surg* 2001; **5**: 588-593 [PMID: 12086896]
40 **Soga J**. Endocrinocarcinomas (carcinoids and their variants) of the duodenum. An evaluation of 927 cases. *J Exp Clin Cancer Res* 2003; **22**: 349-363 [PMID: 14582691]
41 **Burke AP**, Sobin LH, Federspiel BH, Shekitka KM, Helwig EB. Carcinoid tumors of the duodenum. A clinicopathologic study of 99 cases. *Arch Pathol Lab Med* 1990; **114**: 700-704 [PMID: 1694655]
42 **Dalenbäck J**, Havel G. Local endoscopic removal of duodenal carcinoid tumors. *Endoscopy* 2004; **36**: 651-655 [PMID: 15243891]

43 **Yamamoto H**, Miura Y. Duodenal ESD: conquering difficulties. *Gastrointest Endosc Clin N Am* 2014; **24**: 235-244 [PMID: 24679234 DOI: 10.1016/j.giec.2013.11.007]

44 **Uemura M**, Ishii N, Itoh T, Suzuki K, Fujita Y. Effects of carbon dioxide insufflation in esophageal endoscopic submucosal dissection. *Hepatogastroenterology* 2012; **59**: 734-737 [PMID: 22020910 DOI: 10.5754/hge11547]

45 **Maeda Y**, Hirasawa D, Fujita N, Obana T, Sugawara T, Ohira T, Harada Y, Yamagata T, Suzuki K, Koike Y, Kusaka J, Tanaka M, Noda Y. A prospective, randomized, double-blind, controlled trial on the efficacy of carbon dioxide insufflation in gastric endoscopic submucosal dissection. *Endoscopy* 2013; **45**: 335-341 [PMID: 23468193 DOI: 10.1055/s-0032-1326199]

46 **Matsumoto S**, Miyatani H, Yoshida Y. Endoscopic submucosal dissection for duodenal tumors: a single-center experience. *Endoscopy* 2013; **45**: 136-137 [PMID: 22930172 DOI: 10.1055/s-0032-1310123]

47 **Jung JH**, Choi KD, Ahn JY, Lee JH, Jung HY, Choi KS, Lee GH, Song HJ, Kim DH, Kim MY, Bae SE, Kim JH. Endoscopic submucosal dissection for sessile, nonampullary duodenal adenomas. *Endoscopy* 2013; **45**: 133-135 [PMID: 23364841 DOI: 10.1055/s-0032-1326178]

48 **Abe N**, Gotoda T, Hirasawa T, Hoteya S, Ishido K, Ida Y, Imaeda H, Ishii E, Kokawa A, Kusano C, Maehata T, Ono S, Takeuchi H, Sugiyama M, Takahashi S. Multicenter study of the long-term outcomes of endoscopic submucosal dissection for early gastric cancer in patients 80 years of age or older. *Gastric Cancer* 2012; **15**: 70-75 [PMID: 21667133 DOI: 10.1007/s10120-011-0067-8]

49 **Chung IK**, Lee JH, Lee SH, Kim SJ, Cho JY, Cho WY, Hwangbo Y, Keum BR, Park JJ, Chun HJ, Kim HJ, Kim JJ, Ji SR, Seol SY. Therapeutic outcomes in 1000 cases of endoscopic submucosal dissection for early gastric neoplasms: Korean ESD Study Group multicenter study. *Gastrointest Endosc* 2009; **69**: 1228-1235 [PMID: 19249769 DOI: 10.1016/j.gie.2008.09.027]

50 **Oda I**, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627]

51 **Otake Y**, Saito Y, Sakamoto T, Aoki T, Nakajima T, Toyoshima N, Matsuda T, Ono H. New closure technique for large mucosal defects after endoscopic submucosal dissection of colorectal tumors (with video). *Gastrointest Endosc* 2012; **75**: 663-667 [PMID: 22341112 DOI: 10.1016/j.gie.2011.10.037]

52 **Takimoto K**, Imai Y, Matsuyama K. Endoscopic tissue shielding method with polyglycolic acid sheets and fibrin glue to prevent delayed perforation after duodenal endoscopic submucosal dissection. *Dig Endosc* 2014; **26** Suppl 2: 46-49 [PMID: 24750148 DOI: 10.1111/den.12280]

53 **Ohata K**, Murakami M, Yamazaki K, Nonaka K, Misumi N, Tashima T, Minato Y, Shozushima M, Mitsui T, Matsuhashi N, Fu K. Feasibility of endoscopy-assisted laparoscopic full-thickness resection for superficial duodenal neoplasms. *ScientificWorldJournal* 2014; **2014**: 239627 [PMID: 24550694 DOI: 10.1155/2014/239627]

54 **Hoteya S**, Yahagi N, Iizuka T, Kikuchi D, Mitani T, Matsui A, Ogawa O, Yamashita S, Furuhata T, Yamada A, Kimura R, Nomura K, Kuribayashi Y, Kaise M. Endoscopic submucosal dissection for nonampullary large superficial adenocarcinoma/adenoma of the duodenum: feasibility and long-term outcomes. *Endoscopy International Open* 2013; **1**: E2-E7 [DOI: 10.1055/s-0033-1359232]

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MINIREVIEWS

Optimal management of biopsy-proven low-grade gastric dysplasia

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Abstract

Gastric adenocarcinoma generally culminates *via* the inflammation-metaplasia-dysplasia-carcinoma sequence progression. The prevalence of gastric adenomas shows marked geographic variation. Recently, the rate of diagnosis of low-grade dysplasia (LGD) has increased due to increased use of upper endoscopy. Many investigators have reported that gastric high-grade dysplasia has high potential for malignancy and should be removed; however, the treatment for gastric LGD remains controversial. Although the risk of LGD progression to invasive carcinoma has been reported to be inconsistent, progression has been observed during follow-up. Additionally, the rate of upgraded diagnosis in biopsy-proven LGD is high. Therefore, endoscopic resection (ER) may be useful in the treatment and diagnosis of LGD, especially if lesions are found to have risk factors for upgraded histology after ER, such as large size, surface erythema or depressed morphology. Fatal complications in endoscopic submucosal dissection (ESD) are extremely low and its therapeutic and diagnostic outcomes are excellent. Therefore, ESD should be applied preferentially instead of endoscopic mucosal resection.

Key words: Intraepithelial neoplasia; Low-grade dysplasia; Adenoma; Endoscopic resection; Endoscopic submucosal dissection

Core tip: According to the guideline, endoscopic resection or follow-up is recommended for noninvasive category 3 low-grade dysplasias (LGDs), while category 4 lesions such as high-grade dysplasia, non-invasive carcinoma and intramucosal carcinoma should be removed by local resection. However, as LGD has a relatively high underdiagnosis rate and rarely contains submucosal cancer, a follow-up strategy might result in the opportunity for endoscopic therapy being missed. Furthermore, repeated endoscopic examinations with biopsies might impose a psychological and financial burden on the patient. Based on its efficacy and safety, the use of endoscopic submucosal dissection as a primary procedure for LGD should be considered.

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INTRODUCTION

Gastric cancer (GC) is the fourth-most common cancer and the second-leading cause of cancer-related deaths worldwide, and is especially prevalent in Asia-Pacific countries, including South Korea[1]. In general, gastric adenocarcinoma culminates *via* the inflammation-metaplasia-dysplasia-carcinoma sequence progression, which is described as the Correa cascade of multi-step gastric carcinogenesis[2]. Gastric atrophy and intestinal metaplasia are lesions that confer a high risk for the development of gastric adenocarcinoma, and gastric epithelial dysplasia (GED) is considered the penultimate stage of gastric carcinogenesis[3,4]. Understanding the clinicopathological characteristics of GC is important for prevention. Along with the increasing number of endoscopies performed, the detection of precancerous lesions has increased in clinical practice[5].

The prevalence of gastric adenomas shows marked geographic variation. The reported prevalence is approximately 0.5%-3.75% in western countries and approximately 9%-20% in Asian countries where the prevalence of GC is high[6-8]. Some precancerous lesions progress to adenocarcinoma, whereas others remain unchanged for an extended period of time[9,10]. Furthermore, irrespective of used classification, several studies have demonstrated inter-observer variation in the histological assessment of GED[11-13]. Therefore, it is difficult to establish coincident international guidelines for the management of such lesions.

This review discusses the current optimal strategies for managing gastric low-grade dysplasia (LGD). In preparation for this review, we searched for epidemiological studies, clinical studies, meta-analyses and published guidelines related to GED in the Medline and PubMed databases. The search was performed using index words related to LGD ("gastric epithelial dysplasia" or "low grade dysplasia" or "gastric adenoma" or "gastric dysplasia") and treatment ("endoscopic resection" or "endoscopic submucosal dissection").

DEFINITION

Dysplasia is defined as an unequivocally neoplastic but non-invasive lesion, distinguished from regenerative changes[14]. Used initially to define inflammatory bowel diseases, the term is currently applied throughout the gastrointestinal tract and other organs. Grundmann[15] first used the term gastric dysplasia, and the World Health Organization (WHO) defined dysplasia as cellular atypia, abnormal differentiation and disorganized architecture[4,6]. Conventionally, dysplasia was a term used to describe flat or depressed lesions, whereas adenoma described raised circumscribed lesions that were either sessile or pedunculated. Therefore, a WHO committee defined adenoma as a circumscribed benign neoplasm composed of tubular and/or villous structures lined by dysplastic epithelium. On the other hand, Lewin[16] defined adenoma as a circumscribed lesion unassociated with underlying inflammation whether pedunculated, sessile, flat or depressed; and dysplasia was defined as a benign neoplastic lesion associated with underlying inflammation. However, most clinicians use these terms widely without distinction between adenoma and dysplasia in clinical practice.

Although the biological potential of GED as a precancerous lesion is clear, the classification of these lesions has been controversial in the diagnostic approach. For example, Japanese studies have referred to these lesions as borderline (Group 3 or 4), while the terms gastric adenoma or dysplasia have been used widely in Western countries (Table 1)[12,17]. Because dysplasia implies carcinoma in Japan, pathologists are reluctant to use the term gastric adenoma with LGD[18]. Furthermore, intraepithelial gastric neoplasias are classified into adenoma or carcinoma with low and high-grade cytological atypia[19]. Therefore, the term adenoma with low-grade atypia has been substituted for dysplasia in Japan. From the Japanese viewpoint, gastric adenoma with LGD diagnosed using western criteria include typical adenomas of the small intestinal type and tubular structures, and are thus diagnosed as carcinoma without invasion in Japan[18]. The Vienna classification for GED was proposed as a consensus between western and Asian countries (Table 1)[11,20]. In this classification, dysplastic lesions without invasion of the lamina propria are placed as category 3 or 4 according to the degree of cytologic atypia or architectural complexity[9,11]. Category 3 is a non-invasive low-grade neoplasia, also known as low-grade adenoma/dysplasia. Currently, the WHO recommends the terminology of non-invasive low-grade and high-grade intraepithelial neoplasia and defines carcinoma as invasion into the lamina propria or beyond[21].

NATURAL HISTORY

Although several studies have addressed the risk of carcinoma in GED[22-24], its natural course remains unclear. A large cohort study from the Netherlands suggested that the risk of progression to cancer within 10 years was 3.9% in individuals with LGD[25]. The differences among previous studies regarding the natural course of LGD are due primarily to the differences in diagnostic criteria including the classification and grading (Table 1). Additional reasons for these differences include sampling error in forceps biopsy, discrepancies between forceps biopsy and endoscopic resection (ER), and variations in the rate of malignant transformation. As mentioned earlier, noninvasive intramucosal neoplastic lesions with high-grade cellular and architectural atypia are termed intramucosal carcinoma in Japan, whereas the same lesions are diagnosed as high-grade dysplasia (HGD) by most pathologists in western countries[26]. Under these definitions, lesions diagnosed as gastric adenomas in

Table 1 Common reporting classifications of gastric epithelial neoplasia

Vienna classification[11,20]	WHO[21]	JGCA[19]
Negative for neoplasia/dysplasia		Group 1; Normal tissue or non-neoplastic lesion
Indefinite for neoplasia/dysplasia		Group 2; Material for which diagnosis of neoplastic or non-neoplastic lesion is difficult
Noninvasive neoplasia, low grade (low-grade adenoma/dysplasia)	Low-grade intraepithelial neoplasia	Group 3; Adenoma
Noninvasive neoplasia, high grade	High-grade intraepithelial neoplasia	
High grade adenoma/dysplasia		Group 4; Neoplastic lesion that is suspected to be carcinoma
Noninvasive carcinoma		Group 5; Carcinoma
Suspicious of invasive carcinoma		
Invasive carcinoma	Carcinoma	

WHO: World Health Organization; JGCA: Japanese Gastric Cancer Association.

Japan rarely progress to cancer[18]. Yamada *et al*[27] reported follow-up data for 48 gastric adenomas (38 LGD and 10 HGD) with a median of 4.7 years. During the follow-up period, 37 (97%) LGD lesions showed no histological change, while the remaining lesions progressed to HGD. However, this description of an indolent natural course may have been influenced by selection bias and the use of different LGD classifications in Japan. LGD lesions with invasive carcinoma were more likely to be excluded at the time of the first biopsy. Additionally, a substantial number of patients were excluded since they underwent ER or surgery due to a larger lesion or greater malignant potential. Therefore, half of the patients (19/38) in the study had lesions < 0.5 cm, with most lesions (76.3%, 29/38) measuring < 1 cm. This selection bias may influence a favorable LGD prognosis[28]. In contrast, Rugge *et al*[29] performed a prospective long-term follow-up study to evaluate the clinicopathological behavior of GED. A total of 118 gastric non-invasive neoplasias, including 90 LGDs, were followed for a mean of 52 mo. Among 90 LGDs, 48 (53.3%) were no longer detectable and 28 (31.1%) were unchanged; however, 14 (15.5%) LGDs evolved into HGD and GC.

To date, few studies have determined the predictors for malignant transformation of GEDs[30-32]. Gastric inflammation is a well-known risk factor for gastric carcinoma[33,34]. Correa[2] postulated that chronic gastritis may lead to intestinal metaplasia and atrophy, and that these lesions should be considered a GC risk factor as they are frequently found to be closely related to cancer. In a study that evaluated the endoscopic, pathological and immunophenotypic differences in LGD and HGD lesions according to the revised Vienna classification, Jung *et al*[32] determined that the size, color change and ulceration of the lesion, as well as gastritis score of the surrounding mucosa and positive expression of MUC6, were risk factors for malignant transformation. Because of the use of different diagnostic criteria and ethical reason, it is difficult to confirm a consistent natural history of LGD at present. Recent observational studies have indicated that the cancer progression risk of LGD is relatively low[27,29]. Nonetheless, it is possible that LGD can progress to invasive carcinoma[24,29,35]. Therefore, further studies are needed to understand the natural course of LGD to determine the most effective management option for follow-up treatment.

DISCREPANCIES BETWEEN BIOPSY AND ER

The endoscopic forceps biopsy (EFB) is crucial for grading pre-neoplastic gastric lesions and determining an appropriate treatment strategy. Because EFB specimens are not representative of the entire lesion, significant histologic discrepancies have been found between diagnoses based on EFB and subsequent ER (Figure 1). Recent advances in technology such as image-enhanced endoscopy with narrow-band imaging have led to improvements in the diagnostic accuracy of gastric lesions. However, the discrepancy between pre-endoscopic and post-ER diagnoses remains a concern[36]. Several studies have indicated that pretreatment EFB is inadequate for obtaining a correct diagnosis. We retrospectively reviewed 285 lesions that were initially diagnosed as LGD by EFB[37]. After ER, 46 LGDs (16.1%) showed an upgraded histology: 22 HGD (7.7%) and 24 differentiated adenocarcinoma (8.4%)[37]. In another study from South Korea, Kim *et al*[38] reported that the histologic discrepancy rate was 18.7% (51/273) in LGDs detected using forceps biopsy. Among 51 upgraded lesions, 24 lesions (8.8%) were upgraded to a diagnosis of adenocarcinoma.

Discrepancies in EFB and ER diagnoses contribute to the suboptimal treatment of biopsy-proven LGDs. Therefore, it is essential to identify the risk factors affecting these discrepancies for the proper management of LGD. We found that a lesion size ⩾ 2 cm, surface erythema and a depressed-type lesion were significant predictors of upgraded LGDs. Several studies have reported similar results regarding the endoscopic risk factors for histologic discrepancies in patients with LGD (Figure 2). Kim *et al*[38] reported that lesion size and the presence of spontaneous bleeding were significant factors predicting an upgraded histology after ER; in contrast, the presence of whitish discoloration was a significant negative factor. In a different retrospective

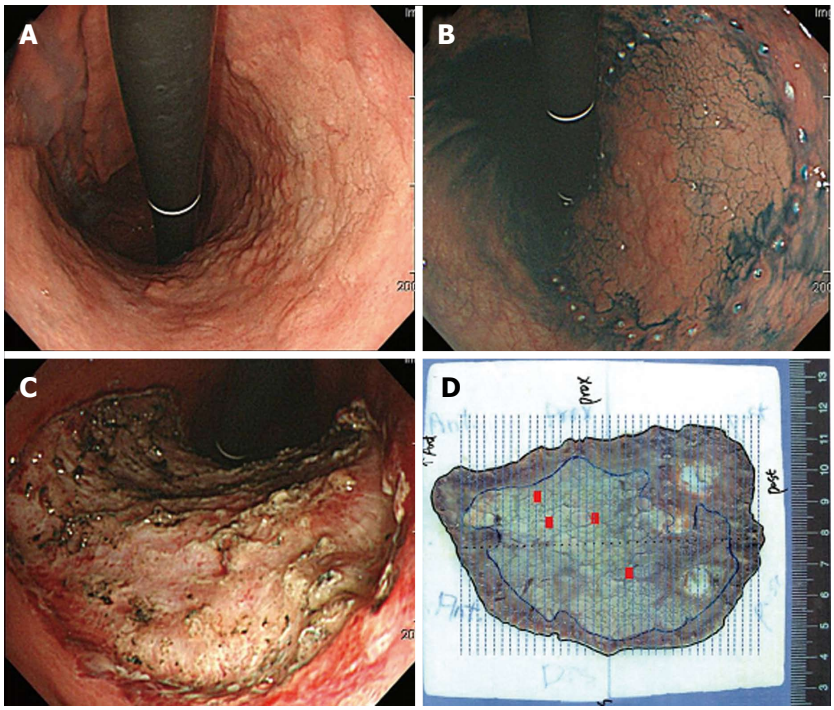

Figure 1 A lesion with a histologic upgraded from extended low-grade dysplasia to adenocarcinoma following endoscopic submucosal dissection. A: White light endoscopy reveals a large elevated mucosal lesion with nodularity in the lesser curvature side of the body. This lesion was diagnosed as LGD by the endoscopic forceps biopsy; B: This lesion is removed by ESD; C: A large mucosal defect is noted over the gastric body after ESD; D: Mapping of the resected specimen. The tumor size is 75 mm, focal cancer lesions (red bar) mixed with LGD are evident. The lateral and vertical margins are free from tumor. LGD: Low-grade dysplasia; ESD: Endoscopic submucosal dissection.

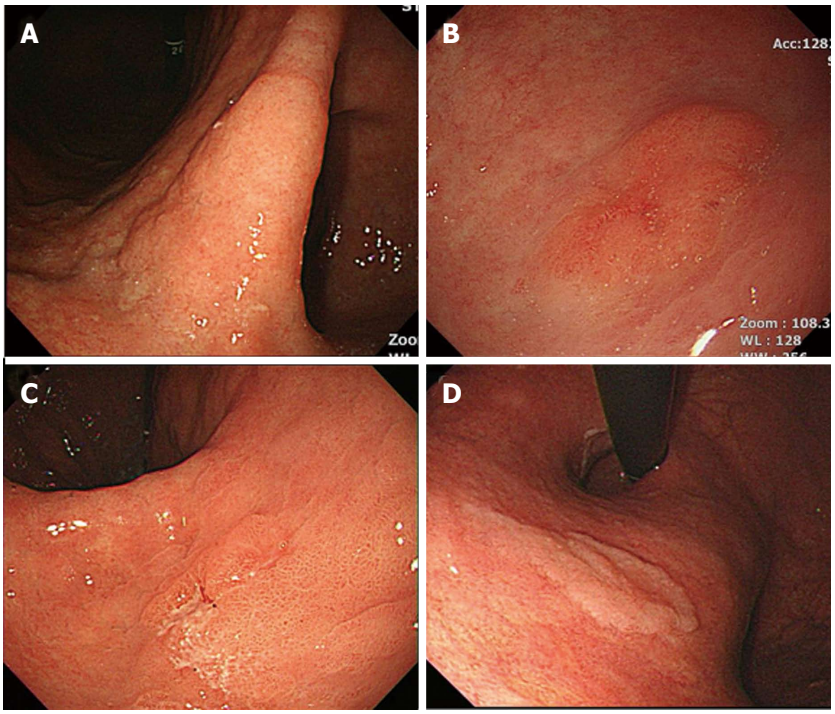

Figure 2 Endoscopic images of biopsy-proven low-grade dysplasia. A-C: lesion size > 2 cm (A), surface erythema (B), and depressed appearance (C) are endoscopic risk factors for an upgraded histology after endoscopic resection; D: In contrast, the presence of whitish discoloration was a negative factor.

study, Cho *et al*[28] demonstrated that a lesion size ⩾ 1 cm, depressed morphology, and erythema were significantly associated with HGD and carcinoma. In a study from Japan[39], a lesion size > 2 cm and depressed appearance were significant independent factors suggesting cancer. To summarize, lesions of larger size and morphology with surface erythema and depression in biopsy-proven LGDs were predictive of an upgraded histology after ER. Therefore, when selecting treatment methods for these lesions, the collection method of the suspected malignant foci should be taken into consideration. ER should be considered for diagnostic and therapeutic purposes in lesions with these risk factors.

MANAGEMENT

In developing a therapeutic plan for LGD management, it is important to identify LGDs that have histological and classical risk factors for GC progression. In South Korea, ERs-including endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD)-are performed widely for the treatment of gastric adenoma, in which early GC and gastric adenoma

are prevalent. According to the revised Vienna classification, ER or follow-up is recommended for noninvasive category 3 LGD lesions, while category 4 lesions such as HGD, non-invasive carcinoma and intramucosal carcinoma should be removed by endoscopic or surgical resection[20]. Some investigators have suggested regular endoscopic surveillance with repetitive biopsy, while others have proposed ER for accurate diagnosis and treatment of LGDs. As mentioned earlier, various factors account for these discrepancies, including differences in diagnostic criteria, inconsistent results among studies of the natural course in LGD, and histologic discrepancies in EFB and ER.

Recent advances in endoscopic techniques have enabled the removal and histological diagnosis of most intra-mucosal lesions regardless of size, shape and location in the stomach[40]. However, performing resections in all patients with LGDs with relatively low malignant potential may lead to significant increases in cost, procedure time, risk of complication, and requirement for advanced technical skills. Although EMR is an easily and rapidly applicable method for therapeutic and diagnostic modalities, it has some limitations. Conventional EMR techniques are unreliable for lesion > 2 cm in diameter due to high rates of positive lateral and/or deep resection margins[41,42]. Even in lesions < 2 cm, the complete resection rate with EMR was 33%-76%[43,44]. Lesion factors, such as tumor size and location, contribute to the difficulty of en bloc resection. To overcome these problems, the development of ESD has allowed complete resection regardless of tumor size and location. In a meta-analysis[45], ESD was significantly more effective than EMR for en bloc resection, complete resection, curative resection and local recurrence. Whereas intra-operative bleeding, perforation risk, and operation time were significantly greater for ESD, overall bleeding risk and all-cause mortality did not differ significantly between ESD and EMR. One meta-analysis[46] showed that procedure-related bleeding (OR = 2.2, 95%CI: 1.58-30.7) and perforation rates (OR = 4.09, 95%CI: 2.47-6.80) during ESD were much higher compared with those for EMR. However, these were not statistically significant in another meta-analysis including 12 studies[45]. Both studies[45,46] showed that ESD was more time-consuming.

Several studies have evaluated endoscopic techniques as a treatment for LGD. Kim *et al*[47] compared the therapeutic outcomes of ESD and EMR in histologically confirmed LGD cases. The en bloc resection rate was significantly lower in the EMR groups (31.1%) compared with the ESD group (75.0%) (P < 0.001). However, no significant difference was observed in the prevalence of remnant lesion or recurrence rate (P = 0.911). On the other hand, Choi *et al*[48] reported a 96.1% complete resection rate using ESD, and the local recurrence rate was 1.4% in patients with biopsy-proven LGD. In this study, no patient had perforation and four (1.4%) patients had significant post-ESD bleeding that was treatable by endoscopic intervention. A multicenter study by the Osaka University ESD study group[49] analyzed a total of 468 subjects with GED. The results showed that the complete en bloc resection rate was 97%, and the incidences of post-ESD bleeding, perforation and serious complication were 5.5%, 4.7% and 0.43%, respectively. Miyamoto *et al*[50] reported that tumor size and location of the lesion are important factors that affect the success rate of en bloc resection. Because not all lesions can be resected en bloc for technical difficulty, another treatment option such as ablation therapy should be considered for the treatment of LGDs[51].

As LGD has a relatively high underdiagnosis rate and rarely contains submucosal cancer, a follow-up strategy might result in the opportunity for endoscopic therapy being missed[49]. Furthermore, repeated endoscopic examinations with biopsies might impose a psychological and financial burden on the patient. Based on its efficacy and safety, the use of ESD as a primary procedure for LGD should be considered.

CONCLUSION

The increased use of upper endoscopy has resulted in increased diagnosis of gastric adenoma. Although many investigators have suggested that gastric HGD should be removed due to its high potential for malignancy[20], the treatment of gastric LGD remains controversial. Although previous studies have reported inconsistent results regarding the risk of LGD progression to invasive carcinoma, such progression can occur during follow-up. Additionally, the rate of upgraded diagnosis in biopsy-proven LGDs is high. Considering these results, the use of ER might enhance treatment and diagnosis, especially of lesions with risk factors such as large size, surface erythema or depressed morphology. Furthermore, the incidence of fatal complications of ESD has been extremely low, with excellent therapeutic and diagnostic outcomes. Therefore, ESD should be applied in preference to EMR.

REFERENCES

1 **Kamangar F**, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol* 2006; **24**: 2137-2150 [PMID: 16682732 DOI: 10.1200/JCO.2005.05.2308]

2 **Correa P**. A human model of gastric carcinogenesis. *Cancer Res* 1988; **48**: 3554-3560 [PMID: 3288329]

3 **Ming SC**, Bajtai A, Correa P, Elster K, Jarvi OH, Munoz N, Nagayo T, Stemmerman GN. Gastric dysplasia. Significance and pathologic criteria. *Cancer* 1984; **54**: 1794-1801 [PMID: 6478415 DOI: 10.1002/1097-0142(19841101)54]

4 **Morson BC**, Sobin LH, Grundmann E, Johansen A, Nagayo T, Serck-Hanssen A. Precancerous conditions and epithelial dysplasia in the stomach. *J Clin Pathol* 1980; **33**: 711-721 [PMID: 7430384 DOI: 10.1136/jcp.33.8.711]

5 **Yeh JM**, Hur C, Kuntz KM, Ezzati M, Goldie SJ. Cost-effectiveness of treatment and endoscopic surveillance of precancerous lesions

to prevent gastric cancer. *Cancer* 2010; **116**: 2941-2953 [PMID: 20564399 DOI: 10.1002/cncr.25030]
6 **Serck-Hanssen A**. Precancerous lesions of the stomach. *Scand J Gastroenterol Suppl* 1979; **54**: 104-105 [PMID: 295493]
7 **Farinati F**, Rugge M, Di Mario F, Valiante F, Baffa R. Early and advanced gastric cancer in the follow-up of moderate and severe gastric dysplasia patients. A prospective study. I.G.G.E.D.--Interdisciplinary Group on Gastric Epithelial Dysplasia. *Endoscopy* 1993; **25**: 261-264 [PMID: 8330542 DOI: 10.1055/s-2007-1010310]
8 **Bearzi I**, Brancorsini D, Santinelli A, Rezai B, Mannello B, Ranaldi R. Gastric dysplasia: a ten-year follow-up study. *Pathol Res Pract* 1994; **190**: 61-68 [PMID: 8065990 DOI: 10.1016/S0344-0338(11)80497-8]
9 **Kamiya T**, Morishita T, Asakura H, Miura S, Munakata Y, Tsuchiya M. Long-term follow-up study on gastric adenoma and its relation to gastric protruded carcinoma. *Cancer* 1982; **50**: 2496-2503 [PMID: 7139542 DOI: 10.1002/1097-0142(19821201)50]
10 **Orlowska J**, Jarosz D, Pachlewski J, Butruk E. Malignant transformation of benign epithelial gastric polyps. *Am J Gastroenterol* 1995; **90**: 2152-2159 [PMID: 8540506]
11 **Schlemper RJ**, Riddell RH, Kato Y, Borchard F, Cooper HS, Dawsey SM, Dixon MF, Fenoglio-Preiser CM, Fléjou JF, Geboes K, Hattori T, Hirota T, Itabashi M, Iwafuchi M, Iwashita A, Kim YI, Kirchner T, Klimpfinger M, Koike M, Lauwers GY, Lewin KJ, Oberhuber G, Offner F, Price AB, Rubio CA, Shimizu M, Shimoda T, Sipponen P, Solcia E, Stolte M, Watanabe H, Yamabe H. The Vienna classification of gastrointestinal epithelial neoplasia. *Gut* 2000; **47**: 251-255 [PMID: 10896917 DOI: 10.1136/gut.47.2.251]
12 **Goldstein NS**, Lewin KJ. Gastric epithelial dysplasia and adenoma: historical review and histological criteria for grading. *Hum Pathol* 1997; **28**: 127-133 [PMID: 9023391 DOI: 10.1016/S0046-8177(97)90095-2]
13 **Tosi P**, Baak JP, Luzi P, Miracco C, Lio R, Barbini P. Morphometric distinction of low- and high-grade dysplasias in gastric biopsies. *Hum Pathol* 1989; **20**: 839-844 [PMID: 2777240 DOI: 10.1016/0046-8177(89)90094-4]
14 **Riddell RH**, Goldman H, Ransohoff DF, Appelman HD, Fenoglio CM, Haggitt RC, Ahren C, Correa P, Hamilton SR, Morson BC. Dysplasia in inflammatory bowel disease: standardized classification with provisional clinical applications. *Hum Pathol* 1983; **14**: 931-968 [PMID: 6629368 DOI: 10.1016/S0046-8177(83)80175-0]
15 **Grundmann E**. Histologic types and possible initial stages in early gastric carcinoma. *Beitr Pathol* 1975; **154**: 256-280 [PMID: 165808 DOI: 10.1016/S0005-8165(75)80034-5]
16 **Lewin KJ**. Nomenclature problems of gastrointestinal epithelial neoplasia. *Am J Surg Pathol* 1998; **22**: 1043-1047 [PMID: 9737235 DOI: 10.1097/00000478-199809000-00001]
17 **Schlemper RJ**, Kato Y, Stolte M. Review of histological classifications of gastrointestinal epithelial neoplasia: differences in diagnosis of early carcinomas between Japanese and Western pathologists. *J Gastroenterol* 2001; **36**: 445-456 [PMID: 11480788 DOI: 10.1007/s005350170067]
18 **Lee SY**. Gastric adenoma with low-grade dysplasia: two countries, two outcomes. *Dig Dis Sci* 2014; **59**: 235-237 [PMID: 24052193 DOI: 10.1007/s10620-013-2860-1]
19 19**Japanese Gastric Cancer Association.** Japanese classification of gastric carcinoma: 3rd English edition. *Gastric Cancer* 2011; **14**: 101-112 [PMID: 21573743 DOI: 10.1007/s10120-011-0041-5]
20 **Dixon MF**. Gastrointestinal epithelial neoplasia: Vienna revisited. *Gut* 2002; **51**: 130-131 [PMID: 12077106 DOI: 10.1136/gut.51.1.130]
21 **Hamilton S**, Aaltonen L, editors. Pathology and genetics of tumours of the digestive system. Lyon, France: IARC Press, 2000
22 **Ginsberg GG**, Al-Kawas FH, Fleischer DE, Reilly HF, Benjamin SB. Gastric polyps: relationship of size and histology to cancer risk. *Am J Gastroenterol* 1996; **91**: 714-717 [PMID: 8677935]
23 **Tsujitani S**, Furusawa M, Hayashi I. Morphological factors aid in therapeutic decisions concerning gastric adenomas. *Hepatogastroenterology* 1992; **39**: 56-58 [PMID: 1568709]
24 **Park SY**, Jeon SW, Jung MK, Cho CM, Tak WY, Kweon YO, Kim SK, Choi YH. Long-term follow-up study of gastric intraepithelial neoplasias: progression from low-grade dysplasia to invasive carcinoma. *Eur J Gastroenterol Hepatol* 2008; **20**: 966-970 [PMID: 18787462 DOI: 10.1097/MEG.0b013e3283013d58]
25 **de Vries AC**, van Grieken NC, Looman CW, Casparie MK, de Vries E, Meijer GA, Kuipers EJ. Gastric cancer risk in patients with premalignant gastric lesions: a nationwide cohort study in the Netherlands. *Gastroenterology* 2008; **134**: 945-952 [PMID: 18395075 DOI: 10.1053/j.gastro.2008.01.071]
26 **Lauwers GY**, Srivastava A. Gastric preneoplastic lesions and epithelial dysplasia. *Gastroenterol Clin North Am* 2007; **36**: 813-829, vi [PMID: 17996792 DOI: 10.1016/j.gtc.2007.08.008]
27 **Yamada H**, Ikegami M, Shimoda T, Takagi N, Maruyama M. Long-term follow-up study of gastric adenoma/dysplasia. *Endoscopy* 2004; **36**: 390-396 [PMID: 15100945 DOI: 10.1055/s-2004-814330]
28 **Cho SJ**, Choi IJ, Kim CG, Lee JY, Kook MC, Park S, Ryu KW, Lee JH, Kim YW. Risk of high-grade dysplasia or carcinoma in gastric biopsy-proven low-grade dysplasia: an analysis using the Vienna classification. *Endoscopy* 2011; **43**: 465-471 [PMID: 21425043 DOI: 10.1055/s-0030-1256236]
29 **Rugge M**, Cassaro M, Di Mario F, Leo G, Leandro G, Russo VM, Pennelli G, Farinati F. The long term outcome of gastric non-invasive neoplasia. *Gut* 2003; **52**: 1111-1116 [PMID: 12865267 DOI: 10.1136/gut.52.8.1111]
30 **Tsukashita S**, Kushima R, Bamba M, Sugihara H, Hattori T. MUC gene expression and histogenesis of adenocarcinoma of the stomach. *Int J Cancer* 2001; **94**: 166-170 [PMID: 11668493 DOI: 10.1002/ijc.1460]
31 **Minematsu H**, Saito Y, Kakinoki R, Andoh A, Kushima R, Fujiyama Y. Evaluation of mucin expression patterns in gastric borderline (group III) lesions. *J Gastroenterol* 2006; **41**: 547-553 [PMID: 16868802 DOI: 10.1007/s00535-006-1798-x]
32 **Jung SH**, Chung WC, Lee KM, Paik CN, Jung JH, Lee MK, Lee YK, Chung IS. Risk factors in malignant transformation of gastric epithelial neoplasia categorized by the revised Vienna classification: endoscopic, pathological, and immunophenotypic features. *Gastric Cancer* 2010; **13**: 123-130 [PMID: 20602200 DOI: 10.1007/s10120-010-0550-7]
33 **Meining A**, Bayerdörffer E, Müller P, Miehlke S, Lehn N, Hölzel D, Hatz R, Stolte M. Gastric carcinoma risk index in patients infected with Helicobacter pylori. *Virchows Arch* 1998; **432**: 311-314 [PMID: 9565339 DOI: 10.1007/s004280050171]
34 **Miehlke S**, Hackelsberger A, Meining A, Hatz R, Lehn N, Malfertheiner P, Stolte M, Bayerdörffer E. Severe expression of corpus gastritis is characteristic in gastric cancer patients infected with Helicobacter pylori. *Br J Cancer* 1998; **78**: 263-266 [PMID: 9683304 DOI: 10.1038/bjc.1998.475]
35 **Rugge M**, Farinati F, Baffa R, Sonego F, Di Mario F, Leandro G, Valiante F. Gastric epithelial dysplasia in the natural history of gastric cancer: a multicenter prospective follow-up study. Interdisciplinary Group on Gastric Epithelial Dysplasia. *Gastroenterology* 1994; **107**: 1288-1296 [PMID: 7926493]
36 **Mine T**. The role of magnifying endoscopy in the diagnosis of early gastric carcinoma. *J Gastroenterol* 2006; **41**: 397-398 [PMID: 16741625 DOI: 10.1007/s00535-006-1822-1]
37 **Kim MK**, Jang JY, Kim JW, Shim JJ, Lee CK, Chang YW, Choe BK. Is lesion size an independent indication for endoscopic resection of biopsy-proven low-grade gastric dysplasia? *Dig Dis Sci* 2014; **59**: 428-435 [PMID: 23912249 DOI: 10.1007/s10620-013-2805-8]
38 **Kim YJ**, Park JC, Kim JH, Shin SK, Lee SK, Lee YC, Chung JB. Histologic diagnosis based on forceps biopsy is not adequate for determining endoscopic treatment of gastric adenomatous lesions. *Endoscopy* 2010; **42**: 620-626 [PMID: 20623445 DOI: 10.1055/s-0030-1255524]
39 **Kasuga A**, Yamamoto Y, Fujisaki J, Okada K, Omae M, Ishiyama A, Hirasawa T, Chino A, Tsuchida T, Igarashi M, Hoshino E, Yamamoto N, Kawaguchi M, Fujita R. Clinical characterization of gastric lesions initially diagnosed as low-grade adenomas on forceps biopsy. *Dig Endosc* 2012; **24**: 331-338 [PMID: 22925285 DOI: 10.1111/j.1443-1661.2012.01238.x]
40 **Onozato Y**, Ishihara H, Iizuka H, Sohara N, Kakizaki S, Okamura S,

Mori M. Endoscopic submucosal dissection for early gastric cancers and large flat adenomas. *Endoscopy* 2006; **38**: 980-986 [PMID: 17058161 DOI: 10.1055/s-2006-944809]

41 **Tanabe S**, Koizumi W, Kokutou M, Imaizumi H, Ishii K, Kida M, Yokoyama Y, Ohida M, Saigenji K, Shimao H, Mitomi H. Usefulness of endoscopic aspiration mucosectomy as compared with strip biopsy for the treatment of gastric mucosal cancer. *Gastrointest Endosc* 1999; **50**: 819-822 [PMID: 10570343]

42 **Inoue H**, Takeshita K, Hori H, Muraoka Y, Yoneshima H, Endo M. Endoscopic mucosal resection with a cap-fitted panendoscope for esophagus, stomach, and colon mucosal lesions. *Gastrointest Endosc* 1993; **39**: 58-62 [PMID: 8454147]

43 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890 DOI: 10.1016/j.gie.2006.03.932]

44 **Kojima T**, Parra-Blanco A, Takahashi H, Fujita R. Outcome of endoscopic mucosal resection for early gastric cancer: review of the Japanese literature. *Gastrointest Endosc* 1998; **48**: 550-554; discussion 554-555 [PMID: 9831855]

45 **Park YM**, Cho E, Kang HY, Kim JM. The effectiveness and safety of endoscopic submucosal dissection compared with endoscopic mucosal resection for early gastric cancer: a systematic review and metaanalysis. *Surg Endosc* 2011; **25**: 2666-2677 [PMID: 21424201 DOI: 10.1007/s00464-011-1627-z]

46 **Cao Y**, Liao C, Tan A, Gao Y, Mo Z, Gao F. Meta-analysis of endoscopic submucosal dissection versus endoscopic mucosal resection for tumors of the gastrointestinal tract. *Endoscopy* 2009; **41**: 751-757 [PMID: 19693750 DOI: 10.1055/s-0029-1215053]

47 **Kim SY**, Sung JK, Moon HS, Kim KS, Jung IS, Yoon BY, Kim BH, Ko KH, Jeong HY. Is endoscopic mucosal resection a sufficient treatment for low-grade gastric epithelial dysplasia? *Gut Liver* 2012; **6**: 446-451 [PMID: 23170148 DOI: 10.5009/gnl.2012.6.4.446]

48 **Choi CW**, Kang DH, Kim HW, Park SB, Kim S, Cho M. Endoscopic submucosal dissection as a treatment for gastric adenomatous polyps: predictive factors for early gastric cancer. *Scand J Gastroenterol* 2012; **47**: 1218-1225 [PMID: 22839759 DOI: 10.3109/00365521.2012.666674]

49 **Kato M**, Nishida T, Tsutsui S, Komori M, Michida T, Yamamoto K, Kawai N, Kitamura S, Zushi S, Nishihara A, Nakanishi F, Kinoshita K, Yamada T, Iijima H, Tsujii M, Hayashi N. Endoscopic submucosal dissection as a treatment for gastric noninvasive neoplasia: a multicenter study by Osaka University ESD Study Group. *J Gastroenterol* 2011; **46**: 325-331 [PMID: 21107615 DOI: 10.1007/s00535-010-0350-1]

50 **Miyamoto S**, Muto M, Hamamoto Y, Boku N, Ohtsu A, Baba S, Yoshida M, Ohkuwa M, Hosokawa K, Tajiri H, Yoshida S. A new technique for endoscopic mucosal resection with an insulated-tip electrosurgical knife improves the completeness of resection of intramucosal gastric neoplasms. *Gastrointest Endosc* 2002; **55**: 576-581 [PMID: 11923778]

51 **Jung SJ**, Cho SJ, Choi IJ, Kook MC, Kim CG, Lee JY, Park SR, Lee JH, Ryu KW, Kim YW. Argon plasma coagulation is safe and effective for treating smaller gastric lesions with low-grade dysplasia: a comparison with endoscopic submucosal dissection. *Surg Endosc* 2013; **27**: 1211-1218 [PMID: 23076459 DOI: 10.1007/s00464-012-2577-9]

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ORIGINAL ARTICLE

Retrospective Study

Re-bleeding events in patients with obscure gastrointestinal bleeding after negative capsule endoscopy

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Author contributions: Magalhães-Costa P, Bispo M and Chagas C designed the research; Magalhães-Costa P performed the research; Magalhães-Costa P analyzed the data; Magalhães-Costa P wrote the paper; Bispo M, Santos S, Couto G, Matos L and Chagas C critically revised the manuscript.

Ethics approval: This study was reviewed and approved by the Centro Hospitalar de Lisboa Ocidental Institutional Review Board.

Informed consent: All study participants, or their legal guardian, provided informed written consent prior to study enrollment.

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Data sharing: Technical appendix, statistical code, and dataset avaliable from the corresponding author at pmagalhaescosta@gmail.com. Participants gave informed consent for data sharing.

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Abstract

AIM: To investigate long-term re-bleeding events after a negative capsule endoscopy in patients with obscure gastrointestinal bleeding (OGIB) and the risk factors associated with the procedure.

METHODS: Patients referred to Hospital Egas Moniz (Lisboa, Portugal) between January 2006 and October 2012 with OGIB and a negative capsule endoscopy were retrospectively analyzed. The following study variables were included: demographic data, comorbidities, bleeding-related drug use, hemoglobin level, indication for capsule endoscopy, post procedure details, work-up and follow-up. Re-bleeding rates and associated factors were assessed using a Cox proportional hazard analysis. The Kaplan-Meier method was used to estimate the cumulative incidence of re-bleeding at 1, 3 and 5 years, and the differences between factors were evaluated.

RESULTS: The study population consisted of 640 patients referred for OGIB investigation. Wireless capsule endoscopy was deemed negative in 113 patients (17.7%). A total of 64.6% of the population was female, and the median age was 69 years. The median follow-up was forty-eight months (interquartile range 24-60). Re-bleeding occurred in 27.4% of the cases. The median time to re-bleeding was fifteen months (interquartile range 2-33). In 22.6% (n = 7) of the population, small-bowel angiodysplasia was identified as the culprit lesion. A univariate analysis showed that age > 65 years old, chronic kidney disease, aortic stenosis, anticoagulant use and overt OGIB were risk factors for re-bleeding; however, on a multivariate analysis, there were no risk factors for re-bleeding. The cumulative risk of re-bleeding at 1, 3 and 5 years of follow-up was 12.9%, 25.6% and 31.5%, respectively.

Patients who presented with overt OGIB tended to re-bleed sooner (median time for re-bleeding: 8.5 mo *vs* 22 mo).

CONCLUSION: Patients with OGIB despite a negative capsule endoscopy have a significant re-bleeding risk; therefore, these patients require an extended follow-up strategy.

Key words: Capsule endoscopy; Gastrointestinal hemorrhage; Anemia; Angiodysplasia; Risk factors

Core tip: This study describes a large cohort of patients with obscure gastrointestinal bleeding in whom the first capsule endoscopy was negative. Re-bleeding events, risk factors and causes were analyzed. A significant risk of re-bleeding was observed; however, independent predictors for re-bleeding were not identified. Re-bleeding due to small-bowel angiodysplasia was a frequent occurrence; therefore, these patients require an extended follow-up strategy, perhaps involving repeated endoscopic procedures if re-bleeding occurs.

Magalhães-Costa P, Bispo M, Santos S, Couto G, Matos L, Chagas C. Re-bleeding events in patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *World J Gastrointest Endosc* 2015; 7(4): 403-410 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/403.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.403

INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) represents approximately 5% of all gastrointestinal bleeding cases and, in most cases, the culprit lesion located in the small-bowel[1]. OGIB is defined as bleeding from the gastrointestinal tract that persists or recurs without an obvious source, as assessed by esophagogastroduodenoscopy (EGD), colonoscopy and radiologic evaluation of the small-bowel[1]. OGIB is classified as either occult or overt; occult OGIB is characterized by iron deficiency anemia (IDA) with or without a positive fecal occult blood test[1,2], and overt OGIB is characterized by clinically perceptible bleeding that recurs or persists despite negative initial endoscopic (EGD and colonoscopy) and radiologic evaluations. Wireless capsule endoscopy (WCE) is a cost-effective investigation in patients with OGIB[3]. In one study, after a WCE evaluation, there was a significant reduction in hospitalizations, additional investigations and units of blood transfused compared to before WCE[4]. Currently, OGIB is the main indication for a capsule endoscopy study. A myriad of studies have analyzed and compared the diagnostic yield (*vs* other techniques)[5-7] and clinical impact of a positive WCE study on patient outcome[8]. Still, a negative WCE study remains a clinical challenge, and little is known about the long-term follow-up of such patients. Therefore, many questions persist about the "protective effect" of a negative WCE study on future re-bleeding events. To date, there are some conflicting data about the re-bleeding rates and predictive factors linked to a re-bleeding event, and in addition, the median follow-up period varies substantially among studies[9-15]. The aim of this study is to assess the long-term outcome (especially re-bleeding events) after a negative WCE study in patients referred for OGIB investigation and risk factors associated with a re-bleeding event.

MATERIALS AND METHODS

We present a retrospective, observational cohort, single center study. Clinical data were obtained from medical records of all patients referred to our tertiary referral hospital - Endoscopy Unit (Hospital Egas Moniz, Centro Hospitalar Lisboa Ocidental, Lisboa) - to undergo a WCE for OGIB investigation between January 2006 and October 2012. All of the patients presented with overt or occult gastrointestinal bleeding according to guidelines[1]. All patients had at least one negative EGD and ileo-colonoscopy before referral for WCE. After signing a written informed consent, every patient underwent a WCE with a PillCam SB (R) (M2A, from January 2006) or SB2© (since June 2007) capsule endoscopy system (Given Imaging, Yoqneam, Israel) according to the standard protocols[16]. All the procedures were performed in an outpatient setting. Since January 2008, a small-bowel purgative preparation with a 2-L polyethylene glycol solution before WCE was introduced in our protocol. Simethicone was also used on a routine basis before all procedures. Two hours after taking the capsule, patients received a clear liquid diet and, two hours later, a light meal, as recommended in the standard protocol. Eight hours after WCE, the patients returned to the Endoscopy Unit, the data recorder was removed, and images were downloaded. The recordings were independently reviewed by four experienced gastroenterologists (Chagas C, Couto G, Santos S, Bispo M) at 8-10 frames per second using the Rapid® Reader. When possible, the colon was also observed. The WCE findings were classified into three types based on the Saurin classification[17,18] as follows: lesions considered to have a high potential for bleeding (P2); lesions with uncertain bleeding potential (P1); and lesions with no bleeding potential (P0). Positive WCE studies were defined as examinations that identified one or more P1 or P2 lesions, whereas those that identified only P0 or no abnormal lesions were regarded as negative WCE studies. Exclusion criteria were as follows: concomitant or not non-gastrointestinal blood loss (hematuria, hemoptyses and gynecological blood loss), incomplete exams (not

Table 1 Clinical characteristics of patients with obscure gastrointestinal bleeding and a negative capsule endoscopy (*n* = 113)

	% (*n*)
Age	
≤ 65 years old	37.2 (42)
> 65 years old	62.8 (71)
Gender	
Female	64.6 (73)
Male	35.4 (40)
Comorbidities	
Chronic kidney disease	12.4 (14)
Aortic stenosis	6.3 (7)
Prior angiodysplasia	3.5 (4)
Medication	
None relevant	54 (61)
Single anti-platelet agent	16.8 (19)
Anticoagulant	7.1 (8)
NSAID	7.1 (8)
Double anti-platelet agent	5.3 (6)
SSRI	3.5 (4)
Occult OGIB	69 (78)
Iron deficiency anemia	63 (71)
Overt OGIB	31 (35)
Melena	19.5 (22)
Hematochezia	11.5 (13)
[Hb] prior to WCE (median; IQR; g/L)	86 (70-100)
Transfusional needs prior to WCE (RBC units; median; IQR)	1 (1-2)
Technical Issues	
Gastric Transit Time (min; median; IQR)	18 (11-37)
Small-bowel Transit Time (min; median; IQR)	253 (216-323)
WCE per Examiner (%)	
Person A	42.5 (*n* = 48)
Person B	38.9 (*n* = 44)
Person C	9.7 (*n* = 11)
Person D	8.9 (*n* = 10)

NSAID: Non-steroidal anti-inflammatory drugs; SSRI: Selective serotonin reuptake inhibitor; OGIB: Obscure gastrointestinal bleeding; [Hb]: Serum hemoglobin; WCE: Wireless capsule endoscopy; IQR: Interquartile range; RBC: Red blood cells.

reaching the ileocecal valve), poor preparation (as dictated by the examiner) and less than twelve months of follow-up. Negative WCE cases were selected and analyzed. A re-bleeding event was defined as occult re-bleeding [a decrease in 20 g/L of [Hb] - (serum hemoglobin) from the patient baseline] or overt re-bleeding (melena, hematochezia). Cases of re-bleeding due to non-small-bowel pathology (*e.g.*, peptic ulcer disease, erosive esophagitis/gastritis/duodenitis, gastroesophageal varices, colorectal carcinoma, *etc.*) detected during follow-up were excluded from further analysis. The median follow-up for all patients strictly monitored for re-bleeding was forty-eight months (interquartile range 24-60). Study variables included the following: demographic data (patient age and gender), comorbidities (chronic kidney disease, aortic stenosis, prior diagnosis of angiodysplasia), relevant medication [use of anticoagulant, antiplatelet agent/s, nonsteroidal anti-inflammatory drugs (NSAIDs), selective serotonin reuptake inhibitors (SSRIs)], hemoglobin level prior to WCE, indication for WCE (occult or overt - melena/hematochezia OGIB), time from OGIB detection to WCE procedure, post procedure details and follow-up [type of treatment for bleeding, hospital admissions (especially for anemia and/or recurrent gastrointestinal bleeding), blood transfusions, need for iron supplementation, additional endoscopies and surgery, re-bleeding causes (if determined) and patient status at the end of follow-up (on-going investigation or treated successfully)].

Statistical analysis

The Statistical Package for Social Science (version 20.0; SPSS Inc., Chicago, IL, United States) was used for all statistical analysis. Continuous variables are expressed as the mean ± SD or median (interquartile range) as appropriate. Qualitative and quantitative differences between subgroups were analyzed using the χ^2 test or Fisher's exact test for categorical parameters and Student's *t* test or Mann-Whitney test for continuous parameters as appropriate. Univariate and multivariate analyses by Cox proportional hazards regression model was performed to identify factors associated with re-bleeding. After the univariate analysis, variables with a $P < 0.05$ were entered in the multivariate analysis. Effect sizes are expressed as hazard ratios (HRs) and 95%CIs. The Kaplan-Meier method was used to estimate the cumulative incidence of re-bleeding at 1, 3 and 5- years of follow-up, and differences between factors were evaluated using the log-rank test. All statistical tests were 2 sided. Statistical significance was set at $P < 0.05$.

RESULTS

Patient characteristics

During the follow-up period, 640 patients were referred for OGIB investigation. In 113 exams (17.7%), the WCE could not find the culprit lesion and was deemed negative (P0 lesions or no abnormal findings). A summary of baseline characteristics is displayed in Table 1. Among the studied population, 73 patients were female (64.6%), with a median age of 69 years old (interquartile range 56-79); 62.8% (*n* = 71) of the patients were > 65 years old. Forty-five patients (39.8%) were taking bleeding-related drugs (single anti-platelet agent: *n* = 19 (16.8%); anticoagulant: *n* = 8 (7.1%); double anti-platelet agent: *n* = 6 (5.3%); non-steroidal anti-inflammatory (NSAIDs): *n* = 8 (7.1%); SSRI: *n* = 4 (3.5%). Thirty-five out of 113 (31%) presented with overt obscure bleeding (overt OGIB) - melena (*n* = 22; 19.5%) and hematochezia (*n* = 13; 11.5%).

Follow-up

The median follow-up was forty-eight months (interquartile range 24-60). After the exclusion of re-bleeding cases due to non-small-bowel pathology, re-bleeding from the small-bowel (or unknown origin) occurred in thirty-one out of 113 negative WCE studies (27.4%). The median time from index negative WCE

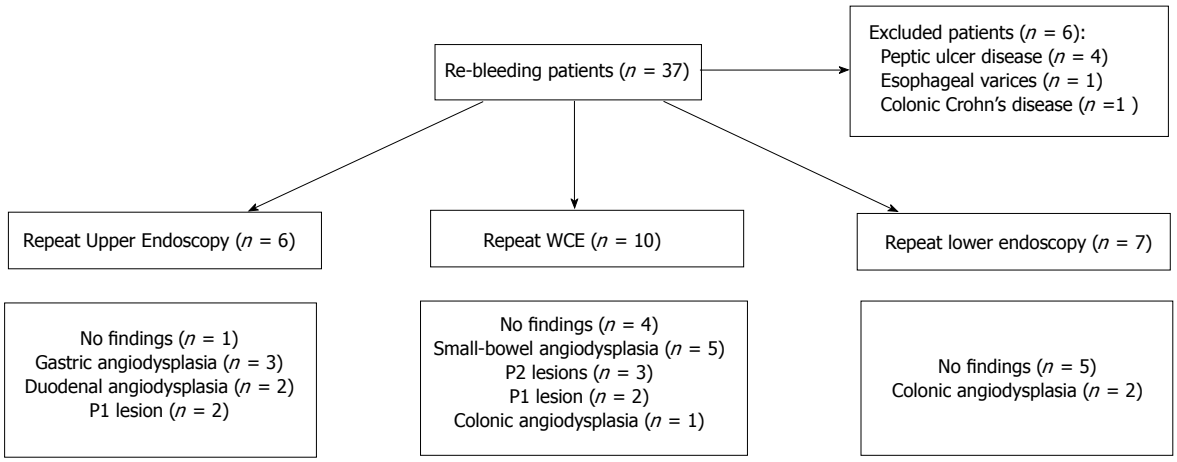

Figure 1 Endoscopic investigations after re-bleeding. WCE: Wireless capsule endoscopy.

Table 2 Characteristics of patients with a negative capsule endoscopy

Variable	All	Non re-bleeders	Re-bleeders	*P*
Age (years old)	67 ± 15	65 ± 15	72 ± 11	0.007
Gender (M/F)	40/73	27/55	13/18	0.386
OGIB presentation (*n*)				
Occult	79	61	18	0.067
Overt	34	21	13	
[Hb] (median)	86	86	79	0.143
Anticoagulant use (*n*)	11	4	7	0.009
Small-bowel Transit time (median)	253	253.5	251.5	0.650

Values are presented in mean ± SD unless stated otherwise. M/F: Male/female; OGIB: Obscure gastrointestinal bleeding; [Hb]: Serum hemoglobin.

to the re-bleeding episode was 15 mo (interquartile range 2-33). Figure 1 provides data regarding endoscopic investigations in patients who re-bled and the associated causes. Among the re-bleeding cases, 29 (94%), were submitted to at least one additional endoscopic procedure. In ten re-bleeding cases (32%), the culprit lesion was/remains unknown; in thirteen cases (42%) an angiodysplasia (small-bowel *n* = 7, colon *n* = 3, stomach *n* = 3) was identified on a subsequent study. Half of the repeated WCE visualized a previously unrecognized small-bowel angiodysplasia. Of those who re-bled from a small-bowel angiodysplasia (*n* = 7), three (all P2 lesions; 43%) were submitted to argon-plasma thermocoagulation (APC) *via* deep enteroscopy (one patient received one APC session, one received two APC sessions and the other patient had to be submitted to five APC sessions), with complete resolution of the gastrointestinal bleeding. Among the total re-bleeding population, five patients (16%) received specific medical therapy (proton pump inhibitor and/or NSAIDs or anticoagulant withdrawal), three patients (9.7%) received non-specific medical therapy (iron supplementation or blood transfusions), and twenty patients (64.5%) did not receive any type of treatment.

Overall, at the end of the follow-up period, twenty-four patients with re-bleeding (77.4%) were considered successfully treated [*i.e.*, despite the re-bleeding event they were asymptomatic, did not require a blood transfusion or iron supplementation and had a normal (Hb) level]. Seven patients (22.6%) remain under close follow-up (requiring regular iron supplementation, blood transfusions).

Risk factor analysis and risk of re-bleeding

A comparison of baseline characteristics between re-bleeders *vs* non re-bleeders is summarized in Table 2. The results of univariate and multivariate analyses regarding factors associated with re-bleeding in patients with a negative WCE are summarized in Table 3. According to a univariate analysis, age > 65 years old, chronic kidney disease, aortic stenosis, anticoagulant use and overt OGIB were detected as factors associated with a significant risk of re-bleeding after a negative WCE. After subjecting the previous variables to a multivariate analysis using a Cox proportional hazards regression model, none of the previously identified factors were able to independently predict future re-bleeding events.

The overall cumulative risk of re-bleeding at 1, 3 and 5-year of follow-up was 12.9%, 25.6% and 31.5%, respectively (Figure 2). To perform a comprehensive analysis, a subgroup comparison between those who initially presented with occult OGIB vs overt OGIB is summarized in Table 4. The overt group tended to re-bleed sooner than the occult group (median time until re-bleeding event: 8.5 mo *vs* 22 mo; *P* = 0.257); however, re-bleeding rates between these two groups were not significantly different (Figure 3; *P* = 0.099).

DISCUSSION

Capsule endoscopy revolutionized the world of gastrointestinal endoscopy, mainly OGIB, by allowing the gastroenterologist to identify the possible cause of OGIB and enhance a directional or specific treatment.

Table 3 Univariate and Multivariate analysis *via* Cox proportional hazard regression model: Re-bleeding risk factors in patients with obscure gastrointestinal bleeding and a negative capsule endoscopy

Variables	Univariate analysis			Multivariate analysis		
	HR	95%CI	*P*	HR	95%CI	*P*
Female	1.408	0.676-2.929	0.361			
Age > 65 years old	3.599	1.364-9.501	0.010	2.591	0.951-7.060	0.063
Chronic kidney disease	3.498	1.265-9.671	0.016	2.252	0.749-6.770	0.148
Aortic stenosis	4.159	1.412-12.247	0.010	1.548	0.352-6.811	0.563
Prior angiodysplasia	3.637	0.851-15.457	0.081			
Bleeding-related drugs	1.586	0.761-3.304	0.219			
Anticoagulant use	3.903	1.542-9.875	0.004	2.699	0.705-10.330	0.147
Overt OGIB	2.104	1.011-4.380	0.047	1.986	0.933-4.231	0.075
[Hb] < 80 g/L	1.857	0.868-3.970	0.111			
Transfusional (RBC) needs prior to WCE	1.122	0.919-1.370	0.257			

Values are presented in mean ± SD unless stated otherwise. HR: Hazard ratio; OGIB: Obscure gastrointestinal bleeding; [Hb]: Serum hemoglobin; RBC: Red blood cells; WCE: Wireless capsule endoscopy.

Capsule endoscopy is a safe and effective technology in the evaluation of small-bowel pathology[1]. Whether a positive or negative WCE study impacts patient outcome remains ill defined. Two recent studies failed to demonstrate that a higher diagnostic yield is related to an improved outcome in patients with OGIB[19,20]. Moreover, on a recent nationwide study by Min *et al*[8], the authors concluded that WCE did not have a significant impact on the long-term outcome of patients with OGIB. Some studies analyzed the long-term outcome defining the occurrence of a re-bleeding event as a primary outcome[9-12,14,15,21]. In the paramount study of Lai *et al*[9], patients with a negative WCE study (n = 18) displayed a low re-bleeding rate (5.6%) when followed for twelve months (median). Another study by Macdonald *et al*[10] that analyzed 49 patients with OGIB (median follow-up = 17 mo) demonstrated a higher re-bleeding rate in this subgroup (negative WCE) of patients (11%) and, when assessing risk factors associated with re-bleeding, identified anticoagulant use as the only independent predictor. Therefore, these first two studies claimed a low re-bleeding probability in patients whose first WCE study was negative, thus advising an expectant approach. Thereafter, it has been postulated that a negative WCE result predicts a favorable prognosis in patients with OGIB and a low risk of re-bleeding. Later, a study by Park *et al*[12] with 51 patients followed for thirty-two months demonstrated a re-bleeding rate of 35.7% in WCE negative patients. Hence, the authors recommended a close follow-up of these patients for at least 2 years. Moreover, two of the most recent studies[14,19] report re-bleeding rates of 23% and 33%, respectively. Additionally, it has been demonstrated that there are no significant difference in the cumulative re-bleeding rates between patients with positive *vs* negative WCE findings[8,12,14].

In the present study, we focused on and followed 113 patients referred for OGIB investigation with a negative WCE. Similar to previous recent retrospective cohort studies[12,14], we demonstrated high re-bleeding rates (27.4%) in this group of patients when followed for longer periods (> 12 mo). Studies that reported lower re-bleeding rates had shorter follow-up periods[9,10,15,22]. To optimize the definition of the risk, we set the minimum follow-up period at 12 mo, and we obtained a median follow-up period of 48 mo (4 years). In approximately 1/3 of the re-bleeders, the culprit lesion remained unknown (*i.e.*, persistently negative endoscopic studies), and when identified, angiodysplasia was the most frequent lesion (42%), mainly small-bowel angiodysplasia (53.8% of all the missed angiodysplasia), which is in line with a previous report[23]. One explanation for these findings might be that some angiodysplasias were missed in the first WCE (although some lesions may have developed after the index WCE). In addition, the natural history of such vascular lesions remains unclear, and their dynamic nature makes them hard to demonstrate consistently. Additionally, it is important to note that knowing that there is a positive correlation between diagnostic yield and small-bowel transit time (SBTT), especially in OGIB[24], as presented in Table 4, SBTT did not differ between re-bleeders and non-re-bleeders; therefore, it is unlikely that re-bleeders had a higher rate of important missed lesions than non-re-bleeders.

In Western countries, angiodysplasia seems to be more frequent than in Asia, and this might be another explanation for the lower re-bleeding rates observed across some of the Asian studies, where small-bowel ulcers dominate the OGIB etiology[8,22]. In patients with recurrent OGIB or IDA who had a negative WCE, a repeat WCE revealed the presence of angiodysplasia in up to 29% of patients (75% of all findings) and led to changes in patient management in two small studies[25,26], which is in line with our data.

Similarly to previous studies[14,15] our median time until re-bleeding was 15 mo, which strengthens the importance of closely following these patients in the first 2 years after index WCE and seemingly over the 3rd year, as our interquartile range for re-bleeding was between 2 and 33 mo. Although the results were not statistically significant (Figure 3; Log-Rank test =

Table 4 Comparison between patients presenting with occult/overt obscure gastrointestinal bleeding

Variable	Occult OGIB	Overt OGIB	*P*
Age (years old)	66	68	0.448
Sex (M/F)	24/54	16/19	0.141
[Hb] (median)	8.9	7.9	0.015
Anticoagulant use (*n*)	8	3	1.000
Time from OGIB to WCE (d; median)	31	29	0.653
Follow-up period (mo; median)	48	42	0.450
Rebleeding cumulative events (at 12 mo) (*n*)	9% (7)	21% (7)	0.133
Rebleeding cumulative events (at 36 mo) (*n*)	20% (13)	39% (11)	
Rebleeding cumulative events (at 60 mo) (*n*)	29% (16)	39% (11)	
Rebleeding cumulative events (at 84 mo) (*n*)	34% (17)	49% (12)	
Rebleeding cumulative events (total) (*n*)	17	12	
Time to rebleeding event (mo; IQR)	22 (6-33)	8.5 (0.5-27)	0.257

Values are presented in mean ± SD unless stated otherwise. OGIB: Obscure gastrointestinal bleeding; M/F: Male/female; [Hb]: Serum hemoglobin; IQR: Interquartile range.

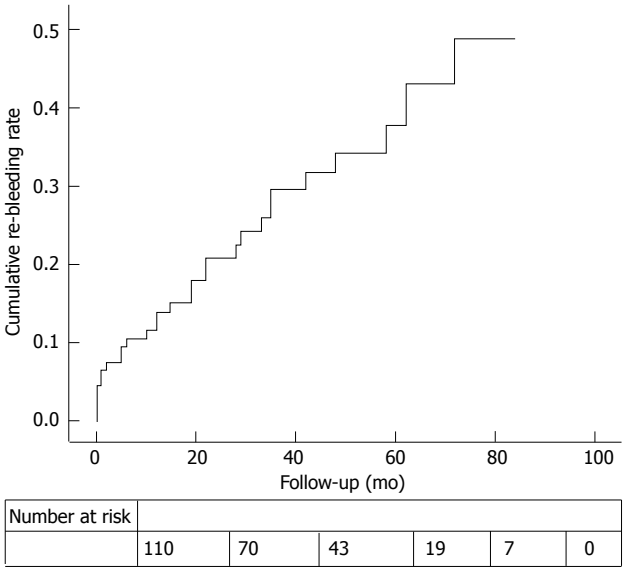

Figure 2 Kaplan-Meier curve showing cumulative re-bleeding rates in the study population.

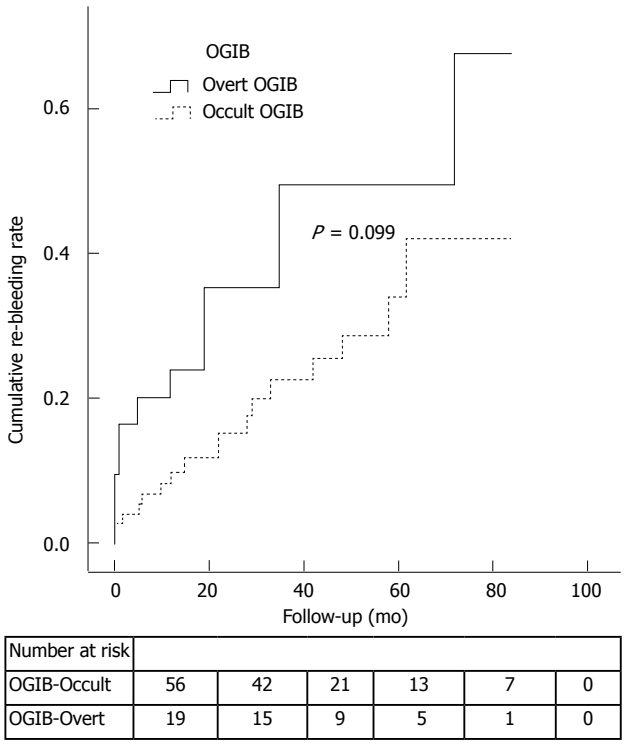

Figure 3 Kaplan-Meier curve showing cumulative rebleeding rates after a negative capsule endoscopy according to initial obscure gastrointestinal bleeding presentation (Log-Rank = 0.099). OGIB: Obscure gastrointestinal bleeding.

0.099), when the subgroups of patients presenting with occult and overt OGIB were analyzed separately, we observed that patients who presented with overt OGIB, in contrast with the occult group, tended to re-bleed sooner (median time until re-bleeding = 8.5 mo *vs* 22 mo).

Previous studies pinpointed anticoagulant intake[10,14] as an independent risk factor for re-bleeding, regardless of WCE results. Others[15] identified younger age (< 65 years old) and the onset of bleeding as independent risk factors for re-bleeding after a negative WCE. Consistent with another recent study[23], our results showed that in a univariate analysis, patients who re-bled were older (HR = 3.599; 95%CI: 1.364-9.501; *P* = 0.010). One explanation is that the prevalence of angiodysplasia (the most frequent re-bleeding lesion in most studies) is known to be higher in older individuals[1], making them a group prone to re-bleeding. It is also known that the incidence of small-bowel vascular lesions (mainly angiodysplasia) in patients with chronic kidney disease is high[27-29], thus making them more likely to re-bleed, as shown in an univariate analysis (HR = 3.498; 95%CI: 1.265-9.671; *P* = 0.016). In our study, as demonstrated previously[14], taking anticoagulants is an important risk factor for re-bleeding (HR = 3.903; 95%CI: 1.542-9.875; *P* = 0.004). Another interesting finding was that even though patients who presented with an overt OGIB tended to re-bleed more than those who presented with occult OGIB (HR = 2.104; 95%CI: 1.011-4.380; *P* = 0.047), a statistically significant difference could

not be found between the groups (Figure 3). Patients with aortic stenosis may have a higher prevalence of angiodysplasia (condition also known as Heyde Syndrome) through the gastrointestinal tract[30,31]. In patients with aortic stenosis, the tendency to harbor angiodysplasia in the gut may pose an elevated risk of re-bleeding events. In this study, there was a trend towards more re-bleeding events in these patients (HR = 4.159; 95%CI: 1.412-12.247; *P* = 0.010). However, when all of these factors were pooled on a multivariate analysis, their statistical significance became null.

Our study limitations were the following: (1) the data were collected from a single tertiary referral hospital and the study had a retrospective design; (2) some of the patients included are followed at other institutions; thus, some follow-up data are missing; and (3) we focused only on patients referred for OGIB with a negative WCE. A comparison of re-bleeding rates with positive WCE cases would have been interesting; however, in a recent study[8], it was demonstrated that re-bleeding rates between positive and negative WCE cases were not significantly different. A leverage point of our study was the very long-term post procedure follow-up period and the relatively large number of patients included.

In conclusion, patients with OGIB with a negative WCE have a significant re-bleeding risk (27.4%), and a follow-up strategy is recommended. In this study, predictive factors for re-bleeding events could not be found using a multivariate analysis; however, a tendency was demonstrated (older age, chronic kidney disease, aortic stenosis, anticoagulants use and overt OGIB), and in future series, a tailored approach/surveillance may be required. Prospective observational studies addressing this topic with long-term follow-up are urgently needed.

COMMENTS

Background

Obscure gastrointestinal bleeding (OGIB) is defined as occult or overt gastrointestinal bleeding of unknown origin that persists or recurs after initial negative endoscopic evaluation (esophagogastroduodenoscopy and colonoscopy). OGIB represents approximately 5% of all gastrointestinal bleeding cases, and the culprit lesion is located in the small-bowel in most instances. Angiodysplasias of the small-bowel account for 30% to 40% of OGIB. Wireless capsule endoscopy (WCE) is a safe and well-accepted technology that enables visualization of the small-bowel.

Research frontiers

A negative (WCE) study remains a clinical challenge, and little is known about the long-term follow-up of such patients. The "protective effect" of a negative WCE study on future re-bleeding events remains controversial. To date, there are some conflicting data about the re-bleeding rates and predictive factors linked to a re-bleeding event, and in addition, median follow-up period varies among studies.

Innovations and breakthroughs

In a retrospective analysis, the authors evaluated the long-term re-bleeding events after a negative WCE in patients referred for OGIB. In a concrete and relatively large cohort from a tertiary center in Europe with long-term follow-up (48 mo), it was found that patients with OGIB, despite a negative WCE, have a significant re-bleeding rate (27.4%). Small-bowel angiodysplasia was the most frequent re-bleeding related lesion (22.6%). The median time from index negative WCE to the re-bleeding episode was fifteen months. After a multivariate analysis, there were no independent predictors for re-bleeding.

Applications

This study suggests that patients with OGIB and a first negative WCE should have an extended follow-up. Although independent predictors for re-bleeding were not found, physicians should recognize some important risk factors for re-bleeding (older age, chronic kidney disease, aortic stenosis, anticoagulants use and overt OGIB) and consider further endoscopic investigations if re-bleeding occurs.

Terminology

OGIB is defined as bleeding from the gastrointestinal tract that persists or recurs without an obvious source being discovered by esophagogastroduodenoscopy, colonoscopy and radiologic evaluation of the small-bowel. Small-bowel capsule endoscopy uses a wireless miniature (pill sized) encapsulated video camera designed to visualize the entire small-bowel.

Peer-review

In a retrospective analysis the authors evaluated the long-term re-bleeding events after a negative wireless capsule endoscopy in patients referred for obscure gastrointestinal bleeding. They found that patients with obscure gastrointestinal bleeding, despite a negative capsule endoscopy, during a 48 mo mo follow-up period have a significant re-bleeding rate (27.4%). They concluded that there are no reliable risk factors that can predict a future re-bleeding event in these patients. The topic is interesting and suitable for publication.

REFERENCES

1 **Raju GS**, Gerson L, Das A, Lewis B. American Gastroenterological Association (AGA) Institute technical review on obscure gastrointestinal bleeding. *Gastroenterology* 2007; **133**: 1697-1717 [PMID: 17983812 DOI: 10.1053/j.gastro.2007.06.007]

2 **Leighton JA**, Goldstein J, Hirota W, Jacobson BC, Johanson JF, Mallery JS, Peterson K, Waring JP, Fanelli RD, Wheeler-Harbaugh J, Baron TH, Faigel DO. Obscure gastrointestinal bleeding. *Gastrointest Endosc* 2003; **58**: 650-655 [PMID: 14595294 DOI: 10.1016/S0016-5107(03)01995-3]

3 **Marmo R**, Rotondano G, Rondonotti E, de Franchis R, D'Incà R, Vettorato MG, Costamagna G, Riccioni ME, Spada C, D'Angella R, Milazzo G, Faraone A, Rizzetto M, Barbon V, Occhipinti P, Saettone S, Iaquinto G, Rossini FP. Capsule enteroscopy vs. other diagnostic procedures in diagnosing obscure gastrointestinal bleeding: a cost-effectiveness study. *Eur J Gastroenterol Hepatol* 2007; **19**: 535-542 [PMID: 17556898 DOI: 10.1097/MEG.0b013e32812144dd]

4 **Carey EJ**, Leighton JA, Heigh RI, Shiff AD, Sharma VK, Post JK, Fleischer DE. A single-center experience of 260 consecutive patients undergoing capsule endoscopy for obscure gastrointestinal bleeding. *Am J Gastroenterol* 2007; **102**: 89-95 [PMID: 17100969 DOI: 10.1111/j.1572-0241.2006.00941.x]

5 **Leighton JA**, Triester SL, Sharma VK. Capsule endoscopy: a meta-analysis for use with obscure gastrointestinal bleeding and Crohn's disease. *Gastrointest Endosc Clin N Am* 2006; **16**: 229-250 [PMID: 16644453 DOI: 10.1016/j.giec.2006.03.004]

6 **Liao Z**, Gao R, Xu C, Li ZS. Indications and detection, completion, and retention rates of small-bowel capsule endoscopy: a systematic review. *Gastrointest Endosc* 2010; **71**: 280-286 [PMID: 20152309 DOI: 10.1016/j.gie.2009.09.031]

7 **Pasha SF**, Leighton JA, Das A, Harrison ME, Decker GA, Fleischer DE, Sharma VK. Double-balloon enteroscopy and capsule endoscopy have comparable diagnostic yield in small-bowel disease: a meta-analysis. *Clin Gastroenterol Hepatol* 2008; **6**: 671-676 [PMID: 18356113 DOI: 10.1016/j.cgh.2008.01.005]

8 **Min YW**, Kim JS, Jeon SW, Jeen YT, Im JP, Cheung DY, Choi MG, Kim JO, Lee KJ, Ye BD, Shim KN, Moon JS, Kim JH, Hong SP, Chang DK. Long-term outcome of capsule endoscopy in obscure gastrointestinal bleeding: a nationwide analysis. *Endoscopy* 2014; **46**: 59-65 [PMID: 24254387 DOI: 10.1055/s-0033-1358803]

9 **Lai LH**, Wong GL, Chow DK, Lau JY, Sung JJ, Leung WK. Long-term follow-up of patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *Am J Gastroenterol* 2006; **101**: 1224-1228 [PMID: 16771942 DOI: 10.1016/j.gie.2006.03.060]

10 **Macdonald J**, Porter V, McNamara D. Negative capsule endoscopy in patients with obscure GI bleeding predicts low rebleeding rates. *Gastrointest Endosc* 2008; **68**: 1122-1127 [PMID: 19028220 DOI: 10.1016/j.gie.2008.06.054]

11 **Lorenceau-Savale C**, Ben-Soussan E, Ramirez S, Antonietti M, Lerebours E, Ducrotté P. Outcome of patients with obscure gastrointestinal bleeding after negative capsule endoscopy: results of a one-year follow-up study. *Gastroenterol Clin Biol* 2010; **34**: 606-611 [PMID: 20822872 DOI: 10.1016/j.gcb.2010.06.009]

12 **Park JJ**, Cheon JH, Kim HM, Park HS, Moon CM, Lee JH, Hong SP, Kim TI, Kim WH. Negative capsule endoscopy without subsequent enteroscopy does not predict lower long-term rebleeding rates in patients with obscure GI bleeding. *Gastrointest Endosc* 2010; **71**: 990-997 [PMID: 20304392 DOI: 10.1016/j.gie.2009.12.009]

13 **Kim JB**, Ye BD, Song Y, Yang DH, Jung KW, Kim KJ, Byeon JS, Myung SJ, Yang SK, Kim JH. Frequency of rebleeding events in obscure gastrointestinal bleeding with negative capsule endoscopy. *J Gastroenterol Hepatol* 2013; **28**: 834-840 [PMID: 23425190 DOI: 10.1111/jgh.12145]

14 **Koh SJ**, Im JP, Kim JW, Kim BG, Lee KL, Kim SG, Kim JS, Jung HC. Long-term outcome in patients with obscure gastrointestinal bleeding after negative capsule endoscopy. *World J Gastroenterol* 2013; **19**: 1632-1638 [PMID: 23539070 DOI: 10.3748/wjg.v19.i10.1632]

15 **Riccioni ME**, Urgesi R, Cianci R, Rizzo G, D'Angelo L, Marmo R, Costamagna G. Negative capsule endoscopy in patients with obscure gastrointestinal bleeding reliable: recurrence of bleeding on long-term follow-up. *World J Gastroenterol* 2013; **19**: 4520-4525 [PMID: 23901227 DOI: 10.3748/wjg.v19.i28.4520]

16 **Mishkin DS**, Chuttani R, Croffie J, Disario J, Liu J, Shah R, Somogyi L, Tierney W, Song LM, Petersen BT. ASGE Technology Status Evaluation Report: wireless capsule endoscopy. *Gastrointest Endosc* 2006; **63**: 539-545 [PMID: 16564850 DOI: 10.1016/j.gie.2006.01.014]

17 **Saurin JC**, Delvaux M, Gaudin JL, Fassler I, Villarejo J, Vahedi K, Bitoun A, Canard JM, Souquet JC, Ponchon T, Florent C, Gay G. Diagnostic value of endoscopic capsule in patients with obscure digestive bleeding: blinded comparison with video push-enteroscopy. *Endoscopy* 2003; **35**: 576-584 [PMID: 12822092 DOI: 10.1055/s-2003-40244]

18 **Gralnek IM**, Defranchis R, Seidman E, Leighton JA, Legnani P, Lewis BS. Development of a capsule endoscopy scoring index for small bowel mucosal inflammatory change. *Aliment Pharmacol Ther* 2008; **27**: 146-154 [PMID: 17956598 DOI: 10.1111/j.1365-2036.2007.03556.x]

19 **Laine L**, Sahota A, Shah A. Does capsule endoscopy improve outcomes in obscure gastrointestinal bleeding? Randomized trial versus dedicated small bowel radiography. *Gastroenterology* 2010; **138**: 1673-1680.e1; quiz e11-e12 [PMID: 20138043 DOI: 10.1053/j.gastro.2010.01.047]

20 **Holleran GE**, Barry SA, Thornton OJ, Dobson MJ, McNamara DA. The use of small bowel capsule endoscopy in iron deficiency anaemia: low impact on outcome in the medium term despite high diagnostic yield. *Eur J Gastroenterol Hepatol* 2013; **25**: 327-332 [PMID: 23183118 DOI: 10.1097/MEG.0b013e32835b7d3a]

21 **Delvaux M**, Fassler I, Gay G. Clinical usefulness of the endoscopic video capsule as the initial intestinal investigation in patients with obscure digestive bleeding: validation of a diagnostic strategy based on the patient outcome after 12 months. *Endoscopy* 2004; **36**: 1067-1073 [PMID: 15578296 DOI: 10.1055/s-2004-826034]

22 **Pongprasobchai S**, Chitsaeng S, Tanwandee T, Manatsathit S, Kachintorn U. Yield, etiologies and outcomes of capsule endoscopy in Thai patients with obscure gastrointestinal bleeding. *World J Gastrointest Endosc* 2013; **5**: 122-127 [PMID: 23515435 DOI: 10.4253/wjge.v5.i3.122]

23 **Cañas-Ventura A**, Márquez L, Bessa X, Dedeu JM, Puigvehí M, Delgado-Aros S, Ibáñez IA, Seoane A, Barranco L, Bory F, Andreu M, González-Suárez B. Outcome in obscure gastrointestinal bleeding after capsule endoscopy. *World J Gastrointest Endosc* 2013; **5**: 551-558 [PMID: 24255747 DOI: 10.4253/wjge.v5.i11.551]

24 **Westerhof J**, Koornstra JJ, Hoedemaker RA, Sluiter WJ, Kleibeuker JH, Weersma RK. Diagnostic yield of small bowel capsule endoscopy depends on the small bowel transit time. *World J Gastroenterol* 2012; **18**: 1502-1507 [PMID: 22509082 DOI: 10.3748/wjg.v18.i13.1502]

25 **Bar-Meir S**, Eliakim R, Nadler M, Barkay O, Fireman Z, Scapa E, Chowers Y, Bardan E. Second capsule endoscopy for patients with severe iron deficiency anemia. *Gastrointest Endosc* 2004; **60**: 711-713 [PMID: 15557946 DOI: 10.1016/S0016-5107(04)02051-6]

26 **Jones BH**, Fleischer DE, Sharma VK, Heigh RI, Shiff AD, Hernandez JL, Leighton JA. Yield of repeat wireless video capsule endoscopy in patients with obscure gastrointestinal bleeding. *Am J Gastroenterol* 2005; **100**: 1058-1064 [PMID: 15842579 DOI: 10.1111/j.1572-0241.2005.40722.x]

27 **Kawamura H**, Sakai E, Endo H, Taniguchi L, Hata Y, Ezuka A, Nagase H, Kessoku T, Yamada E, Ohkubo H, Higrashi T, Sekino Y, Koide T, Iida H, Nonaka T, Takahashi H, Inamori M, Maeda S, Nakajima A. Characteristics of the small bowel lesions detected by capsule endoscopy in patients with chronic kidney disease. *Gastroenterol Res Pract* 2013; **2013**: 814214 [PMID: 24065987 DOI: 10.1155/2013/814214]

28 **Holleran G**, Hall B, Hussey M, McNamara D. Small bowel angiodysplasia and novel disease associations: a cohort study. *Scand J Gastroenterol* 2013; **48**: 433-438 [PMID: 23356721 DOI: 10.3109/00365521.2012.763178]

29 **Karagiannis S**, Goulas S, Kosmadakis G, Galanis P, Arvanitis D, Boletis J, Georgiou E, Mavrogiannis C. Wireless capsule endoscopy in the investigation of patients with chronic renal failure and obscure gastrointestinal bleeding (preliminary data). *World J Gastroenterol* 2006; **12**: 5182-5185 [PMID: 16937529 DOI: 10.3748/wjg.v12.i32.5182]

30 **Heyde EC**. Gastrointestinal bleeding in aortic stenosis. *N Engl J Med* 1958: 259: 196

31 **Williams RC Jr**. Aortic stenosis and unexplained gastrointestinal bleeding. *Arch Intern Med* 1961; **108**: 859-863

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ORIGINAL ARTICLE

Prospective Study

N-butyl-2-cyanoacrylate, iso-amyl-2-cyanoacrylate and hypertonic glucose with 72% chromated glycerin in gastric varices

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Data sharing: The technical appendix, statistical code, and dataset are available from the corresponding author at saratropical@yahoo.com. The participants gave informed consent for the data sharing.

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Abstract

AIM: To compare n-butyl-2-cyanoacrylate, iso-amyl-2-cyanoacrylate and a mixture of 72% chromated glycerin with hypertonic glucose solution in management of gastric varices.

METHODS: Ninety patients with gastric varices presented to Endoscopy Unit of Ain Shams University Hospital were included. They were randomly allocated into three groups; each group included 30 patients treated with intravariceal sclerosant injections in biweekly sessions till complete obturation of gastric varices; Group I (n-butyl-2-cyanoacrylate; Histoacryl®), Group II (iso-amyl-2-cyanoacrylate; Amcrylate®) and Group III (mixture of 72% chromated glycerin; Scleremo® with glucose solution 25%). All the procedures were performed electively without active bleeding. Recruited patients were followed up for 3 mo.

RESULTS: 26% of Scleremo group had bleeding during puncture *vs* 3.3% in each of the other two groups with significant difference, ($P < 0.05$). None of Scleremo group had needle obstruction *vs* 13.3% in each of the other two groups with no significant difference, ($P > 0.05$). Rebleeding occurred in 13.3% of Histoacryl and Amcrylate groups *vs* 0% in Scleremo group with no significant difference. The in hospital mortality was 6.6% in both Histoacryl and Amcrylate groups, while it was 0% in Scleremo group with no significant difference. In the first and second sessions, the amount of Scleremo needed for obturation was significantly high, while the

amount of Histoacryl was significantly low. Scleremo was the less costly of the two treatments.

CONCLUSION: All used sclerosant substances showed efficacy and success in management of gastric varices with no significant differences except in total amount, cost and bleeding during puncture.

Key words: Gastric varices; N-butyl-2-cyanoacrylate; Iso-amyl-2-cyanoacrylate; Hypertonic glucose solution; 72% chromated glycerin

Core tip: We compared n-butyl-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with hypertonic glucose solution (25%) in management of gastric varices. The study included 90 patients who were randomly allocated into three groups, and each group included 30 patients treated with sclerosant injections in biweekly sessions till complete obturation: Group Ⅰ (Histoacryl®), Group Ⅱ (Amcrylate®) and Group Ⅲ (Scleremo® with Glucose 25%). Patients were followed up for 3 mo. We concluded that all used sclerosants showed efficacy and success in management of gastric varices, without significant differences, except in total amount, cost and bleeding during puncture.

Elwakil R, Montasser MF, Abdelhakam SM, Ibrahim WA. N-butyl-2-cyanoacrylate, iso-amyl-2-cyanoacrylate and hypertonic glucose with 72% chromated glycerin in gastric varices. *World J Gastrointest Endosc* 2015; 7(4): 411-416 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/411.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.411

INTRODUCTION

Varices occur in approximately 50% of cirrhotic patients[1,2]. Gastric varices (GV) are less common than esophageal varices (EV), with a prevalence of approximately 20% in patients with portal hypertension[3], and about 15%-25% of GV bleed during the patient's lifetime[4,5].

The management of GV has not been well studied as that of EV. Both the evaluation and treatment of GV are still controversial[6,7].

Cyanoacrylates are synthetic glues that rapidly polymerize on contact with water or blood[8]. Injection therapy with cyanoacrylates is now considered to be the first-line endoscopic intervention for bleeding GV and for the secondary prevention of gastric variceal bleeding[9].

N-butyl-2-cyanoacrylate (Histoacryl®; Germany) has been used extensively in endoscopic therapy for the last 10 years. Another N-butyl-2-cyanoacrylate (Glubran®; Italy) was recently approved for endoscopic use in Europe[10].

Scleremo, a compound of 72% chromated glycerin, is a polyalcohol that is often considered to be a sclerosant chemical irritant, as it causes cell surface protein denaturation leading to thrombo-fibrosis[11]. The compound is commonly used in Europe, but it has not been approved by the FDA for use in the United States[12].

This work aimed at comparing n-butyl-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with a hypertonic glucose solution (25%) in the management of GV in Egyptian patients.

MATERIALS AND METHODS

Patients and methods

This prospective randomized study was conducted on ninety patients who presented with GV at the Endoscopy Unit of Ain Shams University Hospital. Patients with non-variceal causes of upper gastrointestinal bleeding and those with severe co-morbidities were excluded.

The patients were randomly allocated into three groups. Each group included 30 patients who were treated with sclerosant injections in biweekly sessions until the complete obturation of the GV was achieved, with follow-up of 3 mo: (1) Group Ⅰ (Histoacryl® Group); (2) Group Ⅱ (Amcrylate® Group); and (3) Group Ⅲ (Scleremo® with Glucose 25% Group).

The three groups were matched for age, gender, cause of liver cirrhosis (viral hepatitis B or C), Child score and endoscopic findings (including the number, grade of the EV and the size of GV).

All of the included patients underwent: (1) a complete clinical evaluation; (2) laboratory investigations: CBC, liver profile, viral markers (HBs Ag, HB core Ab, HCV Ab) using the ELISA technique; (3) child classification according to the modified Child Pugh's criteria[13]; (4) abdominal ultrasonography for liver and spleen size, portal vein diameter and ascites; (5) upper gastrointestinal endoscopy using the Pentax video endoscope EG 3440. The EV were classified according to their size at the gastroesophageal junction into 4 grades according to Westaby *et al*[14]; The GV were classified into either gastro-EV or isolated GV according to Sarin *et al*[15]; and (6) therapeutic interventions: The intravariceal injection technique was performed according to Soehendra *et al*[16].

The Histoacryl® was diluted as 0.5 mL histoacryl: 0.8 mL lipidol as a contrast agent to dilute the adhesive material to fill the entire varix and to prevent rapid hardening and the obstruction of the needle. The mixture was injected slowly to minimize the risk of embolization and was followed by the injection of 2 mL of distilled water. The first ml of water was injected to force the material into the varix, and the second ml was injected during the withdrawal of the needle to prevent its obstruction[8].

The Amcrylate® was injected slowly followed by injection of 2 mL distilled water without mixing with any other substances[17].

The Scleremo® was mixed with glucose 25% in a ratio of 1:1. The mixture was injected very slowly and with the waiting for moments inside the variceal lumen after injection to give enough time for the sclerosing material to be in contact with the vessel wall. There was no need for an injection of distilled water[11].

Informed consent was obtained from all of the included patients, and the study protocol was approved by the ethical guidelines committee.

All of the procedures were performed electively, without active bleeding. The patients who had bleeding that occurred immediately or after the procedure were treated with additional injections.

The primary end point of this study was the obturation of the GV. The secondary endpoint was the occurrence of bleeding, whether from the puncture site during or immediately after the injection or delayed bleeding (in-hospital or after discharge) and mortality.

Statistical analysis

The statistical review of the study was performed by a biomedical statistician.

The quantitative variables are presented as the mean and the SD. An unpaired (*t*) test was used for the comparisons.

The qualitative variables are presented as numbers and percentages. The χ^2 test was used for the comparisons.

A value of $P < 0.05$ was considered to be statistically significant (S), $P < 0.01$ was considered to be highly significant (HS), and $P > 0.05$ was considered to be non-significant (NS).

RESULTS

This study included 90 Egyptian patients with chronic liver disease. There were 58 males (64.4%, mean age: 50.88 ± 9.08 years) and 32 females (35.6%, mean age: 49.28 ± 8.11 years). A total of 74 patients (82.2%) had hepatitis C virus (HCV), 12 patients (13.3%) had hepatitis B virus (HBV), and 4 patients (4.4%) had both HCV and HBV. According to the Child-Pugh classification, 18 patients (20%) were class A, 36 patients (40%) were class B, and 36 patients (40%) were class C.

The recruited patients were randomly allocated into three groups that were matched for age, gender, cause of chronic liver disease, Child score and endoscopic findings. Each group included 30 patients who were treated with sclerosant injections in biweekly sessions until the complete obturation of GV was achieved. The groups consisted of Group Ⅰ (the Histoacryl® Group), Group Ⅱ (the Amcrylate® Group) and Group Ⅲ (the Scleremo® with glucose 25% Group).

There were non-significant ($P > 0.05$) differences among the 3 groups regarding previous bleeding or previous sclerotherapy for EVs (93.3%, 66.6% and 93.3%, for Groups Ⅰ, Ⅱ, and Ⅲ, respectively) as shown in Table 1.

Table 1 Previous bleeding and previous sclerotherapy for esophageal varices in the 3 groups *n* (%)

		Histoacryl	Amcrylate	Scleremo with glucose	χ^2	*P* value
Previous bleeding	None	2 (6.6)	10 (33.3)	2 (6.6)	11.6	> 0.05 (NS)
	Once	20 (66.6)	8 (26.6)	20 (66.6)		
	Twice	2 (6.6)	8 (26.6)	4 (13.3)		
	3 times	2 (6.6)	0 (0)	0 (0)		
	4 times	4 (13.3)	4 (13.3)	4 (13.3)		
Previous sclerotherapy for EV	None	2 (6.6)	10 (33.3)	2 (6.6)	16.5	> 0.05 (NS)
	Once	6 (20)	6 (20)	0 (0)		
	Twice	6 (20)	0 (0)	4 (13.3)		
	3 times	2 (6.6)	6 (20)	8 (26.6)		
	4 times	14 (46.6)	6 (20)	16 (53.3)		

EV: Esophageal varices; NS: Non-significant.

The endoscopic findings for the 3 studied groups are shown in Table 2. There were non-significant differences among the 3 groups for the location, the size of the GV and associated EV ($P > 0.05$).

Table 3 shows the non-significant differences among the 3 groups regarding the rate of the obturation of the GV ($P > 0.05$). In the first month, the rate of the obturation was 66.6%, 53.3% and 46.6%; in the second month, the rate of the obturation was 86.6%, 80% and 73.3% and in the third month, the rate of the obturation was 93.3%, 93.3% and 100% in the Histoacryl, Amcrylate and Scleremo groups, respectively.

Regarding the number of sessions needed for the obturation of the GV; in the Histoacryl group, 33.3% of the patients needed one session and 66.6% needed two sessions. In the Amcrylate group, 26.6% of the patients needed one session, 70% needed two sessions and 3.3% needed three sessions. In the Scleremo group, 20% of the patients needed one session, 66.6% needed two sessions and 13.3% needed three sessions.

The amount of the sclerosant used per session is shown in Table 4. In the first and second sessions, a significantly high amount of Scleremo was used compared with the Amcrylate and Histoacryl ($P < 0.05$). In the third session, there was insignificant differences among the amounts of the 3 sclerosant materials used ($P > 0.05$).

Regarding problems with the endoscopy, eight patients (26.6%) in the Scleremo group had bleeding of their GV during the puncture compared with one patient (3.3%) in each of the other two groups, with a significant difference ($P < 0.05$). None of the patients in the Scleremo group had needle obstructions during the injections compared with four patients (13.3%) in each of the other two groups, with non-significant differences ($P > 0.05$).

Table 2 Endoscopic findings among the 3 studied groups *n* (%)

		Histoacryl	Amcrylate	Scleremo with glucose	χ^2	*P* value
Site of GV	Fundal	24 (80)	22 (73.3)	18 (60)	1.514	> 0.05
	Cardiac	6 (20)	8 (26.6)	12 (40)		(NS)
Size of GV	L	10 (33.3)	12 (40)	8 (26.6)	2.68	> 0.05
	M	12 (40)	16 (53.3)	14 (46.6)		(NS)
	S	8 (26.6)	2 (6.6)	8 (26.6)		
Associated EV	No EV	2 (6.6)	6 (20)	0 (0)	7.85	> 0.05
	Grade II EV	10 (33.3)	4 (13.3)	6 (20)		(NS)
	Grade III EV	14 (46.6)	16 (53.3)	18 (60)		
	Grade IV EV	4 (13.3)	4 (13.3)	6 (20)		

GV: Gastric varices; EV: Esophageal varices; L: Large tortuous varices; M: Medium nodular varices; S: Small straight varices; NS: Non-significant.

Table 3 Outcomes of gastric varices for rates of obturation and number of sessions *n* (%)

		Histoacryl	Amcrylate	Scleremo with glucose	χ^2	*P* value
Obturation of varices	1st month	20 (66.6)	16 (53.3)	14 (46.6)	1.4	> 0.05
	2nd month	26 (86.6)	24 (80)	22 (73.3)		(NS)
	3rd month	28 (93.3)	28 (93.3)	30 (100)		
No. of sessions	One	10 (33.3)	8 (26.6)	6 (20)	2.5	> 0.05
	Two	20 (66.6)	21 (70)	20 (66.6)		(NS)
	Three	0 (0)	1 (3.3)	4 (13.3)		

GV: Gastric varices; NS: Non-significant.

Bleeding in the Scleremo group during the puncture was controlled by injecting more of the sclerosing mixture and leaving the needle in the puncture site for few minutes to allow time for the blood to clot and occlusion of the puncture to occur. In 2 of the cases in the Scleremo group (Child C) this maneuver failed to stop the bleeding, and an injection of Histoacryl was used to control the bleeding.

Rebleeding (within 5 d of the injection) occurred in 4 cases (13.3%) in both the Histoacryl and the Amcrylate groups, while no cases (0%) of rebleeding were recorded in the Scleremo group, with a non-significant difference ($P > 0.05$).

Two of the patients (6.6%) in each of the Histoacryl and Amcrylate groups died in the hospital 2 d after the injection (due to hepatic comas), while the mortality rate in the Scleremo group was 0%, with a non-significant difference ($P > 0.05$).

There were insignificant ($P > 0.05$) differences among the 3 groups in complications in the form of chest pain (6.6%, 6.6% and 13.3%) in the Histoacryl, Amcrylate and Scleremo groups, respectively, transient dysphagia (13.3%) in the Amcrylate group only, low grade fever in the Histoacryl group only (6.6%); and ulceration in both the Histoacryl and Amcrylate groups only (13.3% *vs* 6.6%).

Regarding the total cost of the sclerosant materials used in the current study, Scleremo was the least costly compared with the Histoacryl and Amcrylate, as shown in Table 5.

Table 4 Total amount of sclerosant used per session

	Histoacryl	Amcrylate	Scleremo with glucose	*P* value
1st session	42 cc	80 cc	126 cc	< 0.05 (S)
2nd session	20 cc	28 cc	74 cc	< 0.05 (S)
3rd session	0	2 cc	10 cc	> 0.05 (NS)

S: Significant; NS: Non-significant.

Table 5 Amount of sclerosants and their cost

	Histoacryl	Amcrylate	Scleremo with glucose
Amount of one ampoule	0.5 cc	0.5 cc	5.0 cc
Total used amount	62 cc	110 cc	210 cc
No. of all injected ampoules	124	220	42
Cost of one ampoule	88 EGP (14.6 USD)	44 EGP (7.3 USD)	15 EGP (2.5 USD)
Cost of all injected ampoules	10912 EGP (1809 USD)	9680 EGP (1605 USD)	630 EGP (104.5 USD)

EGP: Egyptian Pound; USD: United States Dollar.

DISCUSSION

In contrast to the treatment of EV, the endoscopic treatment of GV is still controversial[18]. Treatment options for GV that have been studied in prospective trials include injections of cyanoacrylate-based tissue adhesives, alcohol, sclerosants, and band ligation[3,4,19-21]. The results from this limited number of small studies had varying success rates and were uncontrolled, making it difficult to draw definitive conclusions about their efficacy or the superiority of one therapy over another[22].

The purpose of this prospective randomized study was to compare the efficacy of n-butyl-2-cyanoacrylate (Histoacryl)®, iso-amyl-2-cyanoacrylate (Amcrylate)® and a mixture of 72% chromated glycerin (Scleremo)® with a hypertonic glucose solution (25%) in the management of GV in Egyptian patients.

The present work shows the obturation of varices in all of the groups, with no significant differences ($P > 0.05$) after three months of follow-up. We observed that the obturation of the GV occurred sooner and with fewer sessions in both the Histoacryl and Amcrylate groups than in the Scleremo group. Similarly, it has been previously reported that glue injections had achieved variceal eradication in approximately 75% of patients (range: 50%-100%)[3].

In comparison with the other types of sclerosants that were used in previous studies, obliteration was achieved in only 32% of the sodium tetradecyl sulphate group and 81% of the hypertonic (50%) glucose water group ($P < 0.05$) in the study of Chang *et al*[7].

The Scleremo (72% chromated glycerin) was useful

primarily in the sclerosis of small vessels. Its principal advantage is that it rarely causes extravasation necrosis; its viscosity also allows maximum surface contact time and avoids the risk of an oily base causing the formation of an embolus. The main problems with Scleremo are that it is difficult to work with because it is extremely viscous, that it can be quite painful on injection, and that the chromate moiety is highly allergic[12].

To our knowledge, there is no previous Egyptian study that addresses the efficacy of Scleremo in the management of GV. In the current study, Scleremo with glucose 25% was characterized as being more economical, with a clean and smooth endoscopic field of vision and fewer side effects. However, bleeding from the puncture site, specific dealing during the injection, its high amount and number of sessions required and a delay in the obturation of the varices were its disadvantages.

El-Wakil[11] investigated the efficacy of Scleremo in the management of bleeding EV and demonstrated that the rate of the eradication of EV in the Scleremo group was 75% in comparison with 60% in the Ethanolamine Oleate group.

In the present study, none of the patients in the Scleremo group had needle obstruction during the injection in comparison with four patients (13.3%) in each of the other two groups, with a non-significant difference ($P > 0.05$). Chang *et al*[7] reported the frequent obstruction of the injection needle when using Histoacryl during the treatment of active gastric variceal bleeding, although it achieved a nearly 100% success rate for the initial hemostasis.

In the current study, rebleeding occurred in 4 cases (13.3%) in both the Histoacryl and Amcrylate groups, while no cases (0%) were recorded in the Scleremo group, with an insignificant difference. Previous studies of glue injections for GV have shown a rebleeding rate ranging from 23%-50%[3,21].

In the current study, the mortality rate was (6.6%) in both the Histoacryl and the Amcrylate group compared with 0% in the Scleremo group, with a non-significant difference.

El-Wakil[11] reported that the mortality rate was 5% in the Ethanoleamine Oleate group, while no fatalities were reported in the Scleremo group during the management of bleeding EV.

Kind *et al*[23] treated 174 cirrhotic patients who had actively bleeding GV with cyanoacrylate and then by weekly sessions until their varices were eradicated. The hemostasis, early rebleeding and hospital mortality rates after the cyanoacrylate treatment were 97.1%, 15.5% and 19.5%, respectively. In approximately 75% of the patients, the GV were successfully obliterated.

In the present work, all of the groups reported some minor complications, with non-significant differences among them, in the form of chest pain (6.6%, 6.6% and 13.3%) for the Histoacryl, Amcrylate and Scleremo groups, respectively, transient dysphagia in the Amcrylate group only (13.3%), low grade fever in the Histoacryl group only (6.6%) and ulceration in both the Histoacryl and Amcrylate groups only (13.3% *vs* 6.6%).

It has been previously reported by Ljubicic *et al*[24] that fever, retrosternal discomfort and dysphagia frequently occur with Histoacryl injections and usually resolve within 48 h.

In the study of El-Wakil[11], the Scleremo showed fewer complications than Ethanoleamine Oleate in the form of chest pain (15% *vs* 40%), transient dysphagia (15% *vs* 40%) and low grade fever (5% *vs* 20%). A large post-sclerotherapy ulcer occurred in (10%) of patients in the Ethanolamine Oleate group, while no ulcers were reported in the Scleremo group.

All of the sclerosant substances that we used (Histoacryl, Amcrylate and Scleremo with glucose 25%) showed both efficacy and success in the management of GV, with no significant differences among them except in the total amount required, their cost and incidences of bleeding during the puncture; however, they did vary in their superiority in some aspects.

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COMMENTS

Background

The endoscopic treatment of gastric varices (GV) is still a matter of debate. Treatment options for GV that have been studied in prospective trials include the injection of cyanoacrylate-based tissue adhesives, alcohol and sclerosants. The results from this limited number of small studies had varying success rates and were uncontrolled, making it difficult to draw definitive conclusions about their efficacy or the superiority of one therapy over another.

Research frontiers

Cyanoacrylates are synthetic glues that rapidly polymerize on contact with water or blood. Scleremo, a compound of 72% chromated glycerin, is a polyalcohol that is considered to be a chemical irritant sclerosant that causes cell surface protein denaturation leading to thrombo-fibrosis. The authors compared n-butyl-2-cyanoacrylate (Histoacryl®), iso-amyl-2-cyanoacrylate (Amcrylate®) and a mixture of 72% chromated glycerin (Scleremo®) with hypertonic glucose solution (25%) in the management of GV. All of the sclerosants showed efficacy and success in the management of GV; they differ in the total amount required, cost and the occurrence of bleeding during the puncture.

Innovations and breakthroughs

This is the first Egyptian study that addresses the efficacy of Scleremo® in the management of GV; it is characterized as being economical and clean, with a smooth endoscopic field of vision and few side effects.

Applications

This study may represent a future strategy for the use of a mixture of 72% chromated glycerin (Scleremo®) with a hypertonic glucose solution (25%) in the management of GV.

Terminology

Variceal obturation employs the injection of sclerosant substances leading to the plugging and thrombosis of the varices and an immediate cast of the vessel, followed by the consequent sloughing of the cast after 1-2 wk.

Peer-review

This is a well-researched and well-written article that will be of interest to the readers and will add to the literature on the management of this condition. The endoscopic treatment of GV is still a matter of debate, and controversy exists

on their evaluation and possible pharmacologic and endoscopic treatment. Additionally, Scleremo appears to be the least costly alternative.

REFERENCES

1 **Luketic VA**, Sanyal AJ. Esophageal varices. I. Clinical presentation, medical therapy, and endoscopic therapy. *Gastroenterol Clin North Am* 2000; **29**: 337-385 [PMID: 10836186 DOI: 10.1016/S0889-8553(05)70119-9]

2 **Yoshida H**, Mamada Y, Taniai N, Tajiri T. New methods for the management of gastric varices. *World J Gastroenterol* 2006; **12**: 5926-5931 [PMID: 17009389 DOI: 10.3748/wjg.v12.i37.5926]

3 **Sarin SK**, Jain AK, Jain M, Gupta R. A randomized controlled trial of cyanoacrylate versus alcohol injection in patients with isolated fundic varices. *Am J Gastroenterol* 2002; **97**: 1010-1015 [PMID: 12003381 DOI: 10.1111/j.1572-0241.2002.05622.x]

4 **Sarin SK**. Long-term follow-up of gastric variceal sclerotherapy: an eleven-year experience. *Gastrointest Endosc* 1997; **46**: 8-14 [PMID: 9260698 DOI: 10.1016/S0016-5107(97)70202-5]

5 **Tajiri T**, Onda M, Yoshida H, Mamada Y, Taniai N, Yamashita K. The natural history of gastric varices. *Hepatogastroenterology* 2002; **49**: 1180-1182 [PMID: 12143231]

6 **Christodoulou D**, Tsianos EV, Kortan P, Marcon N. Gastric and ectopic varices- newer endoscopic options. *Annals of Gastroenterology* 2007; **20**: 95-109

7 **Chang KY**, Wu CS, Chen PC. Prospective, randomized trial of hypertonic glucose water and sodium tetradecyl sulfate for gastric variceal bleeding in patients with advanced liver cirrhosis. *Endoscopy* 1996; **28**: 481-486 [PMID: 8886633 DOI: 10.1055/s-2007-1005527]

8 **Seewald S**, Sriram PV, Naga M, Fennerty MB, Boyer J, Oberti F, Soehendra N. Cyanoacrylate glue in gastric variceal bleeding. *Endoscopy* 2002; **34**: 926-932 [PMID: 12430080 DOI: 10.1055/s-2002-35312]

9 **Ryan BM**, Stockbrugger RW, Ryan JM. A pathophysiologic, gastroenterologic, and radiologic approach to the management of gastric varices. *Gastroenterology* 2004; **126**: 1175-1189 [PMID: 15057756 DOI: 10.1053/j.gastro.2004.01.058]

10 **Petersen B**, Barkun A, Carpenter S, Chotiprasidhi P, Chuttani R, Silverman W, Hussain N, Liu J, Taitelbaum G, Ginsberg GG. Tissue adhesives and fibrin glues. *Gastrointest Endosc* 2004; **60**: 327-333 [PMID: 15332018 DOI: 10.1016/S0016-5107(04)01564-0]

11 **El-Wakil MR**. Assessment of chromated glycerin versus ethanolamine oleate in the management of bleeding oesophageal varices in Egyptian patients: a pilot study. *Acta endocopica* 2004; **34**: 691-704

12 **Feied CF**. Mechanism of action of sclerosing agents and rationale for selection of a sclerosing solution. American Vein & Aesthetic Institute. Available from: URL: http://ec.europa.eu/health/scientific_committees/consumer_safety/docs/sccs_o_076.pdf

13 **Pugh RN**, Murray-Lyon IM, Dawson JL, Pietroni MC, Williams R. Transection of the oesophagus for bleeding oesophageal varices. *Br J Surg* 1973; **60**: 646-649 [PMID: 4541913 DOI: 10.1002/bjs.1800600817]

14 **Westaby D**, Melia WM, Macdougall BR, Hegarty JE, Williams R. Injection sclerotherapy for oesophageal varices: a prospective randomised trial of different treatment schedules. *Gut* 1984; **25**: 129-132 [PMID: 6363216 DOI: 10.1136/gut.25.2.129]

15 **Sarin SK**, Kumar A. Gastric varices: profile, classification, and management. *Am J Gastroenterol* 1989; **84**: 1244-1249 [PMID: 2679046]

16 **Soehendra N**, Grimm H, Nam VC, Berger B. N-butyl-2-cyanoacrylate: a supplement to endoscopic sclerotherapy. *Endoscopy* 1987; **19**: 221-224 [PMID: 3500847 DOI: 10.1055/s-2007-1018288]

17 Sarin SK, Negi S. Management of gastric variceal hemorrhage. *Indian J Gastroenterol* 2006; **25** Suppl 1: S25-S28

18 **Binmoeller KF**. Glue for gastric varices: some sticky issues. *Gastrointest Endosc* 2000; **52**: 298-301 [PMID: 10922119 DOI: 10.1067/mge.2000.108042]

19 **Shiha G**, El-Sayed SS. Gastric variceal ligation: a new technique. *Gastrointest Endosc* 1999; **49**: 437-441 [PMID: 10202055 DOI: 10.1016/S0016-5107(99)70039-8]

20 **Thakeb F**, Salama Z, Salama H, Abdel Raouf T, Abdel Kader S, Abdel Hamid H. The value of combined use of N-butyl-2-cyanoacrylate and ethanolamine oleate in the management of bleeding esophagogastric varices. *Endoscopy* 1995; **27**: 358-364 [PMID: 7588349 DOI: 10.1055/s-2007-1005714]

21 **Lo GH**, Lai KH, Cheng JS, Chen MH, Chiang HT. A prospective, randomized trial of butyl cyanoacrylate injection versus band ligation in the management of bleeding gastric varices. *Hepatology* 2001; **33**: 1060-1064 [PMID: 11343232 DOI: 10.1053/jhep.2001.24116]

22 **Qureshi W**, Adler DG, Davila R, Egan J, Hirota W, Leighton J, Rajan E, Zuckerman MJ, Fanelli R, Wheeler-Harbaugh J, Baron TH, Faigel DO. ASGE Guideline: the role of endoscopy in the management of variceal hemorrhage, updated July 2005. *Gastrointest Endosc* 2005; **62**: 651-655 [PMID: 16246673]

23 **Kind R**, Guglielmi A, Rodella L, Lombardo F, Catalano F, Ruzzenente A, Borzellino G, Girlanda R, Leopardi F, Pratticò F, Cordiano C. Bucrylate treatment of bleeding gastric varices: 12 years' experience. *Endoscopy* 2000; **32**: 512-519 [PMID: 10917182 DOI: 10.1055/s-2000-3817]

24 **Ljubicic N**, Spero M. Endoscopic therapy of gastroesophageal variceal haemorrhage. *Acta Clin Croat* 2001; **40**: 117-126

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META-ANALYSIS

Impact of formal training in endoscopic submucosal dissection for early gastrointestinal cancer: A systematic review and a meta-analysis

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Conflict-of-interest: All authors declare non conflict-of-interest.
Data sharing: No additional data are available.

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Abstract

AIM: To summarize the clinical impact of a formal training for the effectiveness and safety of endoscopic submucosal dissection for gastrointestinal cancer.

METHODS: We searched databases including PubMed, EMBASE and the Cochrane Library and Science citation Index updated to August 2014 to include eligible articles. In the Meta-analysis, the main outcome measurements were *en bloc* resection rate, local recurrence rate (R0) and the incidence of procedure-related complications (perforation, bleeding).

RESULTS: *En bloc* resection was high for both, dissecting stomach tumors with an overall percentage of 93.2% (95%CI: 90.5-95.8) and dissecting colorectal tumors with an overall percentage of 89.4% (95%CI: 85.1-93.7). Although the number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins) was small, the overall estimates for R0 resection were 81.4% (95%CI: 72-90.8) for stomach and 85.9% (95%CI: 77.5-95.5) for colorectal tumors, respectively. The analysis showed that the percentage of immediate perforation and bleeding were very low; 4.96 (95%CI: 3.6-6.3) and 1.4% (95%CI: 0.8-1.9) for colorectal tumors and 3.1% (95%CI: 2.0-4.1) and 4.8% (95%CI: 2.8-6.7) for stomach tumors, respectively.

CONCLUSION: In order to obtain the same rate of success of the analyzed studies it is a necessity to create training centers in the western countries during the "several years" of gastroenterology residence first only to teach EGC diagnose and second only to train endoscopic submucosal dissection.

Key words: Endoscopic submucosal dissection; Training

Core tip: Endoscopic submucosal dissection (ESD) has gained widespread use in Asia because of a well-

documented higher *en bloc* and curative resection rates for early neoplastic gastrointestinal lesions. Unfortunately, ESD has not been yet widespread in the West due to remain the very flat learning curve and lack of training resources. In Asia, ESD skills are acquired in the time-honored mentor/apprentice model over a period of few years. Although, there is a great heterogeneity in the medical literature reports about training and learning curve of ESD. In this meta analysis we had analyzed the results from these training centers reports. Because technical maturation often requires measurable standard to achieve.

Tanimoto MA, Guerrero ML, Morita Y, Aguirre-Valadez J, Gomez E, Moctezuma-Velazquez C, Estradas-Trujillo JA, Valdovinos MA, Uscanga LF, Fujita R. Impact of formal training in endoscopic submucosal dissection for early gastrointestinal cancer: A systematic review and a meta-analysis. *World J Gastrointest Endosc* 2015; 7(4): 417-428 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/417.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.417

INTRODUCTION

There are few training centers around the world in which an endoscopy fellow can be trained in the ESD technique. There is probably only a formal ESD training program in Asian countries (Japan, South Korea and China). As ESD is a highly technical and demanding minimal invasive procedure, endoscopists require training before performing the procedure. The operator must possess a good understanding of all aspects of ESD: full knowledge of early GI lesions, the endoscopes, EUS, ESD knives, electro surgical unit parameters, injection agents, sedation, complications and other aspects.

In Asian countries like Japan, South Korea and China, gastrointestinal intraepithelial neoplasm is more prevalent than in Western countries. Accordingly, most medical institutions in Japan provide training (in a stepwise manner): initially, endoscopists participate as an assistant, starting with ESD in the gastric antrum or the rectum with a supervisor, then in the proximal stomach, the colon or the esophagus. In contrast, in Western countries, cases of early gastrointestinal lesions are less diagnosed, resulting in a slow introduction of the ESD technique. Efforts are currently underway to change this situation. Possible solutions to improve training and experience are the use of animal models and the establishment of training centers. Further, deficiencies in training and experience can now be more rapidly overcome as a result of new technologies. As described above, new advances have led to devices that are easy to handle, making it simpler for beginners to perform ESD. Devices with scissors and forceps, like the Clutch Cutter or other covered devices, are easier to use, leading to fewer complications (*e.g*., perforation), although the procedure time is longer than those with non-covered devices. The other new approach in ESD, the use of mesna (2-mercaptoethanesulfonate sodium), may also make submucosal dissection safer and faster.

MATERIALS AND METHODS

Data sources and searches

We searched databases including PubMed, EMBASE and the Cochrane Library and Science citation Index updated to August 2014 to identify related articles in English language that review Endoscopic submucosal dissection training[1-121]. All bibliographies were indentified in the reference lists and were analyzed separately by two experts in ESD during the selection process. The initial searching Medical Subject Headings *(MeSH)* used were "Endoscopic submucosal dissection", afterwards "Endoscopic submucosal dissection training" and finally the articles that does not analyze the operation time, *en bloc* resection rate, local recurrence rate and the incidence of procedure-related complications were excluded (Figure 1A).

Study selection

The inclusion and exclusion criteria are shown in Table 1.

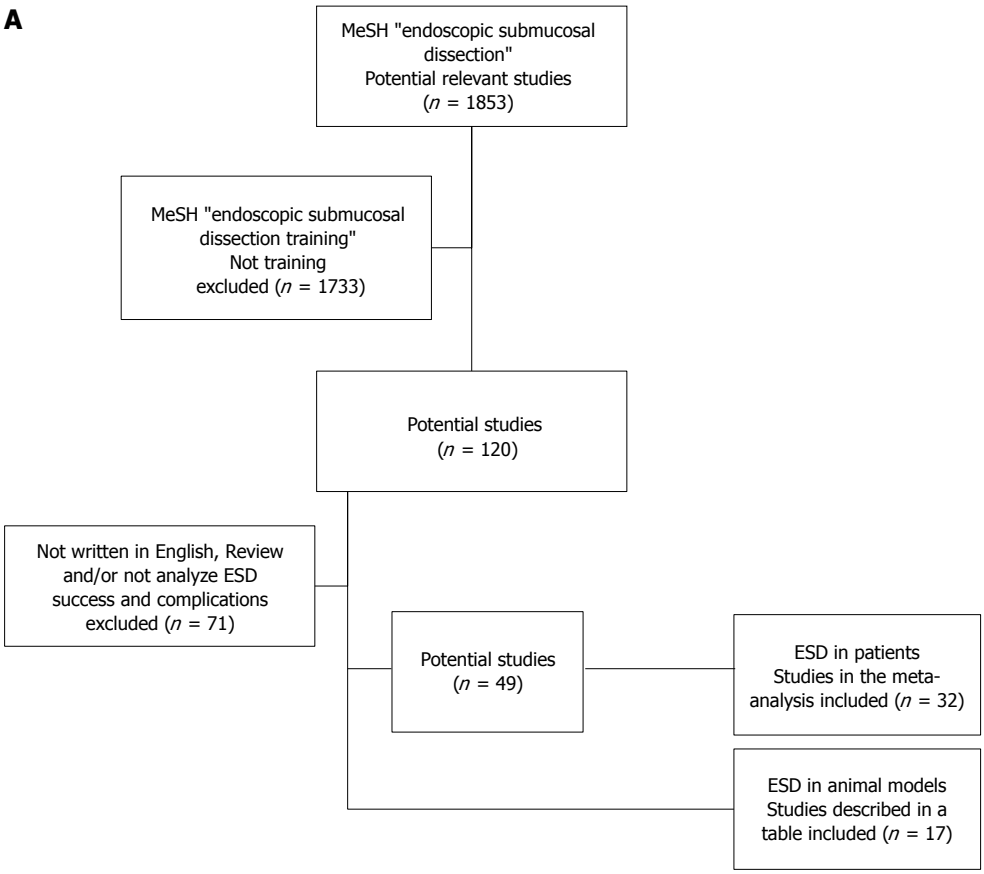
Data extraction and quality assessment

Data were extracted with a predefined MeSH criteria by one investigator and confirmed by the others according to a data extraction form. The following data were collected: year of publication, first author, country, number of participants, site of the lesions and lesions in each group, tumor size and endpoints (*en bloc* resection rate, local recurrence rate, and complications). The definitions of the endpoints were: (1) site of resection; (2) *en bloc* -removal in one piece without fragmentation; (3) local recurrencte rate - during the follow-up an histological diagnosis of tumor at the resected site; (4) operation time - from marking to complete resection; and (5) rate of complications - related bleeding or perforation incidence.

Statistical analysis

Meta-analysis: The statistical review of the study was performed by a biomedical statician of the Infectology department from the National Institute of Medical Sciences and Nutrition S.Z. (Mexico). The DerSimonian/Laird random effects model was used due to expected heterogeneity among studies. Statistical heterogeneity was assessed using the Higgins I^2 test. For the Higgins test, I^2 < 25% indicates low heterogeneity, 25%-50% moderate and > 50% severe heterogeneity. Preplanned analyses included analyses limited to studies including resection of stomach tumors and colorectal tumors using endoscopic submucosal dissection. Data quality assurance and data analysis were conducted using Stata™ 12.0

A



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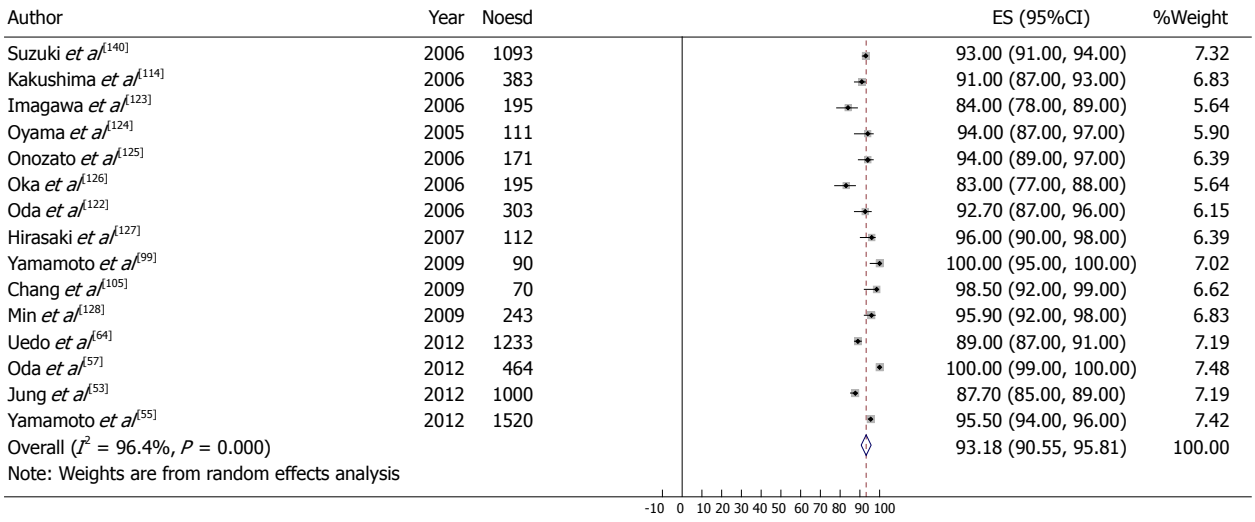
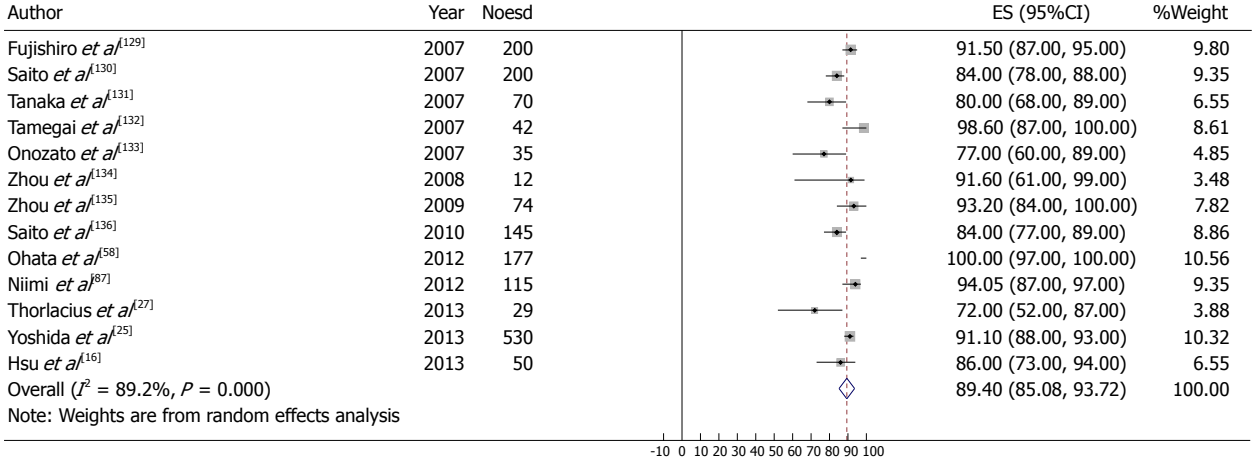


Author	Year	Noesd	ES (95%CI)	%Weight
Suzuki *et al*[140]	2006	1093	93.00 (91.00, 94.00)	7.32
Kakushima *et al*[114]	2006	383	91.00 (87.00, 93.00)	6.83
Imagawa *et al*[123]	2006	195	84.00 (78.00, 89.00)	5.64
Oyama *et al*[124]	2005	111	94.00 (87.00, 97.00)	5.90
Onozato *et al*[125]	2006	171	94.00 (89.00, 97.00)	6.39
Oka *et al*[126]	2006	195	83.00 (77.00, 88.00)	5.64
Oda *et al*[122]	2006	303	92.70 (87.00, 96.00)	6.15
Hirasaki *et al*[127]	2007	112	96.00 (90.00, 98.00)	6.39
Yamamoto *et al*[99]	2009	90	100.00 (95.00, 100.00)	7.02
Chang *et al*[105]	2009	70	98.50 (92.00, 99.00)	6.62
Min *et al*[128]	2009	243	95.90 (92.00, 98.00)	6.83
Uedo *et al*[64]	2012	1233	89.00 (87.00, 91.00)	7.19
Oda *et al*[57]	2012	464	100.00 (99.00, 100.00)	7.48
Jung *et al*[53]	2012	1000	87.70 (85.00, 89.00)	7.19
Yamamoto *et al*[55]	2012	1520	95.50 (94.00, 96.00)	7.42
Overall (I^2 = 96.4%, P = 0.000)			93.18 (90.55, 95.81)	100.00
Note: Weights are from random effects analysis				

C

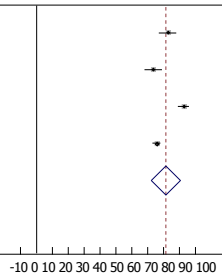


Author	Year	Noesd	ES (95%CI)	%Weight
Fujishiro *et al*[129]	2007	200	91.50 (87.00, 95.00)	9.80
Saito *et al*[130]	2007	200	84.00 (78.00, 88.00)	9.35
Tanaka *et al*[131]	2007	70	80.00 (68.00, 89.00)	6.55
Tamegai *et al*[132]	2007	42	98.60 (87.00, 100.00)	8.61
Onozato *et al*[133]	2007	35	77.00 (60.00, 89.00)	4.85
Zhou *et al*[134]	2008	12	91.60 (61.00, 99.00)	3.48
Zhou *et al*[135]	2009	74	93.20 (84.00, 100.00)	7.82
Saito *et al*[136]	2010	145	84.00 (77.00, 89.00)	8.86
Ohata *et al*[58]	2012	177	100.00 (97.00, 100.00)	10.56
Niimi *et al*[87]	2012	115	94.05 (87.00, 97.00)	9.35
Thorlacius *et al*[27]	2013	29	72.00 (52.00, 87.00)	3.88
Yoshida *et al*[25]	2013	530	91.10 (88.00, 93.00)	10.32
Hsu *et al*[16]	2013	50	86.00 (73.00, 94.00)	6.55
Overall (I^2 = 89.2%, P = 0.000)			89.40 (85.08, 93.72)	100.00
Note: Weights are from random effects analysis				

D

Author	Year	Noesd	ES (95%CI)	%Weight
Oka *et al*[126]	2006	195	83.00 (77.00, 88.00)	24.25
Oda *et al*[122]	2006	303	73.60 (68.00, 79.00)	24.25
Min *et al*[128]	2009	243	93.00 (89.00, 96.00)	25.52
Uedo *et al*[64]	2012	1233	76.00 (73.00, 78.00)	25.97
Overall (I^2 = 95.6%, P = 0.000)			81.45 (72.08, 90.83)	100.00

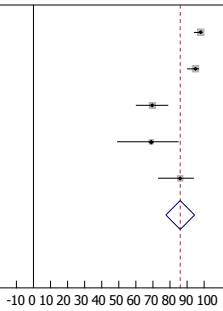
Note: Weights are from random effects analysis



E

Author	Year	Noesd	ES (95%CI)	%Weight
Saito *et al*[136]	2010	145	98.00 (94.00, 99.00)	25.24
Ohata *et al*[58]	2012	177	94.95 (90.00, 97.00)	24.73
Niimi *et al*[87]	2012	115	69.55 (60.00, 79.00)	19.53
Thorlacius *et al*[27]	2013	29	69.00 (49.00, 85.00)	11.98
Hsu *et al*[16]	2013	50	86.00 (73.00, 94.00)	18.53
Overall (I^2 = 90.9%, P = 0.000)			85.99 (77.48, 94.50)	100.00

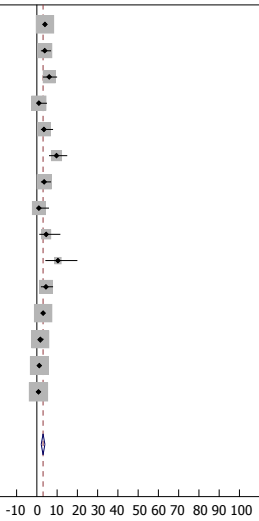
Note: Weights are from random effects analysis



F

Author	Year	Noesd	ES (95%CI)	%Weight
Suzuki *et al*[140]	2006	1093	4.00 (3.00, 5.00)	9.99
Kakushima *et al*[114]	2006	383	3.90 (2.00, 7.00)	6.61
Imagawa *et al*[123]	2006	195	6.10 (3.00, 10.00)	4.76
Oyama *et al*[124]	2005	111	1.00 (0.02, 5.00)	6.63
Onozato *et al*[125]	2006	171	3.50 (2.00, 8.00)	5.61
Oka *et al*[126]	2006	195	9.70 (6.00, 15.00)	3.47
Oda *et al*[122]	2006	303	3.60 (2.00, 7.00)	6.61
Hirasaki *et al*[127]	2007	112	1.00 (0.02, 6.00)	5.63
Yamamoto *et al*[99]	2009	90	4.60 (1.20, 11.60)	2.82
Chang *et al*[105]	2009	70	10.40 (4.20, 20.00)	1.43
Min *et al*[128]	2009	243	4.50 (2.00, 8.00)	5.61
Uedo *et al*[64]	2012	1233	3.10 (2.00, 4.00)	9.99
Oda *et al*[57]	2012	464	1.74 (0.70, 3.30)	9.36
Jung *et al*[53]	2012	1000	1.20 (0.60, 2.10)	10.44
Yamamoto *et al*[55]	2012	1520	0.80 (0.60, 0.90)	11.05
Overall (I^2 = 86.9%, P = 0.000)			3.06 (2.05, 4.07)	100.00

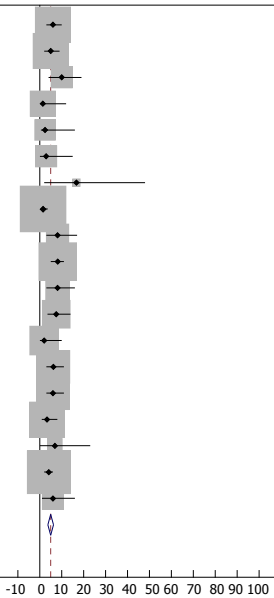
Note: Weights are from random effects analysis



G

Author	Year	Noesd	ES (95%CI)	%Weight
Fujishiro *et al*[129]	2007	200	6.00 (3.00, 10.00)	7.47
Saito *et al*[130]	2007	200	5.00 (2.00, 9.00)	7.47
Tanaka *et al*[131]	2007	70	10.00 (4.00, 19.00)	2.73
Tamegai *et al*[132]	2007	42	1.40 (0.06, 12.00)	3.88
Hurlstone *et al*[137]	2007	42	2.40 (0.50, 16.00)	2.59
Onozato *et al*[133]	2007	35	2.90 (0.07, 15.00)	2.75
Zhou *et al*[134]	2008	12	16.70 (2.00, 48.00)	0.35
Toyonaga *et al*[80]	2010	468	1.50 (0.80, 3.60)	12.57
Zhou *et al*[135]	2009	74	8.10 (3.00, 17.00)	3.05
Isomoto *et al*[138]	2009	292	8.20 (5.00, 11.00)	8.57
Zhou *et al*[135]	2009	74	8.10 (3.00, 16.00)	3.42
Yoshida *et al*[95]	2010	119	7.50 (3.50, 14.00)	4.66
Takeuchi *et al*[139]	2010	50	2.00 (0.05, 10.00)	5.00
Saito *et al*[136]	2010	145	6.20 (3.00, 11.00)	6.51
Ohata *et al*[58]	2012	177	6.00 (3.00, 11.00)	6.51
Niimi *et al*[87]	2012	115	3.30 (0.90, 8.00)	7.37
Thorlacius *et al*[27]	2013	29	6.90 (0.08, 23.00)	1.31
Yoshida *et al*[25]	2013	530	4.10 (2.00, 6.00)	11.07
Hsu *et al*[16]	2013	50	6.00 (1.00, 16.00)	2.73
Overall (I^2 = 46.9%, P = 0.013)			4.96 (3.58, 6.33)	100.00

Note: Weights are from random effects analysis



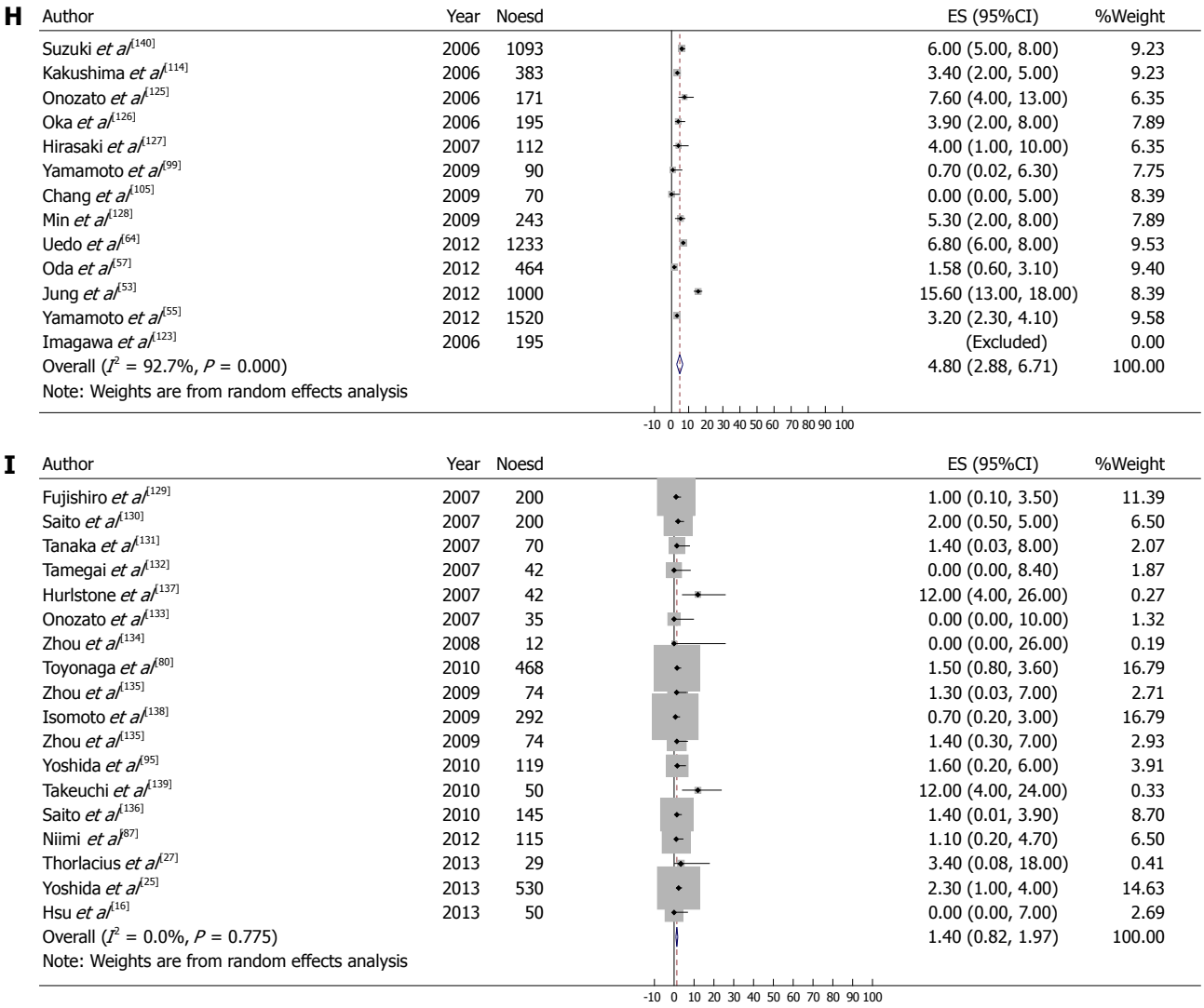


Figure 1 Flow diagram of trial selection and *en-bloc* resection percentage %. A: Flow diagram of trial selection; B: Stomach ESD: *En-bloc* resection percentage %; C: Colorectal ESD: *En-bloc* resection percentage %; D: Stomach ESD: Local recurrence (R0) rate %; E: Colorectal ESD: Local recurrence (R0) rate %; F: Stomach ESD: Perforation rate %; G: Colorectal ESD: Perforation rate %; H: Stomach ESD: Bleeding rate %; I: Colorectal ESD: Bleeding rate %. MeSH: Medical Subject Heading; ESD: Endoscopic submucosal dissection.

(Statistics/Data analysis Special Edition; Statacorp, College Station, Texas, United States). All statistical test in the analysis were two-sided and were conducted with α = 0.05 (95%CI).

RESULTS

Study selection

A total of 1853 were retrieved with the MeSH "endoscopic submucosal dissection" to estimate the potential studies for the meta-analysis. Afterwards, we refine the search including the word training with the MeSH "endoscopic submucosal dissection training" and 1733 were excluded. In the remaining 120 potential studies 71 were excluded because of the exclusion criteria in Table 1[1-12,14-16,18-28,30-33,35-40,42-50,52-62,64-82,95-114].

From the 49 remaining studies 32 were included in the meta-analysis. All of these 32 studies were in human patients respective case/control studies, not randomized controlled trials.

En bloc resection rate (Figures 1B and C)

The present analysis shows that the percentage of *en bloc* resection was high for both, dissecting stomach tumors with an overall percentage of 93.2% (95%CI: 90.5-95.8) and dissecting colorectal tumors with an overall percentage of 89.4% (95%CI: 85.1-93.7).

Local recurrence rate (Figures 1D and E)

Although the number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins) was small, the overall estimates for R0 resection were 81.4% (95%CI: 72-90.8) and 85.9% (95%CI: 77.5-95.5) for stomach and colorectal tumors, respectively.

Procedure-related complications

Data for procedure-related complications were

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
ESD in patients	Case report
Report ESD success *en bloc* resection rate, local recurrence rate	Comment
(R0) and the incidence of procedure-related complications	Review
(perforation, bleeding)	Letters to editor
Written in English	Insufficient data
	Guidelines

ESD: Endoscopic submucosal dissection.

reported in all of the studies included in the meta-analysis. The analysis showed that the percentage of immediate perforation and bleeding were very low.

Perforation rate (Figures 1F and G)

The perforation rate was 3.1% (95%CI: 2.0-4.1) for stomach tumors and 4.96 (95%CI: 3.6-6.3) for colorectal tumors. In most studies, late perforation and bleeding was not reported and thus not included in the current analysis.

Bleeding rate (Figures 1H and I)

The bleeding rate was 4.8% (95%CI: 2.8-6.7) for stomach tumors and 1.4% (95%CI: 0.8-1.9) for colorectal tumors.

Finally, the last 17 studies were in animal models and even though they were not included in the meta-analysis, we resume them in a table that contains: author, year, type of animal model, number of patients, organ and main conclusion (Table 2)[13,17,29,34,41,51,63,83,94,96,115-121].

DISCUSSION

To our knowledge, this systematic review and meta-analysis is the first to analyze the impact of a formal training in ESD for early gastrointestinal cancer. Probably there are ESD formal training centers only in the Asian countries (Japan, China and South Korea). For the above reason almost 100% of the analyzed studies were from Asia. All the studies included in our analysis were done in a formal ESD training setting although most of them does not include the number of trainees and/or a comparison between preceptees *vs* experts and thus not included in the current analysis. The present study shows that the percentage of *en bloc* resection was high for both, dissecting stomach and colorectal tumors. Even with a small number of studies reporting R0 resection (the dissected specimen was revealed free of tumor in both vertical and lateral margins), the overall estimates for R0 resection were 81.4% (95%CI: 72-90.8) and 85.9% (95%CI: 77.5-95.5) for stomach and colorectal tumors respectively. The analysis also showed that the percentage of immediate perforation and bleeding were very low. ESD was developed in Japan in the year 1999 to preserve intact gastrointestinal function and for *en bloc* resection of lesions larger than 2 cm. ESD also has made it possible to resects early gastrointestinal tumors even with large submucosal fibrosis or ulcerative scars in an *en bloc* fashion and it has gradually gained acceptance as a standard treatment for these tumors. The ESD era began with pioneers trained in Japan on South Korea (2003-now) and in China (2006-now) rapidly gaining expertise and acceptance. Hotta *et al*[77] reported that 80 procedures must be carried out to acquire skill at ESD. In order to acquire this skill all the procedures even in animal models must be carried out under supervision of ESD experts and with availability of all the equipment and high trained team. Because this is not just a fact of endoscopic skills but of knowledge, technology and team work. This procedure should never be trained in an experimental ("not supervised by an ESD expert") fashion with animal models just focusing on the dissection technique without firstly make a good analysis of the borders and deepness of the early gastrointestinal cancer (EGC) lesion invasion under an expert supervision. Probably the lack of research, diagnose and case series of early gastrointestinal cancer lesions in the Western countries are due to a lack of formal training centers firstly with certified EGC experts and afterwards ESD experts. In order to obtain the same rate of success of the analyzed studies it is a necessity to create training centers in the western countries during the "several years" of gastroenterology residence first only to teach EGC diagnose and second only to train ESD. In the same manner that the medical techniques should never anticipate the clinic, nor the endoscopic skills, nor the technology or both could substitute tutorial training by an expert.

Although, there is a great heterogeneity in the medical literature reports about training and learning curve of ESD. In this meta analysis we had analyzed the results only from the formal training centers reports. The results presented in the literature that can be included in our meta analysis to clarify the training efficacy concerning the procedure length, completeness and complications such as *En bloc* resection rate, Local recurrence rate, Procedure-related complications, Perforation and Bleeding rate were included. But unfortunately, we can only assume that the procedure was done in a formal training center, such as the one in which some of the authors had been trained. Even when there are very detailed description of the learning curve specially in the Japanese and European reports there is a great heterogeneity of the numeric information presented and thus cannot be included in a meta analysis. There is not uniform information if the procedure was done by a trainee with/without supervision. Also, the analyzed issues in each report has great heterogeneity

Table 2 Endoscopic submucosal dissection studies in animal models

Ref.	Year	Model	*n*	Organ	Main conclusion
González *et al*[17]	2013	Porcine	30	Stomach	A sequential ESD training program of a unique endoscopist contributed to learning ESD for its subsequent application in humans, yielding good results in efficacy and safety
Takizawa *et al*[13]	2013	Porcine	30	Colon	Large mucosal target sites in the rectum and distal colon could be safely removed *en bloc* by means of a hybrid technique, SEMR, with blunt submucosal balloon dissection
Moss *et al*[115]	2012	Porcine	10	Colon	HK-ESD with SG submucosal injection is superior to CSI-EMR for *en bloc* excision of 50 mm diameter lesions. The technique is rapidly learn
Gostout *et al*[41]	2012	Porcine	16	Rectum and colon	Large mucosal target sites in the rectum and distal colon can be safely removed *en bloc* by means of a hybrid technique, ie, submucosal endoscopy with mucosal resection, combining elements of ESD with our SEMF method
Kumano *et al*[117]	2012	Porcine	24	Esophagus	PCH permits more reliable ESD of the esophagus without complications than do SH and HS
Balogh *et al*[51]	2012	Porcine	15	Esophagus	Training in live pig models could help endoscopists to overcome the learning curve and minimize the risk of complications before starting the procedure in humans Reduction in the resection time and low risk of complications, especially bleeding, could be achieved by the application of a flush knife
Tanaka *et al*[63]	2012	Porcine *ex vivo*	10	stomach	*Ex vivo* training model was helpful to endoscopists with experience in gastric ESD in acquiring the basic skills for performing esophageal ESD
Parra-Blanco *et al*[29]	2011	Porcine	18	Stomach	A Clip-band traction technique is feasible, safe, effective, and relatively inexpensive gastric ESD
Von Renteln *et al*[118]	2011	Porcine	12	Stomach	Submucosal mesna injection did not affect ESD procedure times but was associated with a trend toward a lower incidence of intraprocedural bleeding
Tanimoto *et al*[94]	2011	Canine	10	Esophagus	ECE-ESD training is feasible in canine models for postgraduate endoscopy fellows
Hon *et al*[96]	2010	Porcine	10	Colon	Technical proficiency improved by repetition. This setup may be a promising training model for endoscopists working in areas with a low incidence of early gastric cancer
Von Renteln *et al*[119]	2010	Porcine	12	Stomach	The flexible Maryland dissector was demonstrated to be efficient, safe, and feasible for facilitating gastric ESD
Parra-Blanco *et al*[34]	2010	Porcine	30	Esophagus stomach	Training in animal models could help endoscopists overcome the learning curve before starting ESD in humans
Moss *et al*[116]	2010	Porcine	10	Colon	CSI-EMR with submucosal injection of succinylated gelatin is safe and superior to conventional EMR.With experience, total procedure duration is comparable
Von Delius *et al*[120]	2008	Porcine	10	Stomach	PMT-ESD is feasible and safe. With the use of PA-ES, mucosal pieces of various sizes can be resected *en bloc* in gastric locations that are difficult to access by flexible endoscopy alone
Yamasaki *et al*[121]	2006	Porcine	2	Stomach	ESD by submucosal injection of viscous SCMC solution appeared to be an easy, safe, and technically efficient method for dissection of gastric lesions
Neuhaus *et al*[83]	2006	Porcine	17	Stomach	The R-scope (double channel endoscope) facilitated ESD of large gastric areas. Procedure is technically demanding and time-consuming, with a high risk of perforation may be related to an insufficient volume of solution being injected submucosally

HK: Hybrid knife; ESD: Endoscopic submucosal dissection; CSI-EMR: Circumferential submucosal incision endoscopic mucosal resection; SEMF: Mucosal safety valve flap; HS: Hypertonic saline solution; PCH: Photocrosslinkable chitosan hydrogel; SFC: Submucosal fluid cushion; SH: Sodium hyaluronate; ECE: *En bloc* circumferential esophageal; PA-ES: Percutaneously assisted endoscopic surgery; PMT-ESD: PEG-minitrocar ESD; SCMC: Sodium carboxymethylcellulose.

(animal model, human, periods of time, *etc.*) and the results are presented for example in ranges but not in mean ± SD. Because technical maturation often requires measurable standard to achieve. As this procedure become more standardized in the Western countries we can also be able to make more precise comparisons between training centers and learning curve. There are no shortcuts and probably we have to find out the way to establish training centers with the same training scheme as the Asian countries if we are expecting to have similar rates of success, but as always time will say.

COMMENTS

Background

Endoscopic submucosal dissection (ESD) was originally developed to preserve intact gastrointestinal function after *en bloc* resection of early GI cancer lesions larger than 2 cm.

Research frontiers

This systematic review and meta-analysis is the first to analyze the impact of a formal training in ESD for early gastrointestinal cancer.

Innovations and breakthroughs

Authors designed the meta-analysis to systematically evaluate the ESD formal training impact in the early gastrointestinal cancer regarding *en bloc* resection rate, local recurrence rate and procedure-related complications rate.

Applications

The conclusions of this meta-analysis can help the endoscopists to select the right tool to treat early gastrointestinal cancer lesions.

Terminology

ESD is a newly developed technique in which submucosal dissection is carried out using an electrocautery knife to acquire a single-piece specimen, it is developed for *en bloc* removal of large (> 2 cm) GI tract lesions.

Peer-review

This paper is intereting and valuable because technical maturation often requires measurable standard to achieve.

REFERENCES

1 **Spychalski M**, Dziki A. Safe and efficient colorectal endoscopic submucosal dissection in European settings: Is successful implementation of the procedure possible? *Dig Endosc* 2015; **27**: 368-373 [PMID: 25181427 DOI: 10.1111/den.12353]

2 **Yoshida N**, Fernandopulle N, Inada Y, Naito Y, Itoh Y. Training

methods and models for colonoscopic insertion, endoscopic mucosal resection, and endoscopic submucosal dissection. *Dig Dis Sci* 2014; **59**: 2081-2090 [PMID: 25102984 DOI: 10.1007/s10620-014-3308-y]

3 **Sato-Uemura R**, Christiano-Sakai M, Duarte-Jordão R, Guimarães-Horneaux de Moura E, Velázquez-Aviña J, Sobrino-Cossío S, Sakai P. [Endolifter, a new tool for safe and rapid submucosal endoscopic dissection]. *Rev Gastroenterol Mex* 2014; **79**: 161-165 [PMID: 25028055 DOI: 10.1016/j.rgmx.2014.05.004]

4 **Ponsky JL**, Marks JM, Orenstein SB. Retrograde myotomy: a variation in per oral endoscopic myotomy (POEM) technique. *Surg Endosc* 2014; **28**: 3257-3259 [PMID: 24879137]

5 **Draganov PV**, Chang M, Coman RM, Wagh MS, An Q, Gotoda T. Role of observation of live cases done by Japanese experts in the acquisition of ESD skills by a western endoscopist. *World J Gastroenterol* 2014; **20**: 4675-4680 [PMID: 24782619 DOI: 10.3748/wjg.v20.i16.4675]

6 **Aslan F**, Akpinar Z, Seren AR, Alper E, Cekic C, Ekinci N, Vatansever S, Unsal B. Are endoscopic mucosal resection and endoscopic submucosal dissection risky for patients with cirrhosis? *Endoscopy* 2014; **46** Suppl 1 UCTN: E149-E150 [PMID: 24756268 DOI: 10.1055/s-0034-1364946]

7 **Herreros de Tejada A**. ESD training: A challenging path to excellence. *World J Gastrointest Endosc* 2014; **6**: 112-120 [PMID: 24748918 DOI: 10.4253/wjge.v6.i4.112]

8 **Suk KT**, Ham YL, Baik GH, Sung HT, Sohn KM, Kim DY, Hong SH. Efficacy of partial endoscopic submucosal dissection with polypectomy of gastric neoplasm during a learning period. *Hepatogastroenterology* 2013; **60**: 2107-2112 [PMID: 24719955]

9 **Berr F**, Wagner A, Kiesslich T, Friesenbichler P, Neureiter D. Untutored learning curve to establish endoscopic submucosal dissection on competence level. *Digestion* 2014; **89**: 184-193 [PMID: 24714421 DOI: 10.1159/000357805]

10 **Sato K**, Ito S, Kitagawa T, Saida Y, Maetani I. Education and imaging. Gastrointestinal: endoscopic management for a delayed perforation after endoscopic submucosal dissection for early gastric cancer. *J Gastroenterol Hepatol* 2014; **29**: 417 [PMID: 24712042]

11 **Fukami N**. ESD around the world: United States. *Gastrointest Endosc Clin N Am* 2014; **24**: 313-320 [PMID: 24679241 DOI: 10.1016/j.giec.2013.12.004]

12 **Gotoda T**, Ho KY, Soetikno R, Kaltenbach T, Draganov P. Gastric ESD: current status and future directions of devices and training. *Gastrointest Endosc Clin N Am* 2014; **24**: 213-233 [PMID: 24679233 DOI: 10.1016/j.giec.2013.11.009]

13 **Takizawa K**, Knipschield MA, Gostout CJ. Submucosal endoscopy with mucosal resection (SEMR): a new hybrid technique of endoscopic submucosal balloon dissection in the porcine rectosigmoid colon. *Surg Endosc* 2013; **27**: 4457-4462 [PMID: 23836128 DOI: 10.1007/s00465-013-3085-2]

14 **Yoo CH**, Park MI, Park SJ, Moon W, Kim HH, Song JY, Kim do H. Observer variability in gastric neoplasm assessment using the vessel plus surface classification for magnifying endoscopy with narrow band imaging. *Clin Endosc* 2014; **47**: 74-78 [PMID: 24570886 DOI: 10.5946/ce.2014.47.1.74]

15 **Vila JJ**, Kutz M, Fernández-Esparrach G, López-Rosés L, Rodríguez S, Sánchez-Yague A. Endoscopic submucosal dissection in Spain: outcomes and development possibilities. *Rev Esp Enferm Dig* 2013; **105**: 544-552 [PMID: 24467499]

16 **Hsu WH**, Sun MS, Lo HW, Tsai CY, Tsai YJ. Clinical practice of endoscopic submucosal dissection for early colorectal neoplasms by a colonoscopist with limited gastric experience. *Gastroenterol Res Pract* 2013; **2013**: 262171 [PMID: 24391666 DOI: 10.1155/2013/262171]

17 **González N**, Parra-Blanco A, Villa-Gómez M, Gamba A, Taullard A, Silveira A, Sanguinetti A, Olano C, Cohen H. Gastric endoscopic submucosal dissection: from animal model to patient. *World J Gastroenterol* 2013; **19**: 8326-8334 [PMID: 24363524 DOI: 10.3748/wjg.v19.i45.8326]

18 **Yu L**, Xu W, Shen W, Cao L, Liu Y, Li Z, Ding J. Poly(lactic acid-co-glycolic acid)-poly(ethylene glycol)-poly(lactic acid-co-glycolic acid) thermogel as a novel submucosal cushion for endoscopic submucosal dissection. *Acta Biomater* 2014; **10**: 1251-1258 [PMID: 24345554 DOI: 10.1016/j.actbio.2013.12.007]

19 **Iacucci M**, Eustace G, Uraoka T, Saito Y, Fort Gasia M, Love J, Yahagi N. Endoscopic submucosal dissection in the colorectum: Feasibility in the Canadian setting. *Can J Gastroenterol* 2013; **27**: 689-693 [PMID: 24340310]

20 **Draganov PV**, Coman RM, Gotoda T. Training for complex endoscopic procedures: how to incorporate endoscopic submucosal dissection skills in the West? *Expert Rev Gastroenterol Hepatol* 2014; **8**: 119-121 [PMID: 24308749 DOI: 10.1586/17474124.2014.864552]

21 **Gómez V**, Wallace MB. Advances in diagnostic and therapeutic colonoscopy. *Curr Opin Gastroenterol* 2014; **30**: 63-68 [PMID: 24241243 DOI: 10.1097/MOG.0000000000000026]

22 **Kim JY**, Kim WG, Jeon TY, Kim GH, Jeong EH, Kim DH, Park do Y, Lauwers GY. Lymph node metastasis in early gastric cancer: evaluation of a novel method for measuring submucosal invasion and development of a nodal predicting index. *Hum Pathol* 2013; **44**: 2829-2836 [PMID: 24139210 DOI: 10.1016/j.humpath.2013.07.037]

23 **Martinek J**, Stefanova M, Suchanek S, Zavada F, Svobodova B, Strosova A, Zavoral M. Training of different endoscopic skills on ex-vivo animal model. *Simul Healthc* 2014; **9**: 112-119 [PMID: 24096916 DOI: 10.1097/SIH.0b013e31829be99e]

24 **Pham DV**, Shah A, Borao FJ, Gorcey S. Endoscopic submucosal dissection training with ex vivo human gastric remnants. *Surg Endosc* 2014; **28**: 222-226 [PMID: 23996336 DOI: 10.1007/s00464-013-3164-4]

25 **Yoshida N**, Yagi N, Inada Y, Kugai M, Yanagisawa A, Naito Y. Prevention and management of complications of and training for colorectal endoscopic submucosal dissection. *Gastroenterol Res Pract* 2013; **2013**: 287173 [PMID: 23956738 DOI: 10.1155/2013/287173]

26 **Coman RM**, Gotoda T, Draganov PV. Training in endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; **5**: 369-378 [PMID: 23951392 DOI: 10.4253/wjge.v5.i8.369]

27 **Thorlacius H**, Uedo N, Toth E. Implementation of endoscopic submucosal dissection for early colorectal neoplasms in Sweden. *Gastroenterol Res Pract* 2013; **2013**: 758202 [PMID: 23935611 DOI: 10.1155/2013/758202]

28 **Wang HY**, Shih SC, Hung CY, Shieh TY, Chen YB, Chen MJ. Use of artificial tissue to practice endoscopic submucosal dissection. *Endoscopy* 2013; **45** Suppl 2 UCTN: E175-E176 [PMID: 23801289 DOI: 10.1055/s-0032-1326497]

29 **Parra-Blanco A**, González N, González R, Ortiz-Fernández-Sordo J, Ordieres C. Animal models for endoscopic training: do we really need them? *Endoscopy* 2013; **45**: 478-484 [PMID: 23733729 DOI: 10.1055/s-0033-1344153]

30 **Xiong X**, Barkun AN, Waschke K, Martel M. Current status of core and advanced adult gastrointestinal endoscopy training in Canada: Survey of existing accredited programs. *Can J Gastroenterol* 2013; **27**: 267-272 [PMID: 23712301]

31 **Ono S**, Kato M, Nakagawa M, Imai A, Yamamoto K, Shimizu Y. Outcomes and predictive factors of "not self-completion" in gastric endoscopic submucosal dissection for novice operators. *Surg Endosc* 2013; **27**: 3577-3583 [PMID: 23549768 DOI: 10.1007/s00464-013-2929-0]

32 **Uraoka T**, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection: is it suitable in western countries? *J Gastroenterol Hepatol* 2013; **28**: 406-414 [PMID: 23278302 DOI: 10.1111/jgh.12099]

33 **Bok GH**, Cho JY. ESD Hands-on Course Using Ex Vivo and In Vivo Models in South Korea. *Clin Endosc* 2012; **45**: 358-361 [PMID: 23251882 DOI: 10.5946/ce.2012.45.4.358]

34 **Parra-Blanco A**, Gonzalez N, Arnau MR. Ex vivo and in vivo models for endoscopic submucosal dissection training. *Clin Endosc* 2012; **45**: 350-357 [PMID: 23251881 DOI: 10.5946/ce.2012.45.4.350]

35 **Kwon CI**. Endoscopic Submucosal Dissection (ESD) Training and Performing ESD with Accurate and Safe Techniques. *Clin*

Endosc 2012; **45**: 347-349 [PMID: 23251880 DOI: 10.5946/ce.2012.45.4.347]

36 **Ahn JY**, Choi KD, Lee JH, Choi JY, Kim MY, Choi KS, Kim do H, Song HJ, Lee GH, Jung HY, Kim JH, Baek S. Is transnasal endoscope-assisted endoscopic submucosal dissection for gastric neoplasm useful in training beginners? A prospective randomized trial. *Surg Endosc* 2013; **27**: 1158-1165 [PMID: 23093232 DOI: 10.1007/s00464-012-2567-y]

37 **Iacopini F**, Bella A, Costamagna G, Gotoda T, Saito Y, Elisei W, Grossi C, Rigato P, Scozzarro A. Stepwise training in rectal and colonic endoscopic submucosal dissection with differentiated learning curves. *Gastrointest Endosc* 2012; **76**: 1188-1196 [PMID: 23062760 DOI: 10.1016/j.gie.2012.08.024]

38 **Chang DK**. Current status of colorectal endoscopic submucosal dissection in Korea. *Clin Endosc* 2012; **45**: 288-289 [PMID: 22977820 DOI: 10.5946/ce.2012.45.3.288]

39 **Chen MJ**, Liu CY, Chen CJ, Shih SC, Wang HY. Simulating target lesion for endoscopic submucosal dissection training in a live pig model. *Endoscopy* 2012; **44** Suppl 2 UCTN: E300-E301 [PMID: 22933265 DOI: 10.1055/s-0032-1309986]

40 **Kato M**, Nishida T, Yamamoto K, Hayashi S, Kitamura S, Yabuta T, Yoshio T, Nakamura T, Komori M, Kawai N, Nishihara A, Nakanishi F, Nakahara M, Ogiyama H, Kinoshita K, Yamada T, Iijima H, Tsujii M, Takehara T. Scheduled endoscopic surveillance controls secondary cancer after curative endoscopic resection for early gastric cancer: a multicentre retrospective cohort study by Osaka University ESD study group. *Gut* 2013; **62**: 1425-1432 [PMID: 22914298 DOI: 10.1136/gutjnl-2011-301647]

41 **Gostout CJ**, Knipschield MA. Submucosal endoscopy with mucosal resection: a hybrid endoscopic submucosal dissection in the porcine rectum and distal colon. *Gastrointest Endosc* 2012; **76**: 829-834 [PMID: 22854058 DOI: 10.1016/j.gie.2012.05.037]

42 **Uraoka T**, Saito Y, Yahagi N. What are the latest developments in colorectal endoscopic submucosal dissection? *World J Gastrointest Endosc* 2012; **4**: 296-300 [PMID: 22816009 DOI: 10.4253/wjge.v4.i7.296]

43 **Vormbrock K**, Mönkemüller K. Difficult colon polypectomy. *World J Gastrointest Endosc* 2012; **4**: 269-280 [PMID: 22816006 DOI: 10.4253/wjge.v4.i7.269]

44 **Kato M**, Gromski M, Jung Y, Chuttani R, Matthes K. The learning curve for endoscopic submucosal dissection in an established experimental setting. *Surg Endosc* 2013; **27**: 154-161 [PMID: 22806508 DOI: 10.1007/s00464-012-2402-5]

45 **Yoshida N**, Yagi N, Inada Y, Kugai M, Kamada K, Katada K, Uchiyama K, Ishikawa T, Takagi T, Handa O, Konishi H, Kokura S, Inoue K, Wakabayashi N, Abe Y, Yanagisawa A, Naito Y. Possibility of ex vivo animal training model for colorectal endoscopic submucosal dissection. *Int J Colorectal Dis* 2013; **28**: 49-56 [PMID: 22777001 DOI: 10.1007/s00384-012-1531-6]

46 **Lee SP**, Lee HL, Hahm JS, Choi HS, Joe I, Shimizu S. International live endoscopic multichannel demonstration using superfast broadband internet connections. *Clin Endosc* 2012; **45**: 73-77 [PMID: 22741135 DOI: 10.5946/ce.2012.45.1.73]

47 **Goda K**, Fujishiro M, Hirasawa K, Kakushima N, Morita Y, Oda I, Takeuchi M, Yamamoto Y, Uedo N. How to teach and learn endoscopic submucosal dissection for upper gastrointestinal neoplasm in Japan. *Dig Endosc* 2012; **24** Suppl 1: 136-142 [PMID: 22533770 DOI: 10.1111/j.1443-1661.2012.01274.x]

48 **Kakushima N**, Hirasawa K, Morita Y, Takeuchi M, Yamamoto Y, Oda I, Goda K, Uedo N, Fujishiro M. Terminology for training of endoscopic submucosal dissection. *Dig Endosc* 2012; **24** Suppl 1: 133-135 [PMID: 22533769 DOI: 10.1111/j.1443-1661.2012.01257.x]

49 **Uedo N**, Jung HY, Fujishiro M, Lee IL, Zhou PH, Chiu PW, Chang D, Goda K. Current situation of endoscopic submucosal dissection for superficial neoplasms in the upper digestive tract in East Asian countries: a questionnaire survey. *Dig Endosc* 2012; **24** Suppl 1: 124-128 [PMID: 22533767 DOI: 10.1111/j.1443-1661.2012.01281.x]

50 **Fujishiro M**, Jung HY, Goda K, Hirasawa K, Kakushima N, Lee IL, Morita Y, Oda I, Takeuchi M, Yamamoto Y, Zhou PH, Uedo N. Desirable training and roles of Japanese endoscopists towards the further penetration of endoscopic submucosal dissection in Asia. *Dig Endosc* 2012; **24** Suppl 1: 121-123 [PMID: 22533766 DOI: 10.1111/j.1443-1661.2012.01254.x]

51 **Balogh G**, Dubravcsik Z, Szepes A, Madácsy L. [Endoscopic submucosal dissection in our practice -- new possibilities in the endoscopic treatment of neoplastic changes in the alimentary canal]. *Orv Hetil* 2012; **153**: 824-833 [PMID: 22617372 DOI: 10.1556/OH.2012.29382]

52 **Cai MY**, Zhou PH, Yao LQ. Current status of endoscopic resection in China. *Dig Endosc* 2012; **24** Suppl 1: 166-171 [PMID: 22533775 DOI: 10.1111/j.1443-1661.2012.01268.x]

53 **Jung HY**. Endoscopic resection for early gastric cancer: current status in Korea. *Dig Endosc* 2012; **24** Suppl 1: 159-165 [PMID: 22533774 DOI: 10.1111/j.1443-1661.2012.01275.x]

54 **Niimi K**, Fujishiro M, Goto O, Kodashima S, Koike K. Safety and efficacy of colorectal endoscopic submucosal dissection by the trainee endoscopists. *Dig Endosc* 2012; **24** Suppl 1: 154-158 [PMID: 22533773 DOI: 10.1111/j.1443-1661.2012.01251.x]

55 **Yamamoto Y**, Fujisaki J, Ishiyama A, Hirasawa T, Igarashi M. Current status of training for endoscopic submucosal dissection for gastric epithelial neoplasm at Cancer Institute Hospital, Japanese Foundation for Cancer Research, a famous Japanese hospital. *Dig Endosc* 2012; **24** Suppl 1: 148-153 [PMID: 22533772 DOI: 10.1111/j.1443-1661.2012.01278.x]

56 **Hirasawa K**, Kokawa A, Kou R, Oka H, Maeda S, Tanaka K. Determining early gastric cancer lesions appropriate for endoscopic submucosal dissection trainees: a proposal related to curability. *Dig Endosc* 2012; **24** Suppl 1: 143-147 [PMID: 22533771 DOI: 10.1111/j.1443-1661.2012.01258.x]

57 **Oda I**, Odagaki T, Suzuki H, Nonaka S, Yoshinaga S. Learning curve for endoscopic submucosal dissection of early gastric cancer based on trainee experience. *Dig Endosc* 2012; **24** Suppl 1: 129-132 [PMID: 22533768 DOI: 10.1111/j.1443-1661.2012.01265.x]

58 **Ohata K**, Ito T, Chiba H, Tsuji Y, Matsuhashi N. Effective training system in colorectal endoscopic submucosal dissection. *Dig Endosc* 2012; **24** Suppl 1: 84-89 [PMID: 22533759 DOI: 10.1111/j.1443-1661.2012.01272.x]

59 **Uraoka T**, Parra-Blanco A, Yahagi N. Colorectal endoscopic submucosal dissection in Japan and Western countries. *Dig Endosc* 2012; **24** Suppl 1: 80-83 [PMID: 22533758 DOI: 10.1111/j.1443-1661.2012.01279.x]

60 **Matsui N**, Akahoshi K, Nakamura K, Ihara E, Kita H. Endoscopic submucosal dissection for removal of superficial gastrointestinal neoplasms: A technical review. *World J Gastrointest Endosc* 2012; **4**: 123-136 [PMID: 22523613 DOI: 10.4253/wjge.v4.i4.123]

61 **Lee CT**, Chang CY, Tai CM, Wang WL, Tseng CH, Hwang JC, Lin JT. Endoscopic submucosal dissection for early esophageal neoplasia: a single center experience in South Taiwan. *J Formos Med Assoc* 2012; **111**: 132-139 [PMID: 22423666 DOI: 10.1016/j.jfma.2010.12.002]

62 **Nicolás-Pérez D**. [Endoscopic submucosal dissection: only for expert endoscopists?]. *Gastroenterol Hepatol* 2012; **35**: 344-367 [PMID: 22341600 DOI: 10.1016/j.gastrohep.2011.12.010]

63 **Tanaka S**, Morita Y, Fujita T, Wakahara C, Ikeda A, Toyonaga T, Azuma T. Ex vivo pig training model for esophageal endoscopic submucosal dissection (ESD) for endoscopists with experience in gastric ESD. *Surg Endosc* 2012; **26**: 1579-1586 [PMID: 22223113 DOI: 10.1007/s00464-011-2074-6]

64 **Uedo N**, Takeuchi Y, Ishihara R. Endoscopic management of early gastric cancer: endoscopic mucosal resection or endoscopic submucosal dissection: data from a Japanese high-volume center and literature review. *Ann Gastroenterol* 2012; **25**: 281-290 [PMID: 24714247]

65 **Tsuji Y**, Ohata K, Sekiguchi M, Ito T, Chiba H, Gunji T, Yamamichi N, Fujishiro M, Matsuhashi N, Koike K. An effective training system for endoscopic submucosal dissection of gastric neoplasm. *Endoscopy* 2011; **43**: 1033-1038 [PMID: 22135195 DOI: 10.1055/s-0031-1291383]

66 **Inoue H**, Ikeda H, Hosoya T, Yoshida A, Onimaru M, Suzuki M, Kudo SE. Endoscopic mucosal resection, endoscopic submucosal dissection, and beyond: full-layer resection for gastric cancer with nonexposure technique (CLEAN-NET). *Surg Oncol Clin N Am* 2012; **21**: 129-140 [PMID: 22098836 DOI: 10.1016/j.soc.2011.09.012]

67 **Deprez PH**. Endoscopic diagnosis and treatment of upper gastrointestinal tumors. *Endoscopy* 2011; **43**: 966-970 [PMID: 22057760 DOI: 10.1055/s-0031-1291427]

68 **Tanimoto MA**, Torres-Villalobos G, Fujita R, Santillan-Doherty P, Albores-Saavedra J, Chable-Montero F, Martin-Del-Campo LA, Vasquez L, Bravo-Reyna C, Villanueva O, Villalobos JJ, Uribe M, Valdovinos MA. Learning curve in a Western training center of the circumferential en bloc esophageal endoscopic submucosal dissection in an in vivo animal model. *Diagn Ther Endosc* 2011; **2011**: 847831 [PMID: 21976950 DOI: 10.1155/2011/847831]

69 **Berr F**, Ponchon T, Neureiter D, Kiesslich T, Haringsma J, Kaehler GF, Schmoll F, Messmann H, Yahagi N, Oyama T. Experimental endoscopic submucosal dissection training in a porcine model: learning experience of skilled Western endoscopists. *Dig Endosc* 2011; **23**: 281-289 [PMID: 21951087 DOI: 10.1111/j.1443-1661.2011.01129.x]

70 **Sakamoto T**, Saito Y, Fukunaga S, Nakajima T, Matsuda T. Learning curve associated with colorectal endoscopic submucosal dissection for endoscopists experienced in gastric endoscopic submucosal dissection. *Dis Colon Rectum* 2011; **54**: 1307-1312 [PMID: 21904147 DOI: 10.1097/DCR.0b013e3182282ab0]

71 **Lai LH**, Chan FK. Endoscopic submucosal dissection for colonic lesions: why and how should we do it? *J Dig Dis* 2011; **12**: 229-233 [PMID: 21791017 DOI: 10.1111/j.1751-2980.2011.00516.x]

72 **Wang TE**, Wang HY, Lin CC, Chen TY, Chang CW, Chen CJ, Chen MJ. Simulating a target lesion for endoscopic submucosal dissection training in an ex vivo pig model. *Gastrointest Endosc* 2011; **74**: 398-402 [PMID: 21679942 DOI: 10.1016/j.gie.2011.04.014]

73 **Kim EY**, Jeon SW, Kim GH. Chicken soup for teaching and learning ESD. *World J Gastroenterol* 2011; **17**: 2618-2622 [PMID: 21677829 DOI: 10.3748/wjg.v17.i21.2618]

74 **Kim YJ**, Park DK. Management of complications following endoscopic submucosal dissection for gastric cancer. *World J Gastrointest Endosc* 2011; **3**: 67-70 [PMID: 21603034 DOI: 10.4253/wjge.v3.i4.67]

75 **Othman MO**, Wallace MB. Endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) in 2011, a Western perspective. *Clin Res Hepatol Gastroenterol* 2011; **35**: 288-294 [PMID: 21458402 DOI: 10.1016/j.clinre.2011.02.006]

76 **Fukami N**, Ryu CB, Said S, Weber Z, Chen YK. Prospective, randomized study of conventional versus HybridKnife endoscopic submucosal dissection methods for the esophagus: an animal study. *Gastrointest Endosc* 2011; **73**: 1246-1253 [PMID: 21316668 DOI: 10.1016/j.gie.2010.12.004]

77 **Hotta K**, Oyama T, Shinohara T, Miyata Y, Takahashi A, Kitamura Y, Tomori A. Learning curve for endoscopic submucosal dissection of large colorectal tumors. *Dig Endosc* 2010; **22**: 302-306 [PMID: 21175483 DOI: 10.1111/j.1443-1661.2010.01005.x]

78 **Figueroa-Barojas P**, Sobrino-Cossío S, Hernández-Guerrero A, Ramírez-Solís ME, Alonso-Lárraga JO, Rodríguez-Brambila V, Álvaro-Villegas J. [Endoscopic inanimate biological simulators for training in endoscopic mucosal dissection]. *Rev Gastroenterol Mex* 2010; **75**: 380-388 [PMID: 21169104]

79 **Sashiyama H**, Fu KI, Hoshino T, Tsujinaka Y. Education and imaging: Gastrointestinal: gastric anisakiasis presenting as a submucosal tumour diagnosed by endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2010; **25**: 1806 [PMID: 21069912]

80 **Toyonaga T**, Man-i M, Chinzei R, Takada N, Iwata Y, Morita Y, Sanuki T, Yoshida M, Fujita T, Kutsumi H, Hayakumo T, Inokuchi H, Azuma T. Endoscopic treatment for early stage colorectal tumors: the comparison between EMR with small incision, simplified ESD, and ESD using the standard flush knife and the ball tipped flush knife. *Acta Chir Iugosl* 2010; **57**: 41-46 [PMID: 21066982]

81 **Kuroki Y**, Hoteya S, Mitani T, Yamashita S, Kikuchi D, Fujimoto A, Matsui A, Nakamura M, Nishida N, Iizuka T, Yahagi N. Endoscopic submucosal dissection for residual/locally recurrent lesions after endoscopic therapy for colorectal tumors. *J Gastroenterol Hepatol* 2010; **25**: 1747-1753 [PMID: 21039836 DOI: 10.1111/j.1440-1746.2010.06331.x]

82 **Lee JH**, Jung HY. Usefulness of endoscopic ultrasonography in endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2010; **25**: 1715-1716 [PMID: 21039830 DOI: 10.1111/j.1440-1746.2010.06483.x]

83 **Neuhaus H**. Endoscopic mucosal resection and endoscopic submucosal dissection in the West--too many concerns and caveats? *Endoscopy* 2010; **42**: 859-861 [PMID: 20886404 DOI: 10.1055/s-0030-1255724]

84 **Wang AY**, Emura F, Oda I, Cox DG, Kim HS, Yeaton P. Endoscopic submucosal dissection with electrosurgical knives in a patient on aspirin therapy (with video). *Gastrointest Endosc* 2010; **72**: 1066-1071 [PMID: 20869712 DOI: 10.1016/j.gie.2010.06.008]

85 **Tomita T**, Arai E, Kohno T, Kondo T, Kim Y, Oshima T, Hori K, Watari J, Matsumoto T, Miwa H. Outcomes of treatment of argon plasma coagulation therapy in elderly or high-risk patients with early gastric cancer: a comparison of outcomes among experienced and nonexperienced endoscopists. *J Clin Gastroenterol* 2011; **45**: e54-e59 [PMID: 20838235 DOI: 10.1097/MCG.0b013e3181ef3612]

86 **Rieder E**, Swanstrom LL. Advances in cancer surgery: natural orifice surgery (NOTES) for oncological diseases. *Surg Oncol* 2011; **20**: 211-218 [PMID: 20832296 DOI: 10.1016/j.suronc.2010.07.005]

87 **Niimi K**, Fujishiro M, Kodashima S, Goto O, Ono S, Hirano K, Minatsuki C, Yamamichi N, Koike K. Long-term outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. *Endoscopy* 2010; **42**: 723-729 [PMID: 20806156 DOI: 10.1055/s-0030-1255675]

88 **Yen HH**, Chen CJ. Education and Imaging. Gastrointestinal: endoscopic submucosal dissection for gastric inflammatory fibroid polyp. *J Gastroenterol Hepatol* 2010; **25**: 1465 [PMID: 20659241 DOI: 10.1111/j.1440-1746.2010.06424.x]

89 **Ho KY**, Phee SJ, Shabbir A, Low SC, Huynh VA, Kencana AP, Yang K, Lomanto D, So BY, Wong YY, Chung SC. Endoscopic submucosal dissection of gastric lesions by using a Master and Slave Transluminal Endoscopic Robot (MASTER). *Gastrointest Endosc* 2010; **72**: 593-599 [PMID: 20646698 DOI: 10.1016/j.gie.2010.04.009]

90 **Deprez PH**, Bergman JJ, Meisner S, Ponchon T, Repici A, Dinis-Ribeiro M, Haringsma J. Current practice with endoscopic submucosal dissection in Europe: position statement from a panel of experts. *Endoscopy* 2010; **42**: 853-858 [PMID: 20623442 DOI: 10.1055/s-0030-1255563]

91 **Tanimoto MA**. [Submucosal endoscopic dissection]. *Rev Gastroenterol Mex* 2010; **75**: 177-185 [PMID: 20615786]

92 **Parra-Blanco A**, Arnau MR, Nicolás-Pérez D, Gimeno-García AZ, González N, Díaz-Acosta JA, Jiménez A, Quintero E. Endoscopic submucosal dissection training with pig models in a Western country. *World J Gastroenterol* 2010; **16**: 2895-2900 [PMID: 20556835]

93 **Yamashita T**, Zeniya A, Otani S. Endoscopic submucosal dissection (ESD) using the needle knife: its superiority to ESD using the insulation-tipped diathermic knife in physicians intending to master ESD. *Surg Laparosc Endosc Percutan Tech* 2010; **20**: 180-185 [PMID: 20551819 DOI: 10.1097/SLE.0b013e3181e0d5db]

94 **Tanimoto MA**, Torres-Villalobos G, Fujita R, Santillan-Doherty P, Albores-Saavedra J, Gutierrez G, Martin-del-Campo LA, Bravo-Reyna C, Villanueva O, Villalobos JJ, Uribe M, Valdovinos MA. Endoscopic submucosal dissection in dogs in a World Gastroenterology Organisation training center. *World J Gastroenterol* 2010; **16**: 1759-1764 [PMID: 20380009]

95 **Yoshida N**, Yagi N, Naito Y, Yoshikawa T. Safe procedure in endoscopic submucosal dissection for colorectal tumors focused on preventing complications. *World J Gastroenterol* 2010; **16**: 1688-1695 [PMID: 20379999]

96 **Hon SS**, Ng SS, Lee JF, Li JC, Lo AW. In vitro porcine training model for colonic endoscopic submucosal dissection: an inexpensive and safe way to acquire a complex endoscopic technique. *Surg Endosc* 2010; **24**: 2439-2443 [PMID: 20333407 DOI: 10.1007/s00464-010-0982-5]

97 **Teoh AY**, Chiu PW, Wong SK, Sung JJ, Lau JY, Ng EK. Difficulties and outcomes in starting endoscopic submucosal dissection. *Surg Endosc* 2010; **24**: 1049-1054 [PMID: 19911227 DOI: 10.1007/s00464-009-0724-8]

98 **Hyatt BJ**, Paull PE, Wassef W. Gastric oncology: an update. *Curr Opin Gastroenterol* 2009; **25**: 570-578 [PMID: 19816172 DOI: 10.1097/MOG.0b013e328331b5c9]

99 **Yamamoto S**, Uedo N, Ishihara R, Kajimoto N, Ogiyama H, Fukushima Y, Yamamoto S, Takeuchi Y, Higashino K, Iishi H, Tatsuta M. Endoscopic submucosal dissection for early gastric cancer performed by supervised residents: assessment of feasibility and learning curve. *Endoscopy* 2009; **41**: 923-928 [PMID: 19802773 DOI: 10.1055/s-0029-1215129]

100 **Vázquez-Sequeiros E**, de Miquel DB, Olcina JR, Martín JA, García M, Lucas DJ, Garrido E, González C, Blanco AP, Arnau MR, Buenadicha A, Vicente VM, de Argila CM, Milicua JM. Training model for teaching endoscopic submucosal dissection of gastric tumors. *Rev Esp Enferm Dig* 2009; **101**: 546-552 [PMID: 19785494]

101 **Kobayashi N**, Saito Y, Uraoka T, Matsuda T, Suzuki H, Fujii T. Treatment strategy for laterally spreading tumors in Japan: before and after the introduction of endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2009; **24**: 1387-1392 [PMID: 19702907 DOI: 10.1111/j.1440-1746.2009.05893.x]

102 **Neuhaus H**. Endoscopic submucosal dissection in the upper gastrointestinal tract: present and future view of Europe. *Dig Endosc* 2009; **21** Suppl 1: S4-S6 [PMID: 19691732 DOI: 10.1111/j.1443-1661.2009.00864.x]

103 **Ivanov D**, Toyonaga T. The first case of endoscopic submucosal dissection of cecal adenoma in Serbia. *Med Pregl* 2009; **62**: 27-30 [PMID: 19514597]

104 **Fan JK**, Tong DK, Law S, Law WL. Transvaginal cholecystectomy with endoscopic submucosal dissection instruments and single-channel endoscope: a survival study in porcine model. *Surg Laparosc Endosc Percutan Tech* 2009; **19**: 29-33 [PMID: 19238063 DOI: 10.1097/SLE.0b013e3181902ba7]

105 **Chang CC**, Lee IL, Chen PJ, Wang HP, Hou MC, Lee CT, Chen YY, Cho YP, Lin JT. Endoscopic submucosal dissection for gastric epithelial tumors: a multicenter study in Taiwan. *J Formos Med Assoc* 2009; **108**: 38-44 [PMID: 19181606 DOI: 10.1016/S0929-6646(09)60030-9]

106 **Verna EC**, Larghi A. Endoscopic submucosal dissection: learning from the Japanese experience. *Dig Liver Dis* 2009; **41**: 210-211 [PMID: 19167934 DOI: 10.1016/j.dld.2008.12.091]

107 **Goto O**, Fujishiro M, Kodashima S, Ono S, Omata M. Is it possible to predict the procedural time of endoscopic submucosal dissection for early gastric cancer? *J Gastroenterol Hepatol* 2009; **24**: 379-383 [PMID: 19054263 DOI: 10.1111/j.1440-1746.2008.05675.x]

108 **Lee SY**, Kawai T. Transnasal route: new approach to endoscopy. *Gut Liver* 2008; **2**: 155-165 [PMID: 20485641 DOI: 10.5009/gnl.2008.2.3.155]

109 **Sánchez-Salas RE**, Palmer-Román KJ, Dávila Barrios H, Sánchez-Ismayel A, Miquilarena R. [Laparoscopic vesical autoaugmentation: an animal model in rabbits (Oryctolagus cuniculus)]. *Actas Urol Esp* 2008; **32**: 722-726 [PMID: 18788489]

110 **Kakushima N**, Fujishiro M. Endoscopic submucosal dissection for gastrointestinal neoplasms. *World J Gastroenterol* 2008; **14**: 2962-2967 [PMID: 18494043]

111 **Kobayashi N**, Ishikawa T, Hirabayashi K, Fu KI, Hirahara Y, Yamabe Y, Igarashi S, Sekiguchi R. Education and imaging. Gastrointestinal: intramucosal gastric cancer treated by endoscopic submucosal dissection. *J Gastroenterol Hepatol* 2008; **23**: 500 [PMID: 18318828 DOI: 10.1111/j.1440-1746.2008.05337.x]

112 **Yamamoto H**. Technology insight: endoscopic submucosal dissection of gastrointestinal neoplasms. *Nat Clin Pract Gastroenterol Hepatol* 2007; **4**: 511-520 [PMID: 17768396]

113 **Larghi A**, Waxman I. State of the art on endoscopic mucosal resection and endoscopic submucosal dissection. *Gastrointest Endosc Clin N Am* 2007; **17**: 441-469, v [PMID: 17640576]

114 **Kakushima N**, Fujishiro M, Kodashima S, Muraki Y, Tateishi A, Omata M. A learning curve for endoscopic submucosal dissection of gastric epithelial neoplasms. *Endoscopy* 2006; **38**: 991-995 [PMID: 17058163]

115 **Moss A**, Bourke MJ, Metz AJ, McLeod D, Tran K, Godfrey C, McKay G, Chandra AP, Pasupathy A. Beyond the snare: technically accessible large en bloc colonic resection in the West: an animal study. *Dig Endosc* 2012; **24**: 21-29 [PMID: 22211408 DOI: 10.1111/j.1443-1661.2011.01154.x]

116 **Moss A**, Bourke MJ, Tran K, Godfrey C, McKay G, Chandra AP, Sharma S. Lesion isolation by circumferential submucosal incision prior to endoscopic mucosal resection (CSI-EMR) substantially improves en bloc resection rates for 40-mm colonic lesions. *Endoscopy* 2010; **42**: 400-404 [PMID: 20213591 DOI: 10.1055/s-0029-1243990]

117 **Kumano I**, Ishihara M, Nakamura S, Kishimoto S, Fujita M, Hattori H, Horio T, Tanaka Y, Hase K, Maehara T. Endoscopic submucosal dissection for pig esophagus by using photocrosslinkable chitosan hydrogel as submucosal fluid cushion. *Gastrointest Endosc* 2012; **75**: 841-848 [PMID: 22301341 DOI: 10.1016/j.gie.2012.10.035]

118 **von Renteln D**, Dulai PS, Pohl H, Vassiliou MC, Rösch T, Rothstein RI. Endoscopic submucosal dissection with a flexible Maryland dissector: randomized comparison of mesna and saline solution for submucosal injection (with videos). *Gastrointest Endosc* 2011; **74**: 906-911 [PMID: 21802674 DOI: 10.1016/j.gie.2011.05.030]

119 **von Renteln D**, Pohl H, Vassiliou MC, Walton MM, Rothstein RI. Endoscopic submucosal dissection by using a flexible Maryland dissector: a randomized, controlled, porcine study (with videos). *Gastrointest Endosc* 2010; **71**: 1056-1062 [PMID: 20438893 DOI: 10.1016/j.gie.2010.01.049]

120 **von Delius S**, Karagianni A, von Weyhern CH, Feussner H, Schuster T, Schmid RM, Frimberger E. Percutaneously assisted endoscopic surgery using a new PEG-minitrocar for advanced endoscopic submucosal dissection (with videos). *Gastrointest Endosc* 2008; **68**: 365-369 [PMID: 18561928 DOI: 10.1016/j.gie.2008.02.093]

121 **Yamasaki M**, Kume K, Yoshikawa I, Otsuki M. A novel method of endoscopic submucosal dissection with blunt abrasion by submucosal injection of sodium carboxymethylcellulose: an animal preliminary study. *Gastrointest Endosc* 2006; **64**: 958-965 [PMID: 17140905]

122 **Oda I**, Saito D, Tada M, Iishi H, Tanabe S, Oyama T, Doi T, Otani Y, Fujisaki J, Ajioka Y, Hamada T, Inoue H, Gotoda T, Yoshida S. A multicenter retrospective study of endoscopic resection for early gastric cancer. *Gastric Cancer* 2006; **9**: 262-270 [PMID: 17235627]

123 **Imagawa A**, Okada H, Kawahara Y, Takenaka R, Kato J, Kawamoto H, Fujiki S, Takata R, Yoshino T, Shiratori Y. Endoscopic submucosal dissection for early gastric cancer: results and degrees of technical difficulty as well as success. *Endoscopy* 2006; **38**: 987-990 [PMID: 17058162]

124 **Oyama T**, Tomori A, Hotta K, Morita S, Kominato K, Tanaka M, Miyata Y. Endoscopic submucosal dissection of early esophageal cancer. *Clin Gastroenterol Hepatol* 2005; **3**: S67-S70 [PMID: 16013002]

125 **Onozato Y**, Ishihara H, Iizuka H, Sohara N, Kakizaki S, Okamura S, Mori M. Endoscopic submucosal dissection for early gastric cancers and large flat adenomas. *Endoscopy* 2006; **38**: 980-986 [PMID: 17058161]

126 **Oka S**, Tanaka S, Kaneko I, Mouri R, Hirata M, Kawamura T, Yoshihara M, Chayama K. Advantage of endoscopic submucosal dissection compared with EMR for early gastric cancer. *Gastrointest Endosc* 2006; **64**: 877-883 [PMID: 17140890]

127 **Hirasaki S**, Kanzaki H, Matsubara M, Fujita K, Ikeda F, Taniguchi H, Yumoto E, Suzuki S. Treatment of over 20 mm gastric cancer by endoscopic submucosal dissection using an insulation-tipped

diathermic knife. *World J Gastroenterol* 2007; **13**: 3981-3984 [PMID: 17663514]

128 **Min BH**, Lee JH, Kim JJ, Shim SG, Chang DK, Kim YH, Rhee PL, Kim KM, Park CK, Rhee JC. Clinical outcomes of endoscopic submucosal dissection (ESD) for treating early gastric cancer: comparison with endoscopic mucosal resection after circumferential precutting (EMR-P). *Dig Liver Dis* 2009; **41**: 201-209 [PMID: 18571998 DOI: 10.1016/j.dld.2008.05.006]

129 **Fujishiro M**, Yahagi N, Kakushima N, Kodashima S, Muraki Y, Ono S, Yamamichi N, Tateishi A, Oka M, Ogura K, Kawabe T, Ichinose M, Omata M. Outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms in 200 consecutive cases. *Clin Gastroenterol Hepatol* 2007; **5**: 678-683; quiz 645 [PMID: 17466600]

130 **Saito Y**, Uraoka T, Matsuda T, Emura F, Ikehara H, Mashimo Y, Kikuchi T, Fu KI, Sano Y, Saito D. Endoscopic treatment of large superficial colorectal tumors: a case series of 200 endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2007; **66**: 966-973 [PMID: 17524403]

131 **Tanaka S**, Oka S, Kaneko I, Hirata M, Mouri R, Kanao H, Yoshida S, Chayama K. Endoscopic submucosal dissection for colorectal neoplasia: possibility of standardization. *Gastrointest Endosc* 2007; **66**: 100-107 [PMID: 17591481]

132 **Tamegai Y**, Saito Y, Masaki N, Hinohara C, Oshima T, Kogure E, Liu Y, Uemura N, Saito K. Endoscopic submucosal dissection: a safe technique for colorectal tumors. *Endoscopy* 2007; **39**: 418-422 [PMID: 17516348]

133 **Onozato Y**, Kakizaki S, Ishihara H, Iizuka H, Sohara N, Okamura S, Mori M, Itoh H. Endoscopic submucosal dissection for rectal tumors. *Endoscopy* 2007; **39**: 423-427 [PMID: 17354181]

134 **Zhou PH**, Yao LQ, Chen WF. [Endoscopic therapy of adenomatous polyps and early-stage carcinomas of the colon and rectum]. *Zhonghua Wai Ke Zazhi* 2008; **46**: 1386-1389 [PMID: 19094508]

135 **Zhou PH**, Yao LQ, Qin XY. Endoscopic submucosal dissection for colorectal epithelial neoplasm. *Surg Endosc* 2009; **23**: 1546-1551 [PMID: 19263116 DOI: 10.1007/s00464-009-0395-5]

136 **Saito Y**, Uraoka T, Yamaguchi Y, Hotta K, Sakamoto N, Ikematsu H, Fukuzawa M, Kobayashi N, Nasu J, Michida T, Yoshida S, Ikehara H, Otake Y, Nakajima T, Matsuda T, Saito D. A prospective, multicenter study of 1111 colorectal endoscopic submucosal dissections (with video). *Gastrointest Endosc* 2010; **72**: 1217-1225 [PMID: 21030017 DOI: 10.1016/j.gie.2010.08.004]

137 **Hurlstone DP**, Atkinson R, Sanders DS, Thomson M, Cross SS, Brown S. Achieving R0 resection in the colorectum using endoscopic submucosal dissection. *Br J Surg* 2007; **94**: 1536-1542 [PMID: 17948864]

138 **Isomoto H**, Nishiyama H, Yamaguchi N, Fukuda E, Ishii H, Ikeda K, Ohnita K, Nakao K, Kohno S, Shikuwa S. Clinicopathological factors associated with clinical outcomes of endoscopic submucosal dissection for colorectal epithelial neoplasms. *Endoscopy* 2009; **41**: 679-683 [PMID: 19670135 DOI: 10.1055/s-0029-1214979]

139 **Takeuchi Y**, Uedo N, Ishihara R, Iishi H, Kizu T, Inoue T, Chatani R, Hanaoka N, Taniguchi T, Kawada N, Higashino K, Shimokawa T, Tatsuta M. Efficacy of an endo-knife with a water-jet function (Flushknife) for endoscopic submucosal dissection of superficial colorectal neoplasms. *Am J Gastroenterol* 2010; **105**: 314-322 [PMID: 19773749 DOI: 10.1038/ajg.2009.547]

140 **Suzuki H**, Oda I, Sekiguchi M, Abe S, Nonaka S, Yoshinaga S. Process of technical stabilization of gastric endoscopic submucosal dissection at the National Cancer Center in Japan. *Turk J Gastroenterol* 2014; **25**: 619-623 [PMID: 25599770 DOI: 10.5152/tjg.2014.14077]

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CASE REPORT

Bowel perforation due to break and distal passage of the safety ring of an adjustable intra-gastric balloon: A potentially life threatening situation

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Author contributions: Al-Zubaidi AM placed and removed the balloon, the MRP who responsible for case and wrote the case report; Alghamdi HU did the laparotomy; Alzobydi AH participated in the laparotomy; Dhiloon IA done the case; Qureshi LA was peer reviewer.
Ethics approval: The case approved by the Hospital Board Ethical Committee.
Informed consent: Informed consent was taken from the patient.
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Abstract

A 45-year-old man of Middle Eastern origin, morbid obese, with a body mass index of 39 had an intra-gastric balloon, filled with 500 mL of saline/methylene blue and intended as definite therapy, inserted some 8 wk previously. He was admitted to the emergency department with abdominal cramps. An ultrasound of the abdomen was performed in ER which confirmed the balloon to be in place without any abnormality. He was discharged home on symptomatic medication. Patient remains symptomatic therefore he reported back to ER 2 d later. Computed tomography scan was performed this time for further evaluation which revealed a metallic ring present in the small bowel while the intra-gastric balloon was in its proper position. There was no clinical or radiological sign of intestinal obstruction. Patient was hospitalized for observation and conservative management. The following night, patient experienced sudden and severe abdominal pain, therefore an X-ray of the abdomen in erect position was done, which showed free air under the right dome of diaphragm. Patient was transferred to O.R for emergency laparotomy. There were two small perforations identified at the site of the metallic ring entrapment. The ring was removed and the perforations were repaired. Due to increasing prevalence of obesity and advances in modalities for its management, physicians should be aware of treatment options, their benefits, complications and clinical presentation of the known complications. Physicians need to be updated to approach these complications within time, to avoid life-threatening situations caused by these appliances.

Key words: Spatz adjustable balloon; Intragastric balloon; Morbid obesity; Safety ring; Perforation

Core tip: Because the rare reported unexpected complications that the balloon safety ring which designed to prevent its complication it was by it self the cause of

serious complication. The u/s confirmation of balloon position was miss leading so radiographic images was essential when there is suspicious.

Al-Zubaidi AM, Alghamdi HU, Alzobydi AH, Dhiloon IA, Qureshi LA. Bowel perforation due to break and distal passage of the safety ring of an adjustable intra-gastric balloon: A potentially life threatening situation. *World J Gastrointest Endosc* 2015; 7(4): 429-432 Available from: URL: http://www.wjgnet.com/1948-5190/full/v7/i4/429.htm DOI: http://dx.doi.org/10.4253/wjge.v7.i4.429

INTRODUCTION

Obesity is a major health problem, and is challenging the modern world. Its distribution is insidious throughout the world. Because it is a major risk factor for many potential life-threatening conditions, different invasive and non-invasive therapeutic techniques are being used to help the individuals suffering from obesity return to a healthy life.

Among these modalities, intra-gastric balloons are gaining popularity because of their efficacy, safety, and technical ease, as shown by some studies[1,2]. Moreover, it has been recommended as a weight reduction adjuvant before bariatric surgery, and before all kinds of planned surgery in morbidly obese persons; to reduce life-threatening co-morbidities and reduction of surgical risk[3,4].

Most of the reported serious complications with the newer generation of balloons take place 6 mo after placement of the balloon[5]. Here, we are reporting a case of small bowel perforation, secondary to break down and migration of the safety ring of an adjustable intra-gastric balloon (Spatz) that happened 8 wk after its insertion.

CASE REPORT

A 45-year-old man was brought to the emergency department with a history of abdominal cramps, on and off, for a few days, associated with anorexia and nausea. Patient had a history of saline filled adjustable intra-gastric balloon placement for the management of obesity 8 wk ago. Initial investigations including an ultrasound abdomen were unremarkable for any complication or pathology. Symptomatic treatment trial was unsuccessful and patient remained symptomatic, therefore, he reported back to ER.

He was in mild distress this time, but stable hemodynamically. Although his abdomen was soft and bowel sounds were active, a new onset mild generalized abdominal tenderness was noticed on clinical examination, therefore an abdominal computed tomography (CT) scan was planned which later reported the presence of a metallic ring (foreign body) in the small bowel without any sign of perforation or obstruction, while the adjustable balloon was in place (Figure 1).

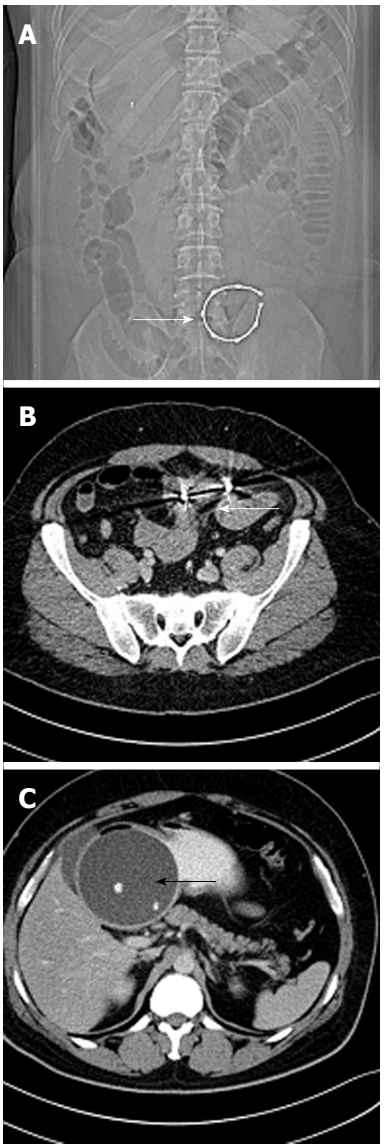

Figure 1 Abdominal computed tomography scan showing the safety ring migrated to the small bowel (A and B) (white arrows) and (C) the balloon was in the stomach (black arrow).

Patient was admitted for observation, advised null per oral, and started on intra-venous fluid. He becomes completely asymptomatic on conservative management. Next morning, patient underwent an upper gastrointestinal endoscopy. Balloon was seen in place but the safety ring was not seen in position, nor was it present in gastric cavity. Therefore, balloon was retrieved. Patient was stable clinically till night when he experienced a sudden and severe abdominal pain.

Plain X-ray film of abdomen was taken that revealed the presence of free air under the right dome of the diaphragm. Surgical team was informed immediately. Mean while NG tube was placed and IV antibiotics were initiated. Patient was transferred to the operation room for an emergency laparotomy. A 10 cm mid-line incision was given small bowel was examined.

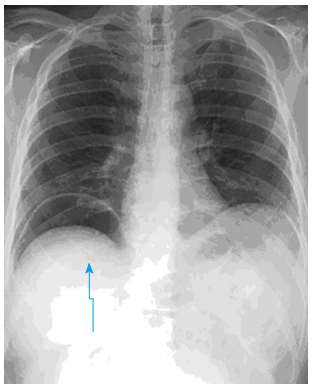

Figure 2 Free air under the diaphragm.

Two perforations were identified in distal jejunum at the site of ring entrapment. Small incision was made at the site of perforation and metallic ring was extracted followed by a successful primary repair of small bowel. Figure 2 shows free air under the diaphragm. Figure 3 shows endoscopic and gross eye views of both balloon and its broken ring after extraction.

DISCUSSION

Intra-gastric balloons were introduced in the early 1980s for the management of morbid obesity. These IGBs have attracted physicians since their first use[6].

Initial results were promising for this less invasive procedure in comparison with surgery for the treatment of morbid obesity[7-9]. Some published results reveal an average weight loss of 11-15 kg within 6 mo[10-13]. Standard IGBs are having significant undesired effects, *e.g.*, nausea or vomiting, and significant abdominal discomfort in initial phase. Balloon deflation and distal migration that may lead to bowel obstruction and a physical adaptation indicated by lack of further weight loss effects by these IGBs[14-17]. Complications of balloon insertion constitutes a diagnostic challenge because majority of patients were presented with non-specific abdominal pain, nausea or vomiting[18-23].

Spatz adjustable balloon system (SPATZ-ABS) is a vibrant bariatric therapy with significantly improved implantation time, having an adjustable size balloon according to desired weight, and a safety ring that prevents distal migration of device in case of rupture of balloon[24].

In our case, the safety ring was detached from the rest of the system and migrated down to the jejunum while the balloon remains in the stomach. It was retrieved endoscopically. The jejunal perforation caused by migration of the safety ring was managed by emergency surgery. This complication was unexpected as there was no clinical sign of intestinal obstruction. Ultrasonography alone was also not helpful in identifying this complication by SPATZ-ABS.

Because of non-specific clinical presentation and inadequacy of ultrasonography alone, we suggest that whenever there is suspicion of a balloon related complication, a combination of plain abdominal X-ray, ultrasound, an upper GI endoscopy and/or CT scan will be an appropriate approach for early detection and management of complication.

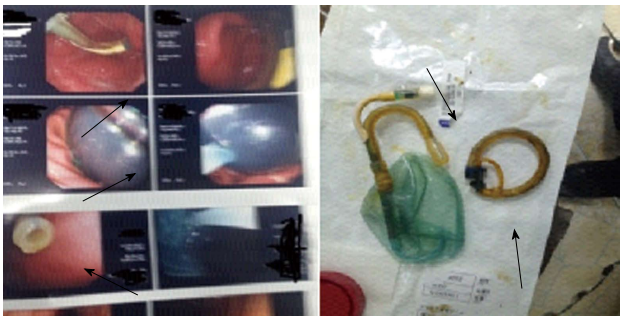

Figure 3 Endoscopic and gross eye views of both balloon and its broken ring after extraction.

COMMENTS

Case characteristics

A 45-year-old patient with history of intragastric Bio enteric balloon, experienced a recurrent cramp and abdominal pain, which became severe when perforation occurs.

Clinical diagnosis

No significant clinical signs, but when perforation occurs there was abdominal tenderness.

Differential diagnosis

Potential perforated duodenal ulcer, acute pancreatitis, acute intestinal obstruction or biliary colic.

Laboratory diagnosis

The CBC, LFT, KFT, and coagulation profile were all within normal parameters.

Imaging diagnosis

U/S abdominal was normal, computed tomography abdominal the ring was migrated down to the small bowel, when perforation occurred X-ray of the abdominal area showed free air under right dome of the diaphragm.

Pathological diagnosis

A pathology sample was not tested, but during surgery two small perforations were closed by sutures.

Treatment

NPO, endoscopic removal of the balloon, Laparotomy for repair of perforation, Pethedin inj, Paracetamol inj, Cefotoxim inj, Metronidazol infusion and *iv* fluid.

Related reports

From this case, any abdominal pain in a patient with an intragastric balloon should be taken seriously, and potential complications managed early.

Peer-review

This case report should be published.

REFERENCES

1 **Genco A**, Bruni T, Doldi SB, Forestieri P, Marino M, Busetto L, Giardiello C, Angrisani L, Pecchioli L, Stornelli P, Puglisi F, Alkilani M, Nigri A, Di Lorenzo N, Furbetta F, Cascardo A, Cipriano M, Lorenzo M, Basso N. BioEnterics Intragastric Balloon: The Italian Experience with 2,515 Patients. *Obes Surg* 2005; **15**: 1161-1164 [PMID: 16197790 DOI: 10.1381/0960892055002202]

2 **Evans JD**, Scott MH. Intragastric balloon in the treatment of patients with morbid obesity. *Br J Surg* 2001; **88**: 1245-1248 [PMID: 11531875]

3 **De Waele B**, Reynaert H, Urbain D, Willems G. Intragastric balloons for preoperative weight reduction. *Obes Surg* 2000; **10**:

58-60 [PMID: 10715647]
4 **Loffredo A**, Cappuccio M, De Luca M, de Werra C, Galloro G, Naddeo M, Forestieri P. Three years experience with the new intragastric balloon, and a preoperative test for success with restrictive surgery. *Obes Surg* 2001; **11**: 330-333 [PMID: 11433911]
5 **Vanden Eynden F**, Urbain P. Small intestine gastric balloon impaction treated by laparoscopic surgery. *Obes Surg* 2001; **11**: 646-648 [PMID: 11594113 DOI: 10.1381/09608920160556913]
6 **Nieben OG**, Harboe H. Intragastric balloon as an artificial bezoar for treatment of obesity. *Lancet* 1982; **1**: 198-199 [PMID: 6119560 DOI: 10.1016/S0140-6736(82)90762-0]
7 **McFarland RJ**, Grundy A, Gazet JC, Pilkington TR. The intragastric balloon: a novel idea proved ineffective. *Br J Surg* 1987; **74**: 137-139 [PMID: 3815032]
8 **Ramhamadany EM**, Fowler J, Baird IM. Effect of the gastric balloon versus sham procedure on weight loss in obese subjects. *Gut* 1989; **30**: 1054-1057 [PMID: 2767500]
9 **Benjamin SB**, Maher KA, Cattau EL, Collen MJ, Fleischer DE, Lewis JH, Ciarleglio CA, Earll JM, Schaffer S, Mirkin K. Double-blind controlled trial of the Garren-Edwards gastric bubble: an adjunctive treatment for exogenous obesity. *Gastroenterology* 1988; **95**: 581-588 [PMID: 3294079]
10 **Roman S**, Napoléon B, Mion F, Bory RM, Guyot P, D'Orazio H, Benchetrit S. Intragastric balloon for "non-morbid" obesity: a retrospective evaluation of tolerance and efficacy. *Obes Surg* 2004; **14**: 539-544 [PMID: 15130235 DOI: 10.1381/096089204323013587]
11 **Mion F**, Napoléon B, Roman S, Malvoisin E, Trepo F, Pujol B, Lefort C, Bory RM. Effects of intragastric balloon on gastric emptying and plasma ghrelin levels in non-morbid obese patients. *Obes Surg* 2005; **15**: 510-516 [PMID: 15946431 DOI: 10.1381/0960892053723411]
12 **Melissas J**, Mouzas J, Filis D, Daskalakis M, Matrella E, Papadakis JA, Sevrisarianos N, Charalambides D. The intragastric balloon - smoothing the path to bariatric surgery. *Obes Surg* 2006; **16**: 897-902 [PMID: 16839490 DOI: 10.1381/096089206777822188]
13 **Hogan RB**, Johnston JH, Long BW, Sones JQ, Hinton LA, Bunge J, Corrigan SA. A double-blind, randomized, sham-controlled trial of the gastric bubble for obesity. *Gastrointest Endosc* 1989; **35**: 381-385 [PMID: 2792672]
14 **Busetto L**, Segato G, De Luca M, Bortolozzi E, MacCari T, Magon A, Inelmen EM, Favretti F, Enzi G. Preoperative weight loss by intragastric balloon in super-obese patients treated with laparoscopic gastric banding: a case-control study. *Obes Surg* 2004; **14**: 671-676 [PMID: 15186637 DOI: 10.1381/096089204323093471]
15 **Imaz I**, Martínez-Cervell C, García-Alvarez EE, Sendra-Gutiérrez JM, González-Enríquez J. Safety and effectiveness of the intragastric balloon for obesity. A meta-analysis. *Obes Surg* 2008; **18**: 841-846 [PMID: 18459025 DOI: 10.1007/s11695-007-9331-8]
16 **Lecumberri E**, Krekshi W, Matía P, Hermida C, de la Torre NG, Cabrerizo L, Rubio MÁ. Effectiveness and safety of air-filled balloon Heliosphere BAG® in 82 consecutive obese patients. *Obes Surg* 2011; **21**: 1508-1512 [PMID: 21221835 DOI: 10.1007/s11695-010-0314-9]
17 **Vilallonga R**, Valverde S, Caubet E. Intestinal occlusion as unusual complication of new intragastric balloon Spatz Adjustable Balloon system for treatment of morbid obesity. *Surg Obes Relat Dis* 2013; **9**: e16-e17 [PMID: 22264907 DOI: 10.1016/j.soard.2011.12.007]
18 **Doldi SB**, Micheletto G, Perrini MN, Librenti MC, Rella S. Treatment of morbid obesity with intragastric balloon in association with diet. *Obes Surg* 2002; **12**: 583-587 [PMID: 12194556]
19 **Pretolesi F**, Redaelli G, Papagni L, Derchi LE. Intragastric balloon for morbid obesity causing chronic gastric dilatation. *Eur Radiol* 2001; **11**: 588-589 [PMID: 11354752]
20 **Forlano R**, Ippolito AM, Iacobellis A, Merla A, Valvano MR, Niro G, Annese V, Andriulli A. Effect of the BioEnterics intragastric balloon on weight, insulin resistance, and liver steatosis in obese patients. *Gastrointest Endosc* 2010; **71**: 927-933 [PMID: 19863955]
21 **Mohammed AE**, Benmousa A. Acute pancreatitis complicating intragastric balloon insertion. *Case Rep Gastroenterol* 2008; **2**: 291-295 [PMID: 21490858]
22 **Benchimol AK**, Cardoso IS, Fandiño J, Bittar T, Freitas S, Coutinho WF. [Non-alcoholic steatohepatitis induced by fast weight loss during the use of intragastric balloon--a case report]. *Arq Bras Endocrinol Metabol* 2007; **51**: 631-634 [PMID: 17684626]
23 **Nikolic M**, Mirosevic G, Ljubicic N, Boban M, Supanc V, Nikolic BP, Zjacic-Rotkvic V, Bekavac-Beslin M, Gacina P. Obesity treatment using a Bioenterics intragastric balloon (BIB)--preliminary Croatian results. *Obes Surg* 2011; **21**: 1305-1310 [PMID: 20352525 DOI: 10.1007/s11695-010-0101-7]
24 **de la Riva S**, Muñoz-Navas M, Rodriguez-Lago I, Silva C. Small-bowel migration: a possible complication of adjustable intragastric balloons. *Endoscopy* 2012; **44** Suppl 2 UCTN: E224 [PMID: 22622757 DOI: 10.1055/s-0032-1309352]

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