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ABOUT COVER

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MINIREVIEWS

Gastrointestinal amyloidosis: A focused review

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Abstract

Amyloidosis, a heterogenous group of disorders, is characterized by the extracellular deposition of autologous, insoluble, fibrillar misfolded proteins. These extracellular proteins deposit in tissues aggregated in ß-pleated sheets arranged in an antiparallel fashion and cause distortion to the tissue architecture and function. In the current literature, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 have been associated with human disease. Classified as a rare disease, amyloidosis is known to have a wide range of possible etiologies and clinical manifestations. The exact incidence and prevalence of the disease is currently unknown. In both systemic and localized amyloidosis, there is infiltration of the abnormal proteins in the layers of the gastrointestinal (GI) tract or the liver parenchyma. The gold standard test for establishing a diagnosis is tissue biopsy followed by Congo Red staining and apple-green birefringence of the Congo Red-stained deposits under polarized light. However, not all patients may have a positive tissue confirmation of the disease. In these cases additional workup and referral to a gastroenterologist may be warranted. Along with symptomatic management, the treatment for GI amyloidosis consists of observation or localized surgical excision in patients with localized disease, and treatment of the underlying pathology in cases of systemic amyloidosis. In this review of the literature, we describe the subtypes of amyloidosis, with a primary focus on the epidemiology, pathogenesis, clinical features, diagnosis and treatment strategies available for GI amyloidosis.

Key Words: Gastroenterology; Hepatology; Amyloidosis; Dysmotility; Endoscopy; Therapeutics

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Core Tip: This manuscript focuses on a rare disease entity that can cause significant morbidity and mortality, especially amongst the elderly patient population. Lack of awareness regarding the possibility of gastrointestinal amyloidosis, which presents with vague symptoms common to a host of disorders, can lead to unnecessary testing and delays in diagnosis, contributing to poor outcomes. Physicians should consider the presence of gastrointestinal amyloidosis, especially in elderly patients with conditions predisposing them to the development of amyloid deposition.

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INTRODUCTION

In 1853, Rudolf Virchow first used the term "amyloid" to describe tissue deposits which showed close similarity to starch after they were dyed with iodine and sulphuric acid[1]. Amyloidosis encompasses a heterogenous group of disorders characterized by the extracellular deposition of autologous fibrillar proteins, which aggregate into a three-dimensional ß-lamina disposition (ß-pleated sheets aligned in an anti-parallel fashion) in tissues, disrupting normal tissue architecture and function[2,3]. According to the Genetic and Rare Disease Information Center (GARD) of the National Institute of Health (NIH), amyloidosis is a rare disease. It is known to have a wide spectrum of possible etiologies and clinical manifestations, thereby making an accurate assessment of epidemiology extremely difficult. According to the data available from the NIH, AL (amyloid light chain) amyloidosis has an incidence of 1 case per 100000 person-years in Western countries[4]. Systemic amyloidosis is more common than localized disease, and the annual incidence of primary systemic amyloidosis is 78% whereas that of secondary systemic amyloidosis is only 6% every year in the United States[4]. In the literature, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 are associated with known disease in humans[5]. Based on the location of production of amyloidogenic precursor protein and its deposition within the tissues, it can be classified into two distinct subtypes: Systemic and localized amyloidosis[6]. GI tract involvement may be a feature of both subtypes[6]. Gastrointestinal (GI) amyloidosis is defined as the presence of GI signs and symptoms along with direct biopsy verification of the disease. However, as per the current literature, GI amyloidosis with direct biopsy verification from the GI tract may be a rare phenomenon. Hence, in this review, we describe the different subtypes of amyloidosis with associated amyloid precursor proteins deposited in tissues. We also describe the incidence rates of amyloidosis reported in different healthcare systems throughout the world. Additionally, we detail the pathogenesis, clinical presentations, methods to establish diagnosis, and the treatment strategies available for GI amyloidosis.

METHODS

A thorough literature search was performed to identify articles on amyloidosis of the GI tract and its clinical presentations. The authors used search engines such as PubMed, Google Scholar, and Ovid MEDLINE to search for published literature on GI amyloidosis between the years 1960 and 2020. A detailed literature search of the articles referenced in the identified publications was also performed. Furthermore, data and statistics available from national organizations such as the GARD were also researched. The keywords used in the literature search included, but are not limited to: "amyloidosis", "gastrointestinal amyloidosis", "localized amyloidosis", "systemic amyloidosis", "amyloid pathogenesis", "hepatic amyloidosis", "amyloidosis treatment", "gastrointestinal amyloidosis treatment", and "gastrointestinal

amyloidosis prognosis". The inclusion criteria set by the authors consisted of articles published between the years 1960 and 2020, published articles available in the English language, data and statistics available from national organizations such as the NIH, and published articles or guidelines related to the therapeutic options available for the management of GI amyloidosis in all clinical settings. The exclusion criteria consisted of duplicate articles or abstracts only, articles published before the year 1950, articles published in a language other than English, and unpublished research on GI amyloidosis. Application of the inclusion and exclusion criteria yielded a total of 3197 articles which were carefully reviewed by all the authors for this review of the literature. A total of 65 references ultimately were used for the purposes of drafting this narrative review.

DISCUSSION

As described earlier, amyloidosis refers to a heterogenous group of disorders characterized by extracellular deposition of fibrillar proteins, which can disrupt tissue structure and function. On electron microscopy, amyloid fibrils are approximately 10 nm in diameter, and on polarized light microscopy after staining with Congo Red (CR) dye, they have the characteristic apple green-birefringence appearance[5]. According to the 2010 recommendations from the Nomenclature Committee of the International Society of Amyloidosis, about 60 heterogeneous amyloidogenic proteins have been identified, out of which 27 have been found to be associated with known human disease[7].

CLASSIFICATION

Amyloidosis can be classified into two main subtypes based on the location of production of the amyloidogenic precursor protein and its deposition within the tissues (Table 1)[6]. The classification is as follows[6,8].

Systemic amyloidosis

The most common subtype. It is characterized by the production of amyloidogenic precursor proteins at a site remote from the organ of amyloid deposition. It can either be due to acquired conditions such as plasma cell dyscrasias, or hereditary conditions due to modifications in the transthyretin (TTR) gene. Table 2 summarizes the common forms of systemic amyloidosis along with organ-specific involvement[8].

Localized amyloidosis

It is characterized by the production of amyloidogenic precursor proteins at the same location as its deposition. It may commonly involve the respiratory tract, urinary bladder, breast, skin, or the GI tract. A single center retrospective analysis by Cowan *et al*[6] reported that out of the 3.3% of patients with biopsy proven amyloidosis, only 21% had amyloidosis restricted to the GI tract[6]. Hence, localized amyloidosis is an uncommon entity.

EPIDEMIOLOGY

According to the GARD, amyloidosis is a rare disease entity. It is known to have a wide spectrum of possible etiologies and clinical manifestations, thereby making an accurate assessment of epidemiology extremely difficult. Furthermore, regional variations in the environment *i.e.*, prevalence of local infections and autoimmune diseases which predispose to chronic inflammation, and genetic factors such as polymorphisms in the genes encoding for amyloid precursors may also contribute significantly to the likelihood of developing the disease[9]. Studies, although limited, have been conducted to evaluate the epidemiology of the disease in the United States and worldwide. According to the latest statistics available from the NIH, AL amyloidosis has an incidence of 1 case per 100000 person-years in Western countries, and in the United States approximately 1275 to 3200 new cases are reported every year[4]. Systemic amyloidosis is more common than localized amyloidosis, and the annual portion of new cases with primary systemic amyloidosis (AL) is 78% whereas secondary systemic amyloidosis (AA) represents only 6% of these cases every year in

Table 1 Differences in systemic and localized gastrointestinal amyloidosis

Systemic gastrointestinal amyloidosis	Localized gastrointestinal amyloidosis
More common subtype	Less common subtype
Amyloid production at a remote location with subsequent deposition in the GI tract	Amyloid production in the GI tract with subsequent deposition locally
Presence of amyloid precursor proteins in the blood	Amyloid precursor proteins absent in the blood
Associated with plasma cell dyscrasia, chronic inflammatory conditions, dialysis, or hereditary conditions	Not associated with an underlying disease pathology
Amyloid precursor protein deposited include AL, AA, Aβ2M and ATTR	Amyloid precursor protein most deposited is AL
Management consists of symptomatic management and treatment of the underlying etiology	Management consists of observation or surgical excision of the localised deposition
Prognosis depends on the type and amount of amyloid deposition	Good prognosis. No transition to systemic type

AL: Monoclonal light chain; AA: Serum amyloid A; Aβ2M: β2-microglobulin amyloid; ATTR: Familial transthyretin-associated amyloidosis; GI: Gastrointestinal.

Table 2 The common forms of systemic amyloidosis with organ involvement

Type of systemic amyloidosis	Causative protein	Organ involvement
Primary systemic amyloidosis	Monoclonal light chain (AL)	Heart, Kidneys, Liver, Peripheral nervous system, Autonomic nervous system, and Gastrointestinal tract
Senile systemic amyloidosis	Wild-type transthyretin (ATTR)	Heart
Hereditary systemic amyloidosis	Mutant transthyretin (ATTR); Apolipoprotein 1 (AApoA1); Mutant fibrinogen A alpha (AFib); Lysozyme (ALys)	Heart; Heart, Kidneys, Liver, Peripheral nervous system, and Skin; Kidneys and Liver; Kidneys and Liver
Isolated Atrial Systemic Amyloidosis	Atrial natriuretic factor (AANF)	Heart
Secondary Systemic Amyloidosis	Serum amyloid A (AA)	Kidneys, Heart, and Gastrointestinal tract
Dialysis-Related Systemic Amyloidosis	β2-microglobulin ($A\beta_2M$)	Osteoarticular tissue, Circulatory system, and Gastrointestinal tract
Finnish-type Systemic Amyloidosis	Gelsolin (AGel)	Lattice dystrophy of cornea, and Corneal neuropathy

the United States[4]. Familial transthyretin-associated amyloidosis, believed to be less common and with a currently unknown incidence rate, constitutes approximately 10% to 20% of diagnosed cases at tertiary hospitals in the United States[4]. Outside the United States, similar trends in incidence have been observed. In the United Kingdom, Pinney *et al*[10] reported a global incidence of amyloidosis of 5 cases per million person-years, out of which 3 cases per million person-years were attributed to the AL amyloidosis and 1 case per million person-years to AA amyloidosis[10]. Similarly, Hemminki *et al*[11] estimated the incidence of amyloidosis to be 8 patients per million person-years in Sweden, from which 3 cases per million person-years were credited to AL amyloidosis and 2 cases per million person-years to AA amyloidosis[11]. Typically, amyloidosis manifests later in life and more commonly affects the older demographic (mean age for the AL subtype is 63 years)[12]. A higher incidence and prevalence of the disease has been reported in males as compared to females[12]. In the United States, the literature also reported a substantial increase in amyloidosis-related mortality from 1.77 to 3.96 per million between 1979 and 2015, with the highest mortality rates noted in the African-American population[13].

Involvement of the GI tract can be seen in both localized (limited only to the gut) and systemic (most commonly AL subtype) amyloidosis. GI amyloidosis is defined as the presence of GI signs and symptoms along with direct biopsy verification of the disease[14]. It is more commonly seen in elderly males. Yen *et al*[15] conducted a single center retrospective cohort study from 2008 to 2017 in 583 amyloid patients and observed that only 96 (16.8%) patients had GI signs and symptoms[15]. Out of these 96

patients, 82 underwent esophagogastroduodenoscopy (EGD) or colonoscopy with biopsy, and it was reported that only 37 (45%) patients had biopsy proven GI amyloidosis, whereas 45 (55%) patients had absence of GI amyloidosis on biopsy[15]. Similarly, another retrospective study which evaluated 2337 patients in a 13-year period using the Boston University Amyloid Treatment and Research Program database reported biopsy proven GI Amyloidosis in only 76 (3.3%) of the patients[6]. Furthermore, on EGD or colonoscopy, the site of highest diagnostic yield from biopsy specimens was found to be the duodenum, followed by the stomach, colon and rectum, and esophagus[6,15]. Hence, it can be concluded that GI amyloidosis with direct biopsy verification from the GI tract is a rare phenomenon. There is also a significant paucity of data on GI amyloidosis with most of it available either from small, retrospective single center studies, or isolated case reports. Therefore, we strongly advocate for the need for additional large multi-center prospective studies to capture the impact of GI amyloidosis globally and its burden on the healthcare system.

PATHOGENESIS

The basic pathogenic mechanism of amyloidosis involves the extracellular deposition of insoluble protein fibrils derived from amyloid precursor proteins in tissues[16]. These are composed of low molecular weight subunits arranged in antiparallel ß-pleated sheets[16]. In GI amyloidosis, infiltration of extracellular misfolded proteins can be seen in the different layers of the GI tract.

Mucosal infiltration

The most common site of mucosal infiltration is the duodenum, followed by the stomach, colorectum and the esophagus[17]. Furthermore, the subtype of amyloid protein deposited governs the clinical presentation[18,19].

AL amyloid deposition is usually seen in the muscularis mucosa, submucosa and muscularis propria, often leading to the formation of protrusions. It may present with symptoms of bowel obstruction.

AA amyloid deposition is seen mainly in the mucosa, which may lead to increased friability and erosions in the involved area. It may present with diarrhea and clinical features of malabsorption.

β2-microglobulin amyloid ($A\beta_2M$) deposition is usually seen in patients on hemodialysis and corresponds to increased mean time on dialysis. $A\beta_2M$ deposits can be seen in the blood vessels of the GI tract, mucosa, submucosa, and muscularis propria. It may present with features of mucosal ulceration.

Neuromuscular infiltration

It is characterized by the deposition of the amyloid proteins in the neuromuscular layer of the GI tract. This can affect the intrinsic nerve plexus (myenteric or submucosal nerve plexus) and the muscularis externa (longitudinal and circular muscles) leading to abnormal peristalsis, abnormal GI transit times and dysmotility[20-22].

Hepatic amyloidosis, a manifestation of systemic amyloidosis, has a similar pathogenic mechanism and is characterized by the extracellular deposition of fibrillar amyloid protein (AL) in the hepatic parenchyma[23]. It is a diagnostic challenge as it shares numerous clinical manifestations with other common chronic liver diseases, and has a poor prognosis particularly in patients with jaundice[23].

CLINICAL MANIFESTATIONS

The clinical manifestations of GI amyloidosis depends on the amount and location of the amyloid deposits, irrespective of whether it is primary or secondary systemic amyloidosis[17]. Patients with localized amyloidosis may have similar clinical features as those with systemic disease. All patients with amyloidosis share common presenting symptoms such as fatigue, light-headedness, anorexia, and weight loss[24]. The common GI-specific abnormalities include.

Gastrointestinal bleeding

May occur from any site of amyloid deposition and can be seen in up to 57% of patients[25]. The underlying cause is commonly mucosal lesions (amyloidoma ulcers,

erosions, polypoid lesions, hematomas or submucosal hemorrhage), vascular friability, or in some cases bowel ischemia[25,26]. Massive occult bleeding from the GI tract is usually seen with dialysis-related amyloidosis[27].

Malabsorption

May present with symptoms such as diarrhea, weight loss, steatorrhea, anorexia, or dizziness and is usually secondary to mucosal infiltration, pancreatic insufficiency, or bacterial overgrowth[28,29].

Protein-losing gastroenteropathy

GI specific manifestations include diarrhea, edema, and ascites. It is secondary to mucosal lesions which may lead to abnormal protein loss from the GI tract[30].

Chronic gastrointestinal dysmotility (Stasis syndrome)

May present with nausea, vomiting, dysphagia, gastroparesis, gastro-oesophageal reflux, loss of appetite, constipation, abdominal pain, bloating, or clinical features of chronic intestinal pseudo-obstruction[20,21,25]. Dysmotility can be secondary to myopathic and neuropathic dysfunction[25]. Some patients may present with persistent diarrhea due to rapid transit times secondary to dysmotility, intestinal inflammation and bacterial overgrowth[25,31,32].

Hepatic amyloidosis

Has no clinical significance in most patients due to mild clinical manifestations[33]. Hepatomegaly and mild elevations in alkaline phosphatase (ALP) are the most frequent findings[34]. Other symptoms include weight loss (72%), fatigue (60%), abdominal discomfort (53%) and anorexia (26%)[25]. Elevated direct serum bilirubin levels (> 2 mg/dL) are often associated with a poor prognosis[25,34].

Uncommon symptoms

Some patients with GI Amyloidosis may have features of cholangitis, pneumatosis intestinalis (gas pockets within the bowel wall), or bowel perforation[35-37].

The physical examination findings in patients with amyloidosis depend on the organ specific infiltration by abnormal proteins[9]. However, from a purely GI perspective, physical examination may reveal macroglossia (enlarged tongue) in up to 50% of the cases[25]. On abdominal examination, hepatosplenomegaly and ascites may be the most frequent findings[34,38].

ESTABLISHING THE DIAGNOSIS

A high degree of clinical suspicion is necessary to establish a definitive diagnosis of GI amyloidosis. Due to the rarity of the condition coupled with non-specific signs and symptoms at the time of presentation, these patients usually undergo extensive and unnecessary testing to identify the cause of clinical presentation. GI amyloidosis should be high on the list of possible differential diagnoses in patients presenting with non-specific GI symptoms and a past medical history of disorders commonly associated with amyloidosis, such as plasma cell dyscrasia, chronic renal failure on hemodialysis, and other chronic inflammatory conditions (*e.g.* rheumatoid arthritis and inflammatory bowel disease). A positive family history of amyloidosis should also alert the provider to suspect GI amyloidosis[9]. Laboratory investigations in these patients may reveal anaemia, mild elevations in ALP levels, elevations of acute phase reactants (due to the underlying chronic inflammatory condition) and deficiencies from malabsorption. Radiological investigations in GI amyloidosis are usually non-specific[39]. Some common features seen on computer tomography (CT) or magnetic resonance imaging (MRI) include[25,39-41]: (1) Diffuse or nodular wall thickening of the involved bowel segment; (2) Dilatation depending upon the degree of hypomotility; (3) Presence of fluid levels in dilated bowel loops; (4) Luminal narrowing secondary to amyloid infiltration or ischemia; (5) Attenuation due to cluster of calcifications or mucosal ulcerations; (6) Presence of polyploid protrusions or masses mimicking cancer; (7) Loss of haustrations; (8) Mesenteric thickening or adenopathy; and (9) Decreased hepatic attenuation with or without areas of calcification (Ultrasound may demonstrate heterogenic hepatic echotexture).

Although radiological investigations may provide a clue to the extent and area of involvement, the gold standard test to establish a diagnosis of GI amyloidosis is tissue

biopsy followed by CR staining and visualization under polarized light microscopy[42]. Based on the patients presenting symptom, an EGD or colonoscopy should be performed to obtain the biopsy specimen. As mentioned earlier, the site of highest diagnostic yield from biopsy specimen in the GI tract has been found to be the duodenum, followed by the stomach, colorectum, and the esophagus[6,15]. A liver biopsy may also be performed to confirm hepatic infiltration of the amyloid proteins; however, a transjugular route should be used to prevent fatal bleeding complications[43,44]. Additionally, the study by Yen *et al*[15] reported biopsy negative disease in 55% of the patients. However, these patients met the Rome IV criteria for several functional bowel disorders, but only 23.2% underwent additional diagnostic studies for functional assessment of the luminal gastrointestinal tract (such as esophageal or anorectal manometry, capsule endoscopy, or gastric emptying studies)[6]. Hence, the authors recommend the need for additional diagnostic studies to evaluate for motility disorders in patients with clinical features of GI amyloidosis but a negative result on biopsy.

Amyloid fibrils appear as amorphous, eosinophilic deposits on routine hematoxylin-eosin stained preparations, which may sometimes be confused with hyaline changes or sclerosis[45]. Hence, CR staining with the characteristic apple-green birefringence of CR-stained deposits under polarized light has been considered the gold standard for a definitive diagnosis since its inception[45]. However, despite a high sensitivity and specificity of the CR-staining method, false negative results may be seen due to the quantity of amyloid deposition in the tissue, the age of the deposits, thickness of the sections for visualization, fixation of the tissues on the slide, or the staining procedure itself[46]. Therefore, newer methods are being developed to act as an adjunct for diagnosis. Digitally reinforced hematoxylin-eosin polarization (DRHEP), a newly introduced technique which uses both routine light microscopy and digital photography, can detect weak birefringence which is not recognized through the microscope objective[45]. Although the use of DRHEP is currently limited to kidney biopsies, its role for GI amyloidosis is currently under investigation[45].

TREATMENT

Once the diagnosis of GI amyloidosis is established, the biopsy specimen needs further analysis to determine the subtype of amyloid deposition which can then help guide therapy[47]. The management of GI Amyloidosis includes:

Symptomatic management

Symptom control in patients with GI amyloidosis is tailored to the clinical presentation. In patients with symptoms of dysmotility (stasis syndrome), dietary modifications, adequate hydration, and the use of pro-kinetic and anti-emetic agents is advised. Dietary modification consists of frequent, small-volume liquid or homogenized foods with low soluble fibre and fat content along with additional nutritional supplementation when necessary[48]. Prokinetic agents such as metoclopramide, erythromycin or domperidone (if indicated) are the mainstay of therapy for dysmotility[48]. Parenteral nutrition is indicated in severe cases of chronic GI dysmotility. Patients with dysphagia may be successfully treated with balloon dilation[49]. For patients with diarrhea or bloating, anti-diarrheal agents such as loperamide should be initiated[50]. Empiric antibiotic therapy should be considered in patients with diarrhea and suspected bacterial overgrowth. In patients with severe diarrhea associated with protein-losing enteropathy, literature reports good response to corticosteroid and octreotide therapy[51,52]. The management for GI bleeding includes triage to appropriate settings, supportive measures, volume resuscitation if needed, and source control through ligation of the bleeding blood vessel. Surgical intervention may be necessary in cases of severe obstruction, uncontrolled GI hemorrhage or bowel ischemia[8,53]. Patients with macroglossia causing airway obstruction or obstructive sleep apnea may need partial resection of the tongue to alleviate symptoms[54].

Treatment of the underlying condition for systemic amyloidosis

No specific treatment protocols currently exist for the management of GI amyloidosis. Therapy varies significantly depending on the cause and type of amyloid protein deposited within the tissues (Table 3). The current management strategies based on the type of amyloid deposits available in literature include:

AL amyloidosis: The therapy is aimed at suppressing the production of monoclonal

Table 3 Management of gastrointestinal amyloidosis based on the amyloid protein

Gastrointestinal amyloidosis	AL amyloidosis	AA amyloidosis	Hereditary amyloidosis	Dialysis-related amyloidosis
Treatment strategy	Systemic: Eligible: Autologous stem cell transplantation (ASCT) for plasma cell dyscrasias. Non-eligible: No standard protocol; combination of Bortezomib, Melphalan and Dexamethasone has shown improved survival. Localized: Observation or localized surgical excision	Chronic inflammatory conditions: Biologics (anti-TNF antibodies, humanized anti-IL6 receptor antibody) and immunosuppressants. Familial mediterranean fever: Colchicine.	Liver production of transthyretin: Orthotopic liver transplantation (OLT). Disease modifying therapy: Transthyretin stabilizers (Tafamidis and Diflunisal), Doxycycline, Patisiran and Inotersen may be used on case-to-case basis	Prevention: Removal of plasmatic β2-microglobulin ($A\beta_2M$) through hemodialysis or peritoneal dialysis. Early renal transplant

immunoglobulin light chains through eradication of the malignant plasma cells[55]. Autologous stem cell transplantation is the standard of care for plasma cell dyscrasias in eligible patients[55]. For patients not eligible to receive autologous stem cell transplantation, the management guidelines are unclear; however, the use of combination therapy with Bortezomib, Melphalan and Dexamethasone has shown improved hematologic response rate and overall survival[56]. The addition of Daratumumab (human monoclonal antibody against CD38) to bortezomib-based therapy has been evaluated but the results are yet to be published[55]. Furthermore, a fully humanized monoclonal IgG1 anti-serum amyloid P component antibody (Dezamizumab) is also under evaluation for AL amyloidosis[57].

AA Amyloidosis: Therapy is specifically directed at controlling the underlying disease which in turn helps reduce the acute phase response and production of serum amyloid A protein. Colchicine is used in the treatment of patients with Familial Mediterranean Fever[58]. Biologic agents (activity against pro-inflammatory cytokines such as TNF-alpha, IL-1, and IL-6), cytotoxic agents and immunosuppressants have a key role to play in the management of underlying chronic inflammatory conditions such as rheumatoid arthritis, inflammatory bowel disease, and psoriatic arthritis among others.

Hereditary amyloidosis: Therapy is aimed to eliminate the source of production of the genetically variant protein. The liver produces most of the circulating TTR in the body. Orthotopic liver transplantation can be used to significantly reduce the production of the mutant protein in patients where the liver is the culprit[59]. Other disease modifying therapies such as TTR Stabilizers (Tafamidis and Diflunisal), Doxycycline, Patisiran and Inotersen may also be considered on a case-to-case basis[59]

Dialysis-related amyloidosis: No medical or pharmacological therapy currently exists for dialysis-related amyloidosis[60]. The prevention and treatment consists of removal of plasmatic $A\beta_2M$ through hemodialysis or peritoneal dialysis using ultrapure dialysate or with more biocompatible and high-flux membranes[60]. Furthermore, early and successful renal transplantation leads to reduction in $A\beta_2M$ levels, which after a few years may lead to regression of the already deposited amyloid proteins[61].

Treatment of localized amyloidosis: It is characterized by deposition of AL amyloid restricted to the GI tract. For patients who are asymptomatic, no intervention may be needed, and observation may be the key; however, patients with recurrent or severe symptoms may require localized surgical excision.

Moreover, the treatment strategies for GI amyloidosis are consistently evolving with a better understanding of the disease pathology and the development of newer agents with target specific actions. Clinical trials to assess the efficacy and the toxicity profile of newer agents are currently ongoing and available at clinicaltrials.gov[62].

PROGNOSIS

The prognosis of GI amyloidosis depends on the extent of involvement of the GI tract, the quantity of deposition and the type of amyloid deposition. Literature reports that patients with AL amyloidosis and GI tract involvement had a worse prognosis than those without GI involvement[63]. Additionally, patients with GI amyloidosis had involvement of additional organs, an increased number of poor prognostic factors, and

a more advanced disease than those without the involvement of the GI tract[63]. Patients with AA amyloidosis were reported to have better median survival outcomes[64]. Involvement of the liver was associated with poor prognosis and increased mortality, particularly in patients with jaundice at the time of initial presentation and those with elevated direct serum bilirubin levels (> 2 mg/dL)[25,34].

CONCLUSION

Amyloidosis is characterised by the extracellular deposition of autologous fibrillar proteins aggregated into three-dimensional ß-pleated sheets aligned in an anti-parallel fashion. Based on the location of production of amyloidogenic precursor protein and its deposition in tissues, it can be divided into two distinct subtypes, systemic and localized amyloidosis. Involvement of the GI tract (GI amyloidosis) may be seen with both subtypes. Patients with GI amyloidosis commonly present with fatigue, light-headedness, anorexia, weight loss, GI bleeding, features of malabsorption, protein-losing enteropathy, or chronic GI dysmotility. Infiltration of amyloid proteins in the liver may also be seen, often presenting with hepatomegaly and mild elevations of ALP. Presence of jaundice with liver involvement (elevated direct bilirubin levels > 2 mg/dL) is associated with a poor prognosis. Radiological investigations are usually non-specific, and a definitive diagnosis is established with a tissue biopsy followed by CR-staining. The characteristic apple-green birefringence of the CR-stained deposits under polarized light is diagnostic. In patients with a negative biopsy from the GI tract, the authors recommend for the need of additional investigations for motility disorders and referral to a gastroenterologist. The use of DRHEP, a newly introduced technique, is also being explored to aid in diagnosis. For all patients with localized GI amyloidosis, the management consists of observation or localized surgical excision; however, for those with systemic GI amyloidosis, therapy is directed towards the underlying disease pathology. Symptomatic management in these patients is tailored to the presenting symptoms. The overall survival outcome depends on the extent of involvement of the GI tract, the quantity, and type of amyloid deposition.

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ORIGINAL ARTICLE

Retrospective Study

Cost-effectiveness of endoscopic ultrasound-guided coils plus cyanoacrylate injection compared to endoscopic cyanoacrylate injection in the management of gastric varices

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Informed consent statement:

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Abstract

BACKGROUND

Cyanoacrylate (CYA) injection can be performed using a standard upper endoscopy technique or under endoscopic ultrasound (EUS) guidance alone or in combination with coils. There is little information available on the economic impact of these treatment methods.

AIM

To compare the cost-effectiveness of treating gastric varices by CYA injection *via* upper endoscopy *vs* coils plus CYA guided by EUS.

METHODS

This was an observational, descriptive, and retrospective study. Patients were allocated into two groups: A CYA group and coils plus CYA group. The baseline characteristics were compared, and a cost analysis was performed.

RESULTS

Overall, 36 patients were included (19 in the CYA group and 17 in the coils + CYA group). All patients in the CYA group had acute bleeding. They underwent a higher mean number of procedures (1.47 *vs* 1, $P = 0.025$), and the mean volume of glue used was 2.15 *vs* 1.65 mL, $P = 0.133$. The coils + CYA group showed a higher technical success rate (100% *vs* 84.2%), with a complication rate similar to the CYA group. The majority of CYA patients required hospitalization, and although the mean total per procedure cost was lower (United States $ 1350.29 *vs* United States

Informed written consent was provided from all study participants or their legal guardians for attendance and research purposes.

Conflict-of-interest statement: Carlos Robles-Medranda is a key opinion leader and consultant for Pentax Medical, Boston Scientific, G-tech medical supply and MD consulting group. The other authors have nothing to disclose.

Data sharing statement: All available data can be requested by contacting the corresponding author.

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$ 2978), the mean total treatment cost was significantly different (United States $ 11060.89 for CYA *vs* United States $ 3007.13 for coils + CYA, $P = 0.03$).

CONCLUSION

The use of EUS-guided coils plus cyanoacrylate is more cost-effective than cyanoacrylate injection when the total costs are evaluated. Larger, randomized trials are needed to validate the cost-effectiveness of the EUS-guided approach to treat gastric varices.

Key Words: Cost-effectiveness; Endoscopic ultrasound-guided therapy; Gastric varices; Gastrointestinal bleeding; Hemostasis; Therapy

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Core Tip: There is little evidence regarding the economic impact of standard endoscopic cyanoacrylate therapy *vs* endoscopic ultrasound (EUS)-guided endovascular therapy in the management of gastric varices. In this retrospective study, we found that patients treated with endoscopic cyanoacrylate injection required hospitalization and had a significantly higher total treatment cost in comparison to those treated with an EUS-guided therapy. The incremental cost-effectiveness ratio analysis shows that in endoscopic therapy, each early rebleeding, adverse events, and day of hospitalization increased health-related costs on United States $ 2670.80, United States $ 8012.40, United States $ 127.18 per presented event, respectively, when comparing with coils + cyanoacrylate group cost and presented events. Each inevitable death on the endoscopic group represented a health-related cost increase on United States $ 8012.40 in comparison with EUS-guided therapy.

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INTRODUCTION

Variceal bleeding is the most expensive of all digestive diseases in terms of hospitalization charges[1]. Although the prevalence of gastric varices (GV) is lower than esophageal varices (5% to 33%), and the risk of bleeding is also lower for GV than esophageal varices, the bleeding from GV can be severe, and the associated mortality rate is high[1]. The incidence of bleeding was reported to be 25%, with re-bleeding rates as high as 40% and mortality rates of 50%[2].

Endoscopy sclerotherapy with cyanoacrylate glue (CYA) has demonstrated higher hemostasis (> 90%) and lower rebleeding rates compared to band ligation or sclerotherapy with alcohol products for the management of GV[3]. However, this procedure has been shown to be associated with significant adverse events. For example, pulmonary embolism due to CYA injection is a serious and sometimes fatal complication, which is seen in 4.3% of cases and is dependent on the volume of glue injected[3]. Other related complications may include hemorrhage from post-injection ulcers, fever, abdominal pain, and needle impaction. In addition, the injection material can cause serious damage to the endoscope[4].

Currently, endoscopic treatments with CYA injection can be performed under direct visualization using a standard gastroscope or under endoscopic ultrasound (EUS) guidance with the injection of CYA alone or in combination with coils[5]. There is little information available in the current literature on the economic impact of these treatment methods for GV.

The aim of this study was to compare the cost-effectiveness of GV treatment with two different techniques, CYA glue injections using a standard gastroscope *vs* the use of coils plus CYA guided by EUS.

P-Reviewer: Goral V
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MATERIALS AND METHODS

Study design

This was an observational, analytic, retrospective cohort study conducted in patients with cirrhosis and variceal bleeding, attended at an academic tertiary center in Guayaquil, Ecuador from November 2014 to March 2016 (Figure 1). The patients were categorized into two groups: One treated with only CYA injection by the standard upper endoscopy technique (CYA group) and the other treated by the EUS-guided insertion of coils + CYA injection (Coils + CYA group). The protocol of the study and consent form were approved by the Institutional Review Board, and the study was conducted according to the Declaration of Helsinki. All patients provided written informed consent for attendance purposes.

Population selection

For the study analysis, we considered ≥ 18 years old patients with gastroesophageal varices type II (GOV II, fundal varices communicating with esophageal varices) and isolated gastric varices type I (IGV I, fundal varices within a few centimeters of the gastric cardia) according to the classification described by Sarin and Kumar[6]. The study included patients with acute bleeding or a history of previous bleeding due to GV (secondary prophylaxis).

We did not include patients with concurrent hepatorenal syndrome and/or multi-organ failure; esophageal stricture; splenic or portal vein thrombosis; a platelets count less than 50.000/mL or an international normalized ratio > 2; pregnancy[7]; as well as patients with incomplete medical reports, or those without 6-mo follow-up.

General approach

One expert endoscopist (Robles-Medranda C) performed all endoscopic procedures in a hospital-based interventional endoscopy suite, where EUS and fluoroscopy were available. Endoscopic procedures were performed under general anesthesia and with antibiotic prophylaxis. After the procedure, the patients in both groups were observed for 2 h in the recovery room before being discharged. Patients were hospitalized if they had active bleeding or if they had early post-treatment bleeding according to the Baveno VI consensus[8]. All patients with acute upper GI bleeding admitted to receive a standard assessment and were given resuscitation fluid, antibiotics, blood components if necessary, and intravenous octreotide (50 μg bolus plus 50 μg/h) for at least 72 h. Upper endoscopy was performed within 24 h of hospital admission.

Endoscopic technique

A 3.2-mm forward-view endoscope (EG29-i10 and EG 2990-I series, Pentax Medical, Hoya Corp, Japan) was used to perform the standard endoscopic technique. EUS was performed using a 3.8-mm working channel linear-array therapeutic echoendoscope (EG 3870UTK; Pentax Medical, Hoya Corp, Japan) attached to an ultrasound console (Avius Hitachi, Tokyo, Japan). Active flow within the GFV was confirmed by color Doppler and fine flow Doppler color before and after the treatment.

CYA injection by upper endoscopy: The 2-Octyl-CYA (Dermabond; Ethicon, Piscataway, NJ, United States) was injected through a 21 or 22 G needle. This type of CYA precludes the need for a diluent, such as lipiodol. After puncturing varix and injecting the CYA, the needle was rinsed with saline solution. A proper dosage has not been established, and it is usually decided by the endoscopist at the time of intervention, taking into account gastric varix size and the initial success in arresting bleeding, considering that larger doses can increase the risk of embolism to distal organs. However, no more than 2.5 mL of CYA was injected per session per our institution's protocol for this technique (Figure 2).

EUS-guided deployment of coil(s) plus CYA injection: First, a standard diagnostic upper endoscopy was performed to classify the varices according to the classification described by Sarin and Kumar[6]. Then, an echoendoscope was positioned in the distal esophagus (anterograde transesophageal, transcrural approach) to endosonographically evaluate the gastric fundus, intramural varices, and gastric varices feeder vessels. Once positioned, water was instilled in order to fill the gastric fundus, improving the acoustic coupling and visualization of the GFV. EUS color Doppler imaging was used to allow direct visualization of the variceal flow. Then, a 19-gauge EUS-FNA needle (Expect flexible; Boston Scientific, United States) was used to puncture the vessel, the stylet was withdrawn, and a syringe with negative pressure was used to evaluate the blood return and therefore the intravascular location. Once

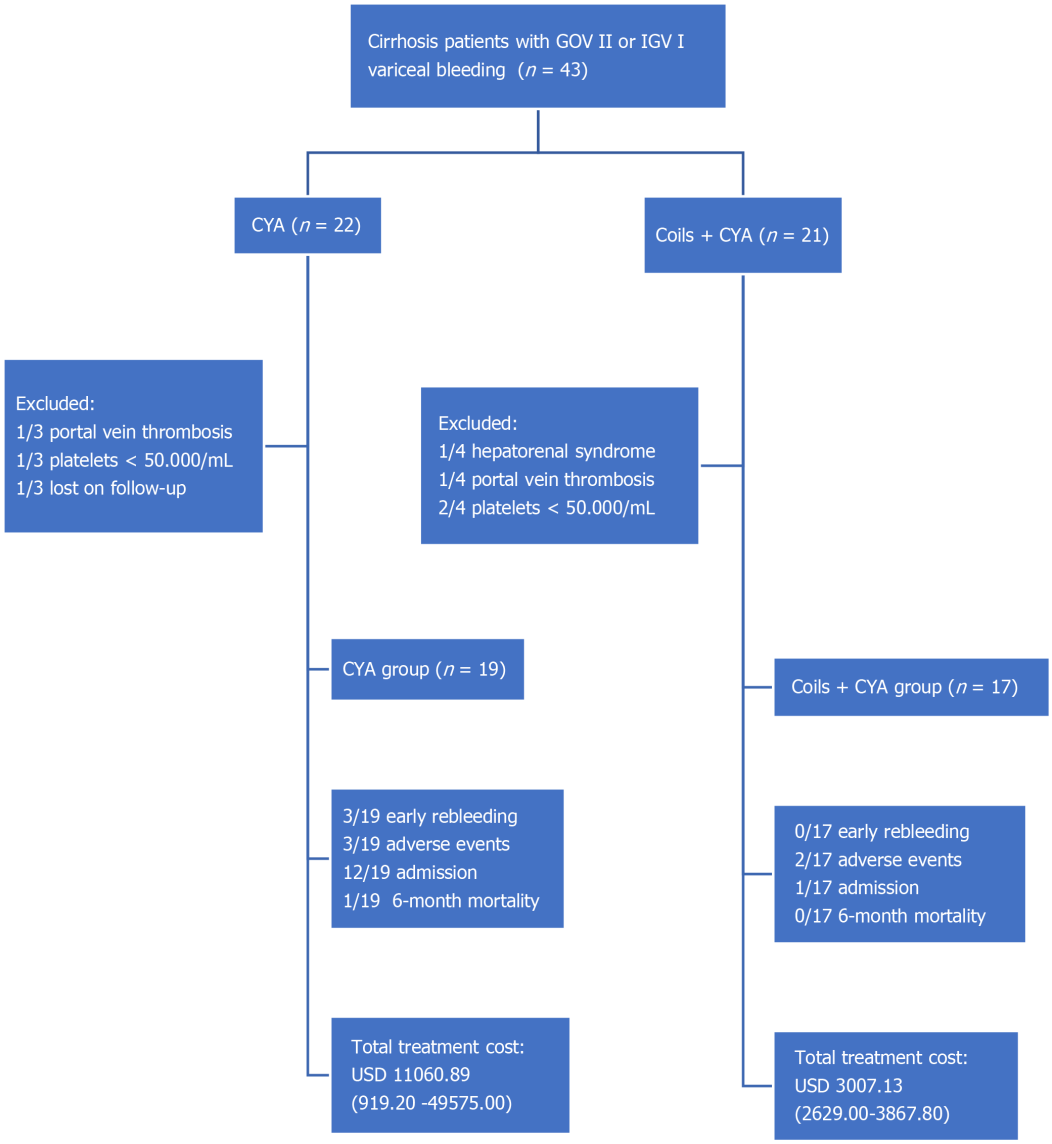

Figure 1 Study flowchart. CYA: Cyanoacrylate; GOV: Gastroesophageal varices; IGV: Isolated gastric varices; USD: United States dollar.

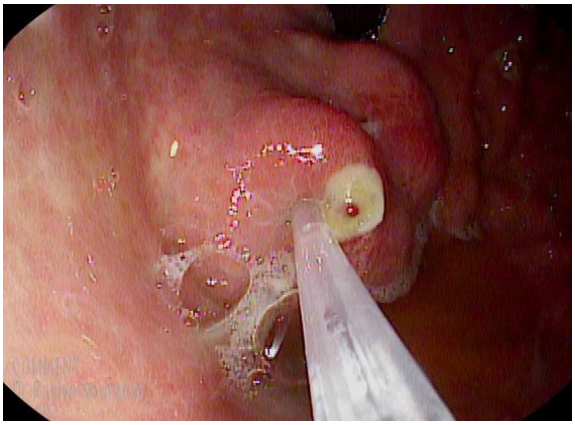

Figure 2 Endoscopic view of actively bleeding type II gastroesophageal varices treated with endoscopic cyanoacrylate injection.

the location was confirmed, 1 mL of saline solution was instilled to prevent blood clotting in the needle lumen, and then 2 mL of water-soluble contrast agent (Ultravist, Bayer, Ecuador) was injected under fluoroscopic evaluation to further ensure the intravascular location and to determine varix flow direction (afferent or efferent), as has been reported in a previous study[9]. Then, coils were delivered, and the 2-Octyl-CYA was injected. The coils used were intravascular embolization coils (10-16 mm coiled diameter, 12-20 cm straight lengths, 0.035 inches in diameter, Nester Embolization Coil; Cook Medical) and were delivered into the vessel through the FNA needle using the stylet as a pusher. Special attention was paid to not place the needle tip at the counter wall because of the risk of perforation, bleeding, and coil extrusion and to allow enough space for the coil to curl. The 2-Octyl-CYA (Dermabond; Ethicon, Piscataway, NJ, United States) was injected using the same needle, and then 1 mL of normal saline solution was injected to rinse the needle. The diameter and number of coils (10 to 16 mm) and the volume of 2-Octyl-CYA injected were calculated according to the diameter of the vessel measured on EUS. After 90 to 120 s, the CYA was solidified, the risk of bleeding due to the puncture decreased, and the needle was withdrawn. The final obliteration of the vessel was evaluated using Doppler imaging 5 min after withdrawal (Figure 3).

Patients follow-up and data abstraction

Efficacy was measured by technical success, defined as successful technique performance, and functional success, defined as the complete obliteration of varix by endoscopy and/or by the absence of Doppler flow on EUS. Safety was determined based on the development of adverse events related to the procedure within and 30 d after the procedure.

Follow-up was performed in accordance with our institution's protocol for these kinds of procedures by standard endoscopy in the CYA group and by EUS and upper endoscopy at 1, 3, and 6 mo post-procedure. Hemostasis, early post-treatment bleeding, and late post-treatment bleeding were considered according to the Baveno VI consensus[7].

Demographic data, endoscopic procedure records, cost variables [both endoscopic procedure and hospitalization; currency: United States of America dollar, United States dollar (USD); ISO 4217 code: USD] and clinical follow-up were obtained from institutional database register (SIAM V2.0, MD Consulting Group, Guayaquil, Ecuador). A 6-mo mortality was confirmed through the Ecuadorian Civil Registration database.

Statistical analysis

Technical considerations: The data analysis was reviewed by the institutional biostatistician (M.P-T.). Statistical analysis was performed using R v3.6.3 (R Foundation for Statistical Computing; Vienna, Austria). A P value < 0.05 was considered to be statistically significant.

Sample size: A sample of 15 participants per study group was calculated using corresponding formula to compare two means (two-samples, one-sided), on the basis of a 5% α error, a 20% β error, κ = 2, and a 3-mo post-bleeding mean charges (standard deviation, ± SD) between CYA-treated cases (USD: 42.450 ± 43.916) and controls (USD: 78.165 ± 47.857), as described by Greenwald *et al*[10].

Baseline characteristics: Demographic and clinical data were described by mean ± SD or median (minimum–maximum range) in accordance with statistical distribution (Shapiro–Wilk test), for quantitative variables, and frequency (percentage) for qualitative variables. Hospitalization length was described in a range of days. Cost variables were described as means considering it properly for economic data in terms of further cost analyses[10] but using the maximum-minimum range for easier comprehension of corresponding distribution. Data were also compared among CYA *vs* coils + CYA groups using Welch Two Sample *t*-test for normal-distributed and cost data, Mann–Whitney *U* test for skewed-distributed data, Pearson's Chi-squared or Fisher's Exact test for qualitative data, and Gray's test for the length of hospitalization.

Cost analysis: The incremental cost-effectiveness ratio (ICER) is a proportion of the difference in the mean cost of procedures between groups and the number of episodes of a specific outcome between groups, such as the number of deaths, adverse events, or days of hospitalization. This ratio represents the amount of money saved to prevent the aforementioned outcomes[11]. The ICER in the present study was established in terms of the following efficacy outcomes: Early re-bleeding, adverse effects, length of

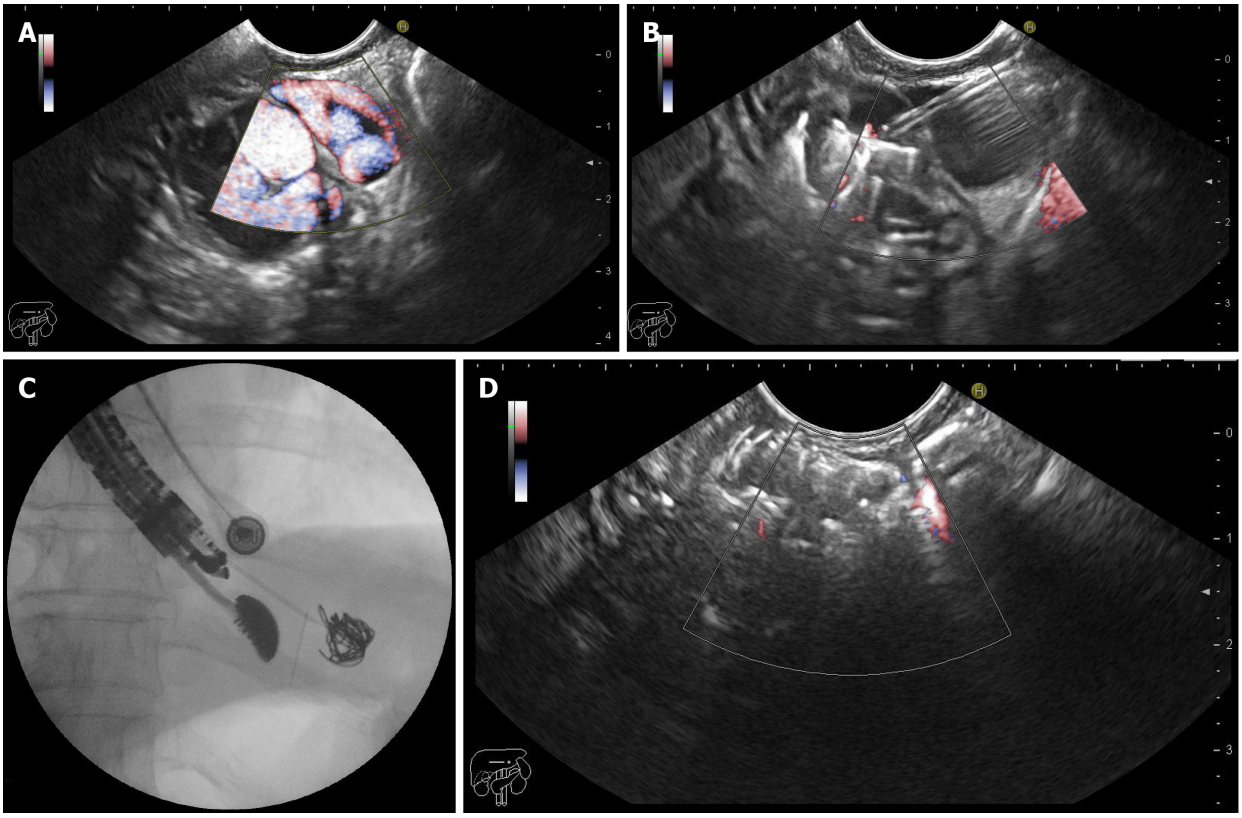

Figure 3 Endoscopic ultrasound-guided coiling plus cyanoacrylate injection for the management of gastric varices. A: Endoscopic ultrasound (EUS)-Doppler evaluation of the gastric varix feeder vessel; B: EUS-guided fine-needle puncture and cyanoacrylate injection; C: Fluoroscopic view of EUS-guided coiling of gastric varices; D: EUS-Doppler demonstrating absence of flow after combined therapy.

hospitalization, and 6-mo mortality. This corresponded to the difference between CYA *vs* coils + CYA in terms of the mean total treatment cost, divided by the difference between the numbers of events in each efficacy outcome, per the corresponding study group (Figure 4).

RESULTS

We enrolled 36 patients in the study (19 in the CYA group and 17 in the coils + CYA group. The overall mean age was 63.06 years old, and 20 (55.5%) patients were men. The baseline data are shown in Table 1.

Regarding the indications for the procedure, all 19 (100%) patients in the CYA group had a history of acute bleeding, while in the coils + CYA group, ten (58.8%) patients underwent the procedure for secondary prophylaxis.

GOV II type varices were predominant in both groups, being present in 12 (63.1%) and 12 (70.5%) patients in the CYA group and coils + CYA group, respectively. The mean varix size was 21.1 ± 8.7 mm in the CYA group and 22.6 ± 6.8 in the coils + CYA group.

The patients in the CYA group underwent a total of 28 procedures, with a mean of 1.47 procedures per patient. In this group, the mean volume of CYA used was 2.15 (0.6-2.4) mL. Conversely, in the coils + CYA, 17 procedures were performed (with a mean of 1 procedure per patient) using a mean volume of 1.65 (1.2-2.4) mL CYA and a mean of 2.1 (1-3) coils per patient. Technical success was achieved in 16 of the 19 (84.2%) patients in the CYA group, with 3 (15.8%) patients showing early rebleeding and with 3 (15.8%) adverse events, represented by 2 cases of pulmonary embolism and one death. In the coils + CYA group, technical success was achieved in all 17 (100%) patients, with no cases of early rebleeding and 2 (7.1%) adverse events (1 episode of fever and 1 of transient abdominal pain).

In relation to treatment modality, 13 (68.4%) patients in the CYA group were hospitalized for a mean of 3.36 (0–14) d, with most of the time spent in the Intensive Care Unit. Nevertheless, only 1 (5.9%) patient was hospitalized in the coils + CYA

Table 1 Baseline characteristics and cost description per intervention

	Total (*n* = 36)	CYA (*n* = 19)	Coils + CYA (*n* = 17)	*P* value
Age (yr), mean ± SD	63.06 ± 10.1	62.83 ± 11.5	63.29 ± 8.8	0.895[1]
Gender (female), *n* (%)	16 (44.4)	9 (47.4)	7 (41.2)	0.970[2]
Indication, *n* (%)				< 0.001[2]
Acute bleeding	26 (72.2)	19 (100.0)	7 (41.2)	
Secondary prophylaxis	10 (27.7)	-	10 (58.8)	
Type of GV, *n* (%)				0.906[2]
GOV II	24 (66.7)	12 (63.1)	12 (70.5)	
IGV I	12 (33.3)	7 (36.9)	5 (29.5)	
Varix size (mm), mean ± SD	21.8 ± 7.8	21.1 ± 8.7	22.6 ± 6.8	0.578[1]
Technical success (*n* of events), *n* (%)	33/36 (91.6)	16/19 (84.2)	17/17 (100)	0.231[3]
Volume of CYA (mL), median (range)	1.8 (0.6–6.6)	1.8 (0.6–6.6)	1.8 (1.2–2.4)	0.136
No of coils, median (range)	2 (1–3)	0	2 (1–3)	N/A

[1]Welch Two Sample *t*-test.
[2]Pearson's Chi-squared test with Yates' continuity correction.
[3]Fisher's Exact Test for Count Data. CYA: Cyanoacrylate; SD: Standard deviation; GV: Gastric varix; GOV: Gastroesophageal varices; IGV: Isolated gastric varices; USD: United States dollar; N/A: Not available.

$$ICER = \frac{mean\ cost\ Coils + CYA_{(u\$s)} - mean\ cost\ CYA_{(u\$s)}}{efficacy\ outcome\ Coils + CYA_{(n)} - efficacy\ outcome\ CYA_{(n)}}$$

Figure 4 The Incremental Cost-Effective ratio equation.

group, and this patient remained in the Emergency Department.

Concerning the financial aspects of the procedures, the cost per procedure with endoscopic CYA injection was USD 816.70 [mean of 1 203.56 (816.70-3266.80)], while it was USD 2247.00 (mean of 2247.00) with the EUS-guided approach. The mean total procedure costs were USD 1350.29 (857.70-3717.80) in the CYA group and USD 2978.00 (2629.00-3270.00) in the coils + CYA group. The hospitalization and mean total treatment costs were much higher in the CYA group, in which patients spent USD 9 710.60 (0-45857.20) and USD 11060.89 (912.20-49575.00), respectively. ICERs analysis lets us to estimate that in CYA group, each early rebleeding, adverse events, and day of hospitalization increased health-related costs on USD 2670.80, USD 8012.40, USD 127.18 per presented event, respectively, when comparing with coils + CYA group cost and presented events (Table 2). Each inevitable death on CYA group represented a health-related cost increase on USD 8012.40 in comparison with coils + CYA group (Table 3).

DISCUSSION

Despite advances in endoscopic techniques and devices, the treatment of gastric varices, particularly bleeding varices, is still a challenging issue. Several previous studies on this subject showed that there were advantages for the standard endoscopic injection of cyanoacrylate in the treatment of gastric variceal bleeding, with high success and low rebleeding rates[1,2]. Thus, cyanoacrylate injection became the first choice of treatment worldwide. Nevertheless, this approach carries a huge risk of adverse events, notably, systemic embolization[8]. To overcome this problem, recent studies suggested a new approach to gastric variceal bleeding using EUS-guided technique with coils deployment plus cyanoacrylate injection in the feeding vessels, with excellent short-term results[8].

Overall, the two groups in the present analysis did not differ in age or gender, although there were slightly more males, which is common for GV[1]. With regard to

Table 2 Study outcomes

	Total (*n* = 36)	CYA (*n* = 19)	Coils + CYA (*n* = 17)	*P* value
Early rebleeding (*n* of events), *n* (%)	3/36 (8.3)	3/19 (15.8)	0	0.231[1]
Adverse events (*n* of events), *n* (%)	5/36 (13.8)	3/19 (15.8)	2/17 (11.8)	1.000[1]
Treatment modality, *n* (%)				0.001[2]
Ambulatory	23 (63.1)	7 (36.8)	16 (94.1)	
Hospitalization	13 (36.1)	12 (63.2)	1 (5.9)	
No of endoscopic procedures, total	45	28	17	N/A
No. of endoscopic procedures per patient, median (range)	1 (1-4)	1 (1-4)	1	0.014[3]
Length of hospitalization (d), range	0–14	0-14	0–1	< 0.001[4]
Intensive care unit	0-11	0-11	-	0.012[4]
Intermediate care unit	0-14	0-14	-	0.001[4]
Emergency Department	0–1	-	0–1	0.303[4]
Cost per procedure (USD)	N/A	816.70	2247.00	N/A
Cost per procedure (USD), mean (range)	1696.29 (816.70-3266.80)	1203.56 (816.70-3266.80)	2247.00	< 0.001[5]
Coil cost (1 coil = $ 300, USD), mean (range)	291.67 (0-900.00)	0	617.65 (300.00-900.00)	< 0.001[5]
CYA cost (1 vial × 0.3 mL = $ 20.5, USD), mean (range)	130.97.00 (41.00-451.00)	146.74 (41.00-451.00)	113.35 (82.00-164.00)	0.141[5]
Total procedure cost (USD), mean (range)	2118.93 (857.70-3717.80)	1350.29 (857.70-3717.80)	2978.00 (2629.00-3270.00)	< 0.001[5]
Hospitalization cost (USD), mean (range)	5158.31 (0-45857.20)	9710.60 (0-45857.20)	70.46 (0-1197.80)	0.010[5]
Total treatment cost (procedure + hospitalization, USD) mean (range)	7277.20 (919.20-49575.00)	11060.89 (919.20-49575.00)	3007.13 (2629.00-3867.80)	0.030[5]

[1]Fisher's Exact Test for Count Data.
[2]Pearson's Chi-squared test with Yates' continuity correction.
[3]Mann–Whitney U test.
[4]Gray's test.
[5]Welch Two Sample *t*-test. CYA: Cyanoacrylate; SD: Standard deviation; GV: Gastric varix; GOV: Gastroesophageal varices; IGV: Isolated gastric varices, USD: United States dollar; N/A: Not available.

Table 3 Incremental Cost Effectiveness Ratio analysis

Efficacy outcome	ICER analysis
Early rebleeding (*n* of events)	(USD 3048.50) - (USD 11060.90)/(0) - (3) = US$ 2670.80
Adverse events (*n* of events)	(USD 3048.50) - (USD 11060.90)/(2) - (3) = US$ 8012.40
Length of hospitalization (total days)	(USD 3048.50) - (USD 11060.90)/(1) - (64) = US$ 127.18
6-mo mortality (*n* of events)	(USD 3048.50) - (USD 11060.90)/(0) - (1) = US$ 8012.40

ICER: Incremental Cost-Effectiveness Ratio; USD: United States of America dollar.

the indications for the procedure, ten (58.8%) patients in the coils + CYA group underwent the procedure for secondary prophylaxis, while all 19 (100%) patients in the CYA group had acute bleeding. In this retrospective analysis from our unit, the use of EUS-guided coils plus CYA was the preferred technique for the prevention of rebleeding.

Only fundal GOV II and IGV I varices were included in the present work because it is generally accepted that GOV I varices are best treated with endoscopic band ligation. Currently, there is no established treatment for IGV II vessels. We observed that the patients in the CYA group required significantly more procedures and a significantly larger mean amount of CYA to achieve hemostasis and variceal remission. Moreover, with the EUS approach, the coils work as a frame that retains

CYA within varix, with a fewer amount of cyanoacrylate needed to achieve obliteration, thus reducing the risk of adverse events, including embolism[5]. In our study, a mean of 1.65 (1.2-2.4) mL of CYA was used in the coils + CYA group, with two adverse events, one episode of fever and one transient abdominal pain, neither requiring hospitalization.

Technical success with the EUS coils + CYA method was achieved in all 17 (100%) patients (in one session), a much better performance compared with the CYA group. The EUS-guided technique used in this trial targets the perforating vessel instead of depending on direct variceal puncturing. Perforating vessels are thought to be the source of varix, and blocking the feeder, thus effectively decreasing the blood flow in gastric varix. Moreover, the use of EUS permits direct variceal visualization, which contributes to technical success, since the visual field with the standard endoscopic method can be obscured by blood and residue in the stomach. Despite this advantage, there were no differences in the numbers of patients with early rebleeding between the two groups in this study.

Although the cost per procedure and mean total procedure cost were higher for the EUS-guided approach, the total treatment costs were much higher in the CYA group, in which patients spent USD 11060.89 (912.20-49575.00). The later may be related to the fact that most patients in the latter group were hospitalized, and most of their time was spent in the Intensive Care Unit, which greatly increased the costs.

Overall, the use of EUS-guided coils plus CYA technique was more cost-effective than the current standard endoscopic therapy. The ICER demonstrated that the EUS-guided approach was advantageous in terms of cost savings. By performing this technique, we saved USD 2670.80 by preventing one early rebleed episode and USD 8012.40 by avoiding one death.

However, this study has some limitations. First, the patients who underwent the endoscopic CYA injection were all in an acute stage, and thus had a more severe clinical impairment, which naturally required more interventions, increased the length of hospitalization, and raised costs. Second, only adverse events in patients who were already hospitalized or returned to our facility after an exam were counted. Adverse events that occurred at home probably also generate costs and should be considered in future cost analyses. Finally, this study was designed retrospectively and conducted in a single center institution with a relatively small number of patients.

In a recent study, Romero-Castro *et al*[7] performed a thorax computed tomography (CT) scan on all patients who underwent an EUS-guided CYA injection, and they reported a very high incidence of asymptomatic pulmonary embolism that could have been missed by a clinical evaluation after the procedure. If a thorax CT was added to our EUS technique, the final treatment costs would significantly increase.

It is important to recognize that using hospital charges to estimate the costs of treatment poses a problem, because charges are different among institutions, and the treatment costs remain unknown for other institutions.

CONCLUSION

In conclusion, this preliminary analysis showed that the use of EUS-guided coils plus cyanoacrylate injection is more cost-effective than cyanoacrylate injection when the total costs are evaluated. Larger, multi-center studies are needed to address the cost effects of the EUS-guided approach of gastric varices.

ARTICLE HIGHLIGHTS

Research background

Bleeding gastric varices implies high morbidity and mortality in cirrhotic and noncirrhotic patients. Bleeding and rebleeding episodes, as well as their management, have a high health-related cost impact.

Research motivation

Currently, there is insufficient data about the cost-effectiveness of available therapies, mainly endoscopic cyanoacrylate injection and endoscopic ultrasound (EUS)-guided therapy for the management of gastric varices.

Research objectives
The study's main objective was to evaluate the cost-effectiveness of treating gastric varices, whether by the standard endoscopic cyanoacrylate injection or by the novel EUS-guided combined coiling and cyanoacrylate injection technique.

Research methods
This was an observational, descriptive, and retrospective study conducted in a single tertiary center. Patients with actively bleeding gastric varices and those with a history of bleeding were treated with either one of the two modalities. We evaluated the technical success and adverse event rates and the procedure and overall treatment costs.

Research results
We described a significantly higher number of procedures needed to achieve obliteration of gastric varices in the endoscopic cyanoacrylate group, with a higher number of admissions in this cohort. Technical and adverse events rates were not significantly different in the two groups. In terms of cost, endoscopic cyanoacrylate injection has a significantly higher mean total treatment cost, probably explained by a higher reintervention rate and hospitalization cost.

Research conclusions
In our study, EUS-guided combined therapy with coiling and cyanoacrylate injection proved to be more cost-effective than endoscopic cyanoacrylate injection in terms of the overall treatment cost.

Research perspectives
We encourage researchers to conduct a multicenter, randomized trial with a long-term follow-up comparing the endoscopic cyanoacrylate therapy *vs* the EUS-guided combined therapy with coiling and cyanoacrylate injection, in order to define formal therapeutical guidelines.

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CASE REPORT

Histoplasmosis and inflammatory bowel disease: A case report

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Abstract

BACKGROUND

Infection with *Histoplasma capsulatum* can lead to a disseminated disease involving the gastrointestinal tract presenting as diffuse abdominal pain and inflammatory diarrhea which may mimic inflammatory bowel disease (IBD).

CASE SUMMARY

In the current report, we discuss the case of a 41-year old male who presented to the emergency department with complaints of high-grade intermittent fevers and severe abdominal pain with associated diarrhea and hematochezia. Laboratory results demonstrated transaminitis and elevated erythrocyte sedimentation rate, C-reactive protein and ferritin levels. The patient's presentation was thought to be an exacerbation of his underlying IBD, but further investigations revealed a positive Histoplasma antigen in the urine. The patient was offered a colonoscopy and biopsy to confirm the diagnosis; however, he refused. He was treated with itraconazole and showed significant improvement of his symptoms, thereby confirming the diagnosis of gastrointestinal histoplasmosis.

CONCLUSION

Here within, we provide a review of IBD, evaluation of chronic diarrhea, and gastrointestinal histoplasmosis.

Key Words: Histoplasmosis; Inflammatory bowel disease; Intestine; Endoscopy; Gastroenterology; Case report

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Core Tip: Histoplasmosis can lead to a disseminating disease state affecting a large number of organ systems, leading to a wide range of pathology. This includes the gastrointestinal tract. We present herein, a case of gastrointestinal histoplasmosis in a patient with long standing ulcerative colitis that presented in a manner very similar to acute exacerbation of inflammatory bowel disease. This case highlights the importance of keeping gastrointestinal histoplasmosis amongst the differential diagnoses in cases that present similarly to acute exacerbation of inflammatory bowel disease in order to prevent inappropriate delays in diagnosis, unnecessary procedures, and increased morbidity and mortality.

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INTRODUCTION

Histoplasma capsulatum (H. capsulatum) var. *capsulatum* is a dimorphic fungus that is known to have prevalence throughout the world. In the Unites States, *Histoplasma capsulatum* is mainly endemic in the Ohio and Mississippi valley regions[1]. In the environment, it exists in its hyphal form, producing spores which are inhaled by humans initiating the infection[2]. In the body, the spores transform into the yeast phase, evading intercellular killing and being transported by macrophages to any organ in the body. This leads to disseminated histoplasmosis (DH). Dissemination to the gastrointestinal (GI) tract, known as gastrointestinal histoplasmosis (GIH), most commonly involves the colon and terminal ileum[3]. The most common presenting symptoms in patients with GIH are abdominal pain and inflammatory diarrhea[4]. Inflammatory bowel disease (IBD) is characterized by chronic inflammation of the intestinal mucosa through a complex immune mediated mechanism. The 2 main subtypes of IBD, Crohn's disease and ulcerative colitis (UC), are based on the histological involvement of the bowel. Common symptoms of IBD include diarrhea or constipation, hematochezia, severe diffuse abdominal pain, unintentional weight loss, significantly reduced apatite, fatigue and fever. Inflammatory diarrhea is a common feature seen both in GIH and IBD. The similarities in presentation, the pattern of the involvement of the gastrointestinal (GI) tract and the associated inflammation is the reason GIH is considered an IBD mimic. However, it is not commonly considered as one of the differential diagnoses in these patients. In patients with diagnosed IBD, GIH may be mistaken for an acute exacerbation of the underlying pathology. Our case report and review of the literature provides a step by step approach regarding IBD, GIH, and evaluating patients with chronic diarrhea. We strongly advocate and urge physicians to test patients with inflammatory diarrhea for *H. capsulatum*, particularly in endemic regions and those diagnosed with IBD presenting with a clinical picture suggesting exacerbation. Early diagnosis of GIH prevents inappropriate or delayed therapy, unnecessary surgical interventions and adverse outcomes.

CASE PRESENTATION

Chief complaints

A 41-year old male presented to the emergency department (ED) with chief complaints of high-grade intermittent fevers and severe abdominal pain.

History of present illness

The patient described the fever as episodic, high grade (maximum temperature of 103F), without chills or rigors, and associated with a non-productive cough for one week. He also complained of severe, intermittent, diffuse abdominal pain associated with diarrhea and hematochezia for 2 d prior to this ED visit. He did not have a sore throat, rhinorrhea, abdominal pain, joint pain or rash.

History of past illness

The patient had a past medical history significant for UC. The patient had lived in the Great Lakes region for his entire life, worked in construction for many years and had no history of recent travel. He lived with 3 young children who all had recently suffered from a viral respiratory tract infection lasting approximately 1 wk. He had pets at home including a gecko, a rabbit and 2 dogs. 10 mo prior, he had presented to the ED with similar complaints of diffuse abdominal pain and diarrhea associated with haematochezia for 6 wk. Investigation for common conditions such as gastrointestinal infections, endocrine disorders, food allergies and medication changes were ruled out, and a decision was made to perform a colonoscopy with tissue biopsy. Biopsy from the colon revealed non-specific histological findings *i.e.* crypt abscess, mild architectural distortion of the lamina propria and chronic inflammation. Markers of acute inflammation such as erythrocyte sedimentation rate (ESR) and c-reactive protein (CRP) were also found to be elevated, suggesting a diagnosis of UC. The patient was started on prednisolone 40 mg daily which lead to resolution of his symptoms. A decision was made to have the patient continue on prednisolone 40 mg daily after failed attempts to switch the regimen to mesalamine lead to mesalamine-induced pancreatitis, and treatment with Vedolizumab lead to an allergic reaction after the second dose.

Personal and family history

Family history was significant for IBD in his mother. The patient had no other significant past medical history.

Physical examination

On examination, he was febrile with a temperature of 103F, heart rate 112 beats/min, and blood pressure 124/74 mmHg. On abdominal examination, no tenderness was noted but mild splenomegaly was appreciated. The working diagnosis of the patient's presentation at this time was believed to be an acute exacerbation of his underlying UC.

Laboratory examinations

Laboratory investigations were ordered, and infectious disease was consulted, with recommendations to start broad spectrum antibiotics until a definite cause could be established. Laboratory investigations revealed a Hemoglobin of 11.8 g/dL, white blood cell (WBC) count of 4.1 × 10^9 cells/L with 70% granulocytes, 22% lymphocytes and 0.1% eosinophils. Procalcitonin was elevated at 0.39 and elevations in the liver enzymes were also noted with alanine aminotransferase 232 U/L, Alkaline phosphatase 266 U/L and aspartate transaminase 79 U/L. Blood cultures showed no growth, and stool analysis was negative for *Clostridium difficile* (*C. diff*) and parasites. Interestingly, *H. capsulatum* antigen was detected in the urine. Hence, the working diagnosis was changed from an acute exacerbation of UC to GIH.

Imaging examinations

To confirm the diagnosis of GIH, the patient was offered a colonoscopy with biopsy, however he refused this stating that he preferred treatment for *H. capsulatum* based on the high specificity of the urine antigen testing.

FINAL DIAGNOSIS

Based on the positive urine antigen for *H. capsulatum,* and the patients refusal to have repeat colonoscopy with biopsy, the presumed diagnosis was GIH.

TREATMENT

The patient was started on oral itraconazole 200 mg twice daily for presumed GIH infection.

OUTCOME AND FOLLOW-UP

Over the next several days, the patient experienced significant improvement of his symptoms confirming our diagnosis of GIH. He was subsequently discharged home on oral itraconazole for 6 mo, oral corticosteroids for his UC and an appointment to follow-up with his gastroenterologist within 6 wk.

DISCUSSION

This case report and brief review of the literature places great emphasis on keeping *H. capsulatum* as one of the differential diagnoses in patients with IBD presenting to the hospital with a clinical picture of an acute exacerbation of their underlying disease. In patients presenting to the ED with complaints of diffuse abdominal pain and chronic diarrhea with hematochezia, it is standard clinical practice to obtain a stool analysis and rule out *C. diff* and parasitic infection. However, specific tests for *H. capsulatum* are not usually performed. In this article, we discuss the presentation and management of patients with IBD. We also review the classification of specific subtypes of chronic diarrhea and further investigations that might be necessary to investigate the underlying pathology. Furthermore, we discuss the presentation and management of GIH, a subtype of DH, and advocate for the importance of considering *H. capsulatum* infection as a differential diagnosis in patients with IBD.

Diarrhea in IBD

IBD is a disease characterized by chronic inflammation of the intestinal mucosa through a complex immune mediated mechanism. The exact cause of IBD is currently unknown, but it is believed to be due to an abnormal intestinal mucosal immune response to environmental triggers leading to inflammation of the epithelial lining of the GI mucosa[5]. The immune system of the GI tract plays a vital role in providing an appropriate immune response to harmful pathogens, while inducing an immune tolerance to harmless food materials and commensal flora[6]. Literature reports a rise in incidence and prevalence of IBD in the adult and pediatric populations[7]. Although the exact reason for this increase is not clear, it is believed that an alteration in lifestyle and nutritional habits may play a significant role[8]. The Rochester epidemiology project noted an increase in the incidence and prevalence of IBD between 2001 and 2011, but this was attributed to an increase in overall life expectancy[9]. In light of increasing westernization and industrialization, Asian countries such as India, China and Iran are reporting significantly increased numbers of cases of IBD[10].

IBD can be classified into 2 major subtypes based on the clinical picture and distinct pathological characteristics[11]:

Ulcerative colitis: A chronic inflammatory condition characterized by relapsing and remitting episodes of inflammation limited only to the mucosal layer of the colon. The mucosa is involved in a continuous fashion with almost all cases reporting involvement of the rectum.

Crohn's disease: A chronic inflammatory condition characterized by a full thickness (transmural) involvement of the bowel and the presence of skip lesions (areas of disease between normal appearing bowel). It most commonly involves the ileum and the proximal part of the colon; however, any part of the GI tract may be involved.

The spectrum of symptoms in patients with IBD depend on the severity of the inflammation and can range from very mild to severe. The common symptoms of IBD include diarrhea or constipation, hematochezia, severe diffuse abdominal pain, unintentional weight loss, significantly reduced appetite, fatigue, and fever.

The initial step in the evaluation of a patient with IBD includes a detailed history and physical examination. The history may be critical in differentiating patients with IBD from other organic and functional causes. A thorough physical examination in patients with IBD may reveal mild to moderate abdominal tenderness without distention. Initial laboratory investigations may reveal an elevation of the markers of inflammation *i.e.* ESR and CRP. In patients with acute diarrhea as the presenting symptom, stool studies to rule out infectious etiologies such as *C. diff* and parasites should also be performed. Fecal calprotectin, a stool marker for inflammation, can also be used to determine the presence of intestinal inflammation in patients with clinical suspicion of IBD[12]. If the fecal calprotectin value is above the reference range (50 mcg/g), ileocolonoscopy with biopsy and/or small bowel imaging can be used to diagnose IBD and assess the degree of mucosal inflammation[13]. Although

ileocolonoscopy with biopsy is the preferred method to establish a definitive diagnosis and assess the degree of inflammation, radiological imaging modalities such as computed tomography (CT) enterography, magnetic resonance enterography (preferred over CT enterography), capsule endoscopy, or GI Ultrasound can also be used in certain situations[14]. The management of IBD is primarily focused on providing symptomatic relief, rapid induction of steroid-free remission, and prevention of complications of the disease and its treatment[15]. The choice of therapy is based on the extent and degree of the severity of the disease, its responsiveness to previous therapy, and the individual patient characteristics[15]. Some agents used in the treatment of IBD include Sulfasalazine, Mesalamine, Olsalazine, Balsalazide, Corticosteroids, Azathioprine, 6-Mercaptopurine, Methotrexate, Infliximab, Adalimumab and Tacrolimus.

Due to the chronic inflammation in IBD, patients can present with multiple complications. These complications are usually associated with a specific subtype of IBD due to the pattern of the inflammation, but some may be shared between the two. The complications include[16]:

Common complications: Colon cancer, Arthritis, Uveitis, Primary Sclerosing Cholangitis and hypercoagulable states.

Ulcerative colitis: Toxic Megacolon, perforation of the colon and severe dehydration.

Crohn's disease: Bowel obstruction, ulcers, fistulas and anal fissures.

Evaluation of patients with chronic diarrhea

Diarrhea is objectively defined as passing a stool weight or volume greater than 200 g or 200 mL per 24 h[17]. According to the Centers for Disease Control and Prevention, chronic diarrhea is defined as diarrhea that lasts for longer than 2-4 wk[18]. The initial investigation into the evaluation of chronic diarrhea starts with an extensive history and examination to formulate a preliminary differential diagnosis. The appearance of the stool can be categorized into one of the three major subtypes for further diagnostic investigations[19]:

Fatty (Malabsorptive) diarrhea: The initial investigations in patients with malabsorptive diarrhea are aimed at ruling out anatomic defects. Radiological investigations of the abdomen, and sigmoidoscopy or colonoscopy with or without biopsy may help to diagnose the specific underlying etiology. A positive stool chymotrypsin level confirmed with a positive secretin test is diagnostic for pancreatic insufficiency.

Inflammatory diarrhea: In patients with a suspected inflammatory cause of their diarrhea, stool analysis is always the initial investigation of choice. Stool analysis positive for blood, WBC, and fecal calprotectin points toward a diagnosis of IBD. This can be confirmed with a colonoscopy and biopsy of the involved bowel. In patients with absence of WBC in the stool and a negative stool analysis, additional investigations are needed to identify the underlying cause. Testing for *C. diff* has become standard practice in patients with inflammatory diarrhea. We strongly advocate and urge physicians to test for *H. capsulatum*, particularly for patients in endemic regions and in those with IBD, as literature reports a high prevalence of GIH in autopsy specimens.

Watery diarrhea: The initial investigation of choice is the measurement of the fecal osmotic gap. A high fecal osmotic gap (> 125 mOsm per kg) along with a history of increased diarrhea on consumption of dairy products and a positive hydrogen breath test confirms the diagnosis of lactose intolerance. A normal fecal osmotic gap with improvement in the symptoms on dietary modification is usually seen in patients with irritable bowel syndrome. However, patients with a normal fecal osmotic gap and no improvement with dietary modifications may require further workup for Celiac disease, which includes a celiac panel. Patients with low osmolar gap (< 50 mOsm per kg) may need additional imaging, blood, and urine testing to investigate other possible etiologies.

It is important to recognize that diarrhea is not a disease but rather a symptom of the underlying pathology. Patients with ulcerative colitis will have inflammatory diarrhea with the presence of pus and blood on stool analysis. Furthermore, mimics of IBD such as GIH may also present with inflammatory diarrhea such as that in our case report. Therefore, it becomes extremely important to differentiate an acute exacerbation of UC from other causes in order to initiate appropriate therapy early and

prevent adverse outcomes.

H. capsulatum and the gastrointestinal tract

Histoplasmosis is an endemic mycosis caused by a dimorphic fungus called *H. capsulatum*. The two distinct varieties of *Histoplasma* that are pathogenic to humans include *H. capsulatum* var. *capsulatum* which is prevalent worldwide in endemic areas, and *H. capsulatum* var. duboisii which is restricted to the Sub-Saharan Africa region[1]. In the United States, endemic regions with a high prevalence of histoplasmosis include areas centered in the Ohio and Mississippi river valleys. An analysis of the data from hospital records in 2002 revealed 3370 inpatient stays and 254 deaths associated with histoplasmosis with almost 90% of these hospitalizations in the midwestern and southern regions of the United States[20]. *H. capsulatum* var. *capsulatum* is dimorphic meaning that it exists in two distinct forms. It grows in its hyphal form in soil, and bird and bat guano, but upon inhalation of the spores, it transforms into the pathogenic yeast form, replicating inside the macrophages[2]. These macrophages can transport the yeast to virtually any organ in the body leading to DH[2]. Although *H. capsulatum* is non-contagious and humans are the dead-end or accidental hosts for fungal replication, it appears to be specifically well adapted to the mammalian host cells. The pathogenic yeast phase is equipped to evade intercellular killing by macrophages with mechanisms to degrade reactive oxygen species, regulate lysosomal pH and capture essential nutrients that might otherwise be deprived[2]. Human infections by *H. capsulatum* usually present as acute pulmonary histoplasmosis, chronic pulmonary histoplasmosis, cutaneous histoplasmosis, rheumatologic histoplasmosis, ocular histoplasmosis, mediastinal histoplasmosis, broncholithiasis, and progressive disseminated histoplasmosis extending to the brain[21]. DH is commonly seen in immunocompromised states with low CD4 cell counts (< 200 cells/mm^3), such as in acquired immune deficiency syndrome patients and also rarely in patients with human T-lymphotropic virus 1 infection.

DH to the GI tract, also known as GIH, is a rare entity. Involvement of the GI tract in DH is very non-specific, may involve any area of the GI tract and is usually seen in immunocompromised patients. However, the most common sites of involvement are the terminal ileum and the colon due to abundance of lymphoid tissue[3]. The involvement becomes less common more proximally in the intestine[3]. Literature reports high rates of GIH in autopsy specimens, indicating a higher prevalence of asymptomatic disease[22]. The most common presenting symptoms in patients with GIH are abdominal pain and diarrhea[4]. This diarrhea could be intermittent and typical of that seen in other diseases, or could be unremitting and associated with malabsorption[23]. Bloody diarrhea may also be present in a subset of patients with GIH and often mimics IBD, thereby making it difficult to differentiate between IBD and GIH, such as that in our case[24]. Other symptoms associated with GIH may include irregular fevers with or without chills and night sweats, anorexia, weight loss of varying degrees, and abdominal distention[25]. On physical examination, patients may have hepatosplenomegaly, peripheral lymphadenectasis, abdominal tenderness and rebound tenderness concerning for peritonitis[25]. The similarities in presentation, the pattern of the involvement of the GI tract and the associated inflammation is the reason as to why GIH is considered a mimic of IBD.

Laboratory investigations in patients with GIH may reveal an elevation in the alkaline phosphatase levels, lactate dehydrogenase, and increased levels of markers of inflammation such as ESR, CRP and serum ferritin levels[26]. In our case, elevations in all of the liver enzymes were noted along with elevations in the ESR and CRP. Pancytopenia may indicate an underlying immunocompromised state. Although none of these investigations are diagnostic for *H. capsulatum*, they direct the physician to consider an infectious etiology as a differential diagnosis for the presenting symptoms. For patients with suspected DH, Histoplasma antigen enzyme immunoassay of the serum and urine should be performed. Urine antigen-enzyme immunoassay has a high sensitivity (89.47%) and specificity (100%) in the detection of *H. capsulatum*[27]. Radiological investigations such as CT scan and magnetic resonance imaging may also help point physicians towards a diagnosis of GIH, while ruling out other etiologies of bloody diarrhea. The radiological findings with GIH may include[28]: Bowel wall thickening; Mass-like lesions in the bowel; Signs suggesting small bowel obstruction; Bowel perforations, although rare, may show free intraperitoneal air; Hepatosplenomegaly; Generalized lymphadenopathy.

The most common endoscopic findings in patients with GIH are unifocal or multifocal mucosal ulcerations[28]. Polypoid lesions, strictures, and obstructing masses may also be noted[29]. The definitive diagnosis of GIH is always established with colonoscopy and biopsy of the lesions which may reveal the typical 2 to 4-micron yeast

structure of *H. capsulatum*. Although the histopathology specimens of the fungus can be stained with hematoxylin and eosin, it is better visualized using the methenamine silver or periodic acid-schiff stain. It is also always preferable to have culture evidence of *H. capsulatum* for diagnosis. However, in our case, a colonoscopy with biopsy was offered to the patient, who refused the procedure as he had a colonoscopy with biopsy 10 mo prior to establish a diagnosis of UC and did not wish to undergo the procedure again. After learning about the positive results of the urine antigen testing for *H. capsulatum* and that GIH can be a mimic for an acute exacerbation of UC, the patient wanted to proceed with the treatment for GIH and deferred the procedure to a later date if there was no improvement in his symptoms.

The treatment of DH and the selection of the appropriate agent for therapy depends primarily on the severity of the disease. The treatment strategy (summarized in Table 1) can be classified as[30]:

Severe disease: Liposomal Amphotericin B 3 mg/kg daily, or Amphotericin lipid complex 5 mg/kg daily, or Amphotericin deoxycholate 0.7 to 1 mg/kg daily for one to two weeks followed by itraconazole 200 mg twice daily for a minimum of 2 mo.

Mild to moderate disease: Itraconazole 200 mg twice daily for a minimum of 2 mo.

CNS histoplasmosis: Liposomal Amphotericin 5 mg/kg daily for four to six weeks followed by itraconazole 200 mg two to three times daily for a minimum of 2 mo.

Most patients with disseminated Histoplasmosis respond well to antifungal therapy. Early diagnosis and treatment of the GIH is essential to prevent serious adverse outcomes. Perforation of the bowel and hemorrhage are two of the most serious complications reported in patients with GIH.

The clinical manifestations of GIH may mimic other GI diseases such as IBD, including UC and Crohn's disease, tuberculosis, carcinomas and lymphomas. However, it is commonly not considered as one of the differential diagnoses in patients presenting with abdominal pain and chronic diarrhea with hematochezia[4]. This usually leads to inappropriate or delayed therapy, unnecessary surgical interventions and adverse outcomes. Our article places great emphasis on the importance of testing in order to rule out GIH in patients who present with clinical characteristics of a sudden onset acute exacerbations of IBD without an underlying cause.

CONCLUSION

H. capsulatum is a dimorphic fungus endemic in the Ohio and Mississippi valley regions. *H. capsulatum* var. *capsulatum* is prevalent worldwide and is seen in the United States. *H. capsulatum* exists in its hyphal form in the environment and inhalation of the spores produced by this form are infectious to humans. After infection of the host, it transforms into the pathogenic yeast form which replicates inside the macrophages and evades intracellular killing. Macrophages can disseminate the fungus to any organ in the body leading to DH. In the gastrointestinal tract, most common sites of involvement are the terminal ileum and the colon due to abundance of lymphoid tissue. The most common presenting symptoms in patients with GIH are abdominal pain and diarrhea. GIH often mimics IBD due to similarities in presentation, the pattern of the involvement of the GI tract and the associated inflammation. Hence, for patients with inflammatory diarrhea, or those with diagnosed IBD with clinical characteristics of a possible acute exacerbation without an underlying cause, GIH should be among the differential diagnoses. The diagnosis of GIH is confirmed with colonoscopy and biopsy of the involved region of the GI tract. The treatment of DH depends on the severity of the disease.

Table 1 Treatment strategies based on the severity of disseminated histoplasmosis

Disseminated histoplasmosis	Mild disease	Moderate disease	Severe disease	CNS histoplasmosis
Treatment	Itraconazole 200 mg twice daily (minimum of 2 mo)	Itraconazole 200 mg twice daily (minimum of 2 mo)	Liposomal Amphotericin B 3 mg/kg daily for 1-2 wk or Amphotericin lipid complex 5 mg/kg daily for 1-2 wk or Amphotericin deoxycholate 0.7 to 1 mg/kg daily for 1-2 wk followed by Itraconazole 200 mg twice daily (minimum of 2 mo)	Liposomal Amphotericin 5 mg/kg daily for 4-6 wk followed by Itraconazole 200 mg 2-3 times daily (minimum of 2 mo)

CNS: Central nervous system.

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OPINION REVIEW

Dilation assisted stone extraction for complex biliary lithiasis: Technical aspects and practical principles

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Abstract

Common bile duct stones are frequently diagnosed worldwide and are one of the main indications for endoscopic retrograde cholangio-pancreatography. Endoscopic sphincterotomy (EST) has been used for the removal of bile duct stones for the past 40 years, providing a wide opening to allow extraction. Up to 15% of patients present with complicated choledocholithiasis. In this context, additional therapeutic approaches have been proposed such as endoscopic mechanical lithotripsy, intraductal or extracorporeal lithotripsy, or endoscopic papillary large balloon dilation (EPLBD). EPLBD combined with EST was introduced in 2003 to facilitate the passage of large or multiple bile duct stones using a balloon greater than 12 mm in diameter. EPLBD without EST was introduced as a simplified technique in 2009. Dilation-assisted stone extraction (DASE) is the combination of two techniques: EPLBD and sub-maximal EST. Several studies have reported this technique as safe and effective in patients with large bile duct stones, without any increased risk of adverse events such as pancreatitis, bleeding, or perforation. Nevertheless, it is difficult to analyze the outcomes of DASE because there are no standard techniques and definitions between studies. The purpose of this paper is to provide technical guidance and specific information about the main issues regarding DASE, based on current literature and daily clinical experience in biliary referral centers.

Key Words: Dilation-assisted stone extraction; Endoscopic papillary large balloon dilation;

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Core Tip: This narrative and practical review has been written to clarify some issues and key points regarding the treatment of difficult common bile duct stone using dilation assisted stone extraction technique.

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INTRODUCTION

Bile duct stones most frequently result from the migration of gallstones from the gallbladder into the biliary tree. Common bile duct (CBD) stones are the main indication for endoscopic retrograde cholangiopancreatography (ERCP), which has transformed bile duct stone removal from a major operation to a minimally invasive procedure. The success rate is from 85% to 95%[1,2]. A critical step to obtaining successful stone extraction is to provide an adequate opening for the stones that are to be removed by endoscopic sphincterotomy alone, endoscopic papillary balloon dilation (EPBD) alone, or a combination of both[1]. In more than 90% of cases, conventional treatment is based on endoscopic sphincterotomy (EST) with stone extraction using a Fogarty balloon catheter or Dormia-type basket. Difficulties in stone extraction may be due to the stone(s) being too large to pass through the intrapancreatic portion of the bile duct or the biliary sphincterotomy site[3]. This could occur in a small number of cases, approximately 5%-10%, in which the conventional treatment is not enough to obtain the complete removal of the stone, known as "complex" lithiasis[1,4]. The most complete definition of "complex" lithiasis includes the presence of multiple (10 or more) or large stones (with a diameter ≥ 15 mm, called macrolithiasis), anatomical conditions such as strictures, sigmoid-shaped CBD, disproportion between the size of distal bile duct and the stone (difference greater than 2 mm), post-surgical altered anatomy, duodenal stenosis, peri ampullary diverticula (PAD), and difficult access to the major papilla[1,5]. In the past, the established approach to fragment "complex lithiasis" was mechanical lithotripsy (ML), a technique introduced and described for the first time in 1985 by Riemann *et al*[6]; it requires the use of a large basket to trap the stone, a crank handle is then used to apply tension to the wires and to crush the stone against a metal sheath[6,7]. Other commonly used techniques are: Extracorporeal shock wave lithotripsy, cholangioscopy-assisted electrohydraulic or laser lithotripsy, plastic ore self-expanding metal stent (SEMS) placement, and endoscopic papillary large balloon dilation (EPLBD) also known as dilation assisted stone extraction (DASE)[2,3,8,9].

Almost all endoscopists who deal with the biliary tract have a clear understanding of the difficulties and frustration resulting from the failure to extract large stones through the papilla, despite maximal EST extended until duodenal fold. The concept behind DASE technique lies in the enlargement of the papillary section to an extent that allows large stones to pass through and out in the duodenum, even without their fragmentation. The first systematic experience of EPLBD was observed in 2003 by Ersoz *et al*[10], who applied this technique in 58 patients in whom endoscopic sphincterotomy and standard basket/balloon extraction were unsuccessful in the removal of CBD stones. EST followed by dilatation of the ampulla and distal bile duct with a large-diameter esophageal/pyloric type pneumatic balloon (10-20 mm) was effective in the clearance of large bile duct stones (15-28 mm) in 95% of patients. The purpose was to allow easy removal of the stones by making the distal bile duct more adaptable and shaped.

Complications occurred in nine patients (15.5%), including cholangitis and mild pancreatitis in 3% of patients and bleeding in 9%[10]. Since then, this technique has spread rapidly all over the world, experiencing more or less use, due in part to technical variations, and due to the production of dedicated devices. Global interest in EPLBD procedure was demonstrated by publication of numerous articles, reviews, meta-analyses, randomized controlled trials (RCTs), and guidelines from the main endoscopy associations.

The aim of this paper is to provide technical features and practical advice both from updated literature and daily experience of our biliary referral center, in which more than 25 DASE procedures are performed each year.

INDICATIONS OF DILATION ASSISTED STONE EXTRACTION

ASGE and ESGE recommend limited sphincterotomy combined with endoscopic papillary large-balloon dilation as the first-line approach to remove difficult CBD stones[1,2]. The complete stone clearance rate in all sessions of the DASE procedure ranges from 70% to 97.5%, with an overall complication rate of 12%, based on published clinical series and trials[2,3,5,11]. When reviewing the published literature, we need to consider the heterogeneity of the reported data, particularly the dimension of the biliary stones that are being removed and the extension of the biliary sphincterotomy. Many studies, for example, include stones from 10 mm upwards, while others consider only biliary stones wider than 13-15 mm. In the latter group, the efficacy of DASE in the clearance of the biliary tract is higher than EST alone, as shown by an RCT published on 2017. In this study, CBD stone clearance was achieved in 74% of patients in the EST group and in 96.1% of patients in the endoscopic sphincterotomy plus large-balloon dilation group. As reported, EST was complete in both groups and not partial, as usually occurs in the classic DASE technique described[12]. Another meta-analysis of 18 studies with 2789 patients showed that the efficacy and safety of DASE was superior to those of EST for the removal of large CBD stones, both across all ERCP sessions (odds ratio [OR]: 2.68) and during the first ERCP session (88% *vs* 79% in the EST group). Moreover, less mechanical lithotripsy and shorter procedure times are needed after DASE to manage large stones, with a significantly lower incidence of adverse events (OR: 0.63)[13]. Based on these findings, ESGE and ASGE guidelines published in 2019 recommend sphincterotomy combined with EPLBD as first-line therapy to remove difficult CBD stones[1,2]. Another possible use for DASE is the treatment of lithiasis recurrence, previously approached with EST, a scenario in which a further enlargement of the sphincterotomy could be associated with an increased risk of bleeding and perforation[14].

PROCEDURAL TECHNIQUE

As in standard procedures, before starting with the dilation, a guide wire is placed in the bile duct through the papilla major, under fluoroscopic monitoring, and after cholangiography; then a sphincterotomy is performed over the guide wire. When a physician is considering dilation assisted stone extraction, the extent of the sphincterotomy should not be too limited as the safety of the technique likely depends on at least partially severing the sphincter muscle. At this point, to get a better view of the radiological anatomy of the biliary tree, it is strongly advised to perform a high-pressure cholangiography using a Fogarty catheter, to exclude suspicion of distal bile duct tight stricture before starting with dilation. The best-selling biliary catheters for pneumatic dilation are wire-guided, with a balloon length from 3 to 5.5 cm and variable diameters (10 to 20 mm). They are compatible with 3.2 mm working channel endoscopes and 3.8 mm working channel duodenoscope and have embedded platinum/indium radio-opaque markers to facilitate balloon placement using fluoroscopy. From the DASE technique literature, nuances of the technique, including positioning of the balloon, and duration and size of balloon dilation are still not certain. Some authors recommend positioning the balloon across the papilla leaving more than one-half of its length on the duodenal side, although this advice results primarily from subjective experience. Other authors propose pushing the biliary stones upward before proceeding with the inflation phase, to minimize the risk of traumatic damage caused by their "crushing" between the balloon and the choledocic wall, while others recommend positioning more than one-half of the balloon inside the bile duct to exploit the pneumatic compressive action to break, at least partially, the

biliary stones[4,15,16]. These are a few examples of how there is not uniform agreement on the DASE technique in the literature. From our experience, we found that fragmenting the stones or moving them proximally is not fundamental, since the placement of the dilating balloon, even deflated, is enough to do it. Once the balloon is positioned so its midpoint is on the papillary sphincter, it should be inflated with a dilute contrast medium, which allows fluoroscopic monitoring. Gradual and slow inflation under endoscopic and fluoroscopic monitoring is recommended ("step-by-step" technique) to prevent the "watermelon seed" effect. It may be necessary to put either traction or inward pressure on the balloon catheter to maintain its position during inflation. Once the target pressure has been reached, inflation should be maintained for 30-60 s until the balloon waist disappears or better until the stenosis gradually reaches the diameter suitable for the removal of the stones. If there is residual waist formation or extensive longitudinal narrowing of the balloon, even when the maximum pressure target has been reached, it is not recommended to inflate more; at least until checking the papilla to exclude complications. Then, if the initial balloon diameter is felt to be too small, a second inflation using a larger diameter balloon can be performed. It has been reported in the literature that the balloon waist persistence could be caused by scar tissue on the papilla, causing higher incidence of perforation. The gradual application of balloon pressure in patients with long-standing large bile duct stones is suggested to prevent sudden tearing of the ampullary roof reducing the incidence of traumatic wall damage[4,15,17,18]. After the dilation phase, a standard retrieval balloon or basket may be used to pull down the stones. At the end, high-pressure cholangiography should be performed to check CBD clearance and exclude complications (Figure 1). Of note, pneumatic dilation is considered a painful procedure and should be performed under deep sedation or general anesthesia.

SPHINCTEROTOMY YES OR NO?

At the beginning, DASE procedure was performed after a complete EST, to reduce the incidence of acute post ERCP pancreatitis (PEP), a complication reported as being more frequent in patients undergoing EPBD instead of EST alone[19-21]. However, data from more recent studies do not seem to confirm this evidence[17,22,23].

In 2009, Jeong *et al*[24] showed that large-balloon sphincteroplasty (LBS) without EST is safe in patients with large bile duct stones, although with a lower efficacy; the complete duct clearance by LBS alone without mechanical lithotripsy was achieved in 76.3% of patients, while complete stone retrieval was achieved by LBS alone in the first session in 65.8% of patients[24]. The latest trial published by Kogure *et al*[25], involving 171 patients (all over 60-years-old) across 19 Japanese centers, asserts that EPLBD without EST is significantly more effective than EST alone for the removal of large (≥ 10 mm) CBD stones in a single session. No difference in adverse events (AEs) were recorded[25].

An "intermediate" approach proposed by Kim and colleagues was that pneumatic dilation has to be preceded by a minor (less than half) EST made from the orifice of the papilla proximally but not extended beyond the horizontal fold or the transverse fold of the papilla. The rationale for this approach in that the subsequent pneumatic dilation could spread the tension stress on the biliary side more that on the pancreatic one, reducing risk of PEP as well as bleeding and perforation, whereas the overall success rate was not affected[26] (Table 1).

Subsequent studies and meta-analyses have shown contradictory results in terms of efficacy and safety of DASE preceded or not by EST[4,25,27-29]. Of note, few studies have investigated Oddi's sphincter (SO) function after EPLBD procedure: Cheon *et al*[30] performed endoscopic manometric studies on 86 patients before and after the EBPLD, and found that dilation procedure resulted in significative and prolonged loss of SO function after 1 wk and 1 year, irrespective of the association with or without EST[30]. To date, the European, American and Japanese guidelines recommend, among patients with large or difficult-to-remove bile duct stones, to choose limited EST followed by large balloon dilation over EST alone. The approach of EPLBD without EST should be limited to patients with coagulopathies and in those who have previously undergone sphincterotomy[1,2,31].

Table 1 Main characteristics across different studies of patients underwent to endoscopic large balloon papillary dilation

Ref.	Study design	EPLBD/EST patients, n°	Stone dimension, cut off, mm	EST prior EPLBD	Dilation time after waist disappearance, s	CBD clearance at first session, EPLBD/EST, %	EML, EPLBD/EST, %	AEs, EPLBD/EST, %
Li *et al*[51], 2018	Retrospective, single center	161-60	≥ 10	Complete	60	98.8/98.3	18/28.3	6.8/6.7
Karsenti *et al*[12], 2017	Prospective, randomized, multicentric	77-73	≥ 13	Complete	Na	96.1/74	3.9-35.6	8.1-9.3
Kuo *et al*[29], 2019	Retrospective, single center	58-31	≥ 15	Partial	120	98.3/83.9	3.4-10.4	3.4-12.9
Teoh *et al*[33], 2013	Prospective, randomized, multicentric	73-78	≥ 13	Partial	30	89–88.8	28.8-46.2	6.8-10.3
Jun Bo *et al*[34], 2013	Prospective, randomized, single center	63-69	≥ 15	Partial	30	80.9-60.8	7.9-24.6	11.6-7.9
Kogure *et al*[25], 2020	Prospective, randomized, multicentric	86-85	≥ 12	None	< 10	90.7-78.8	30.2-48.2	9.3-9.4
Our experience (2016-2020)	Retrospective, unpublished	72-83	≥ 15	Complete	30	88-79.1	6.4-5.5	10.3-10

AEs: Adverse events; CBD: Common bile duct; EML: Endoscopic mechanical lithotripsy; EPLBD: Endoscopic papillary large balloon dilation; EST: Endoscopic sphincterotomy.

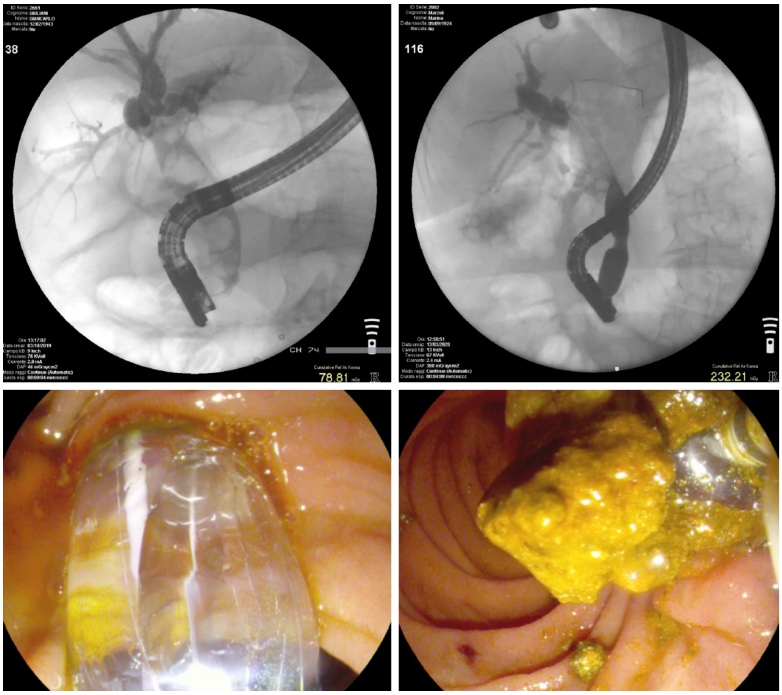

Figure 1 Radiologic and endoscopic view of macrolithiasis treated with dilation assisted stone extraction.

BALLOON DIAMETER AND DILATION TIME

Biliary catheters for pneumatic dilation are wire-guided, with a balloon length from 3 to 5.5 cm and diameters from 10 to 20 mm. The choice of the balloon type and the diameters to be reached must be carefully evaluated by radiological images review pre-ERCP and cholangiography during the procedure. The final diameter of the balloon shouldn't exceed the diameter of the distal bile duct (even in case of larger stone), then it should be gradually and slowly pressurized using contrast medium

injection according to the corresponding atmosphere reported by the manufacturer's instructions, until waist disappearance. Final balloon dilation should be maintained no more than 30-60 s or better until the stenosis gradually gives way. Indeed, in a recent multicentric trial involving 1920 patients, Meng *et al*[32] showed that the rate of PEP was significantly higher in the case of dilation time longer than 180 s[32].

Distal CBD stricture or small extrahepatic duct size should be considered contraindications to DASE. Therefore, it is necessary to exclude, beyond any reasonable doubt, the presence of unknown or misdiagnosed pre-papillary tight and uncompressible stricture. For this purpose, it could be useful to acquire cholangiography images from various perspectives moving the radiological arch or the operating bed and checking carefully also the portion of the CBD that usually hides behind the duodenoscope. In a large study, Park *et al*[15] analyzed AEs following DASE according to severity and reported that perforation occurred when no obvious distal CBD stricture was identified and when there was discrepancy between distal CBD and balloon diameter. Moreover, the rate of severe-to-fatal AEs was higher when balloons larger than 15 mm were used to dilate the CBD[18].

CLINICAL AND ECONOMICAL ADVANTAGES OF DASE

Some RCTs have investigated the economic advantages of the DASE technique compared to EST alone. The study of Teoh *et al*[33] showed that the cost of hospitalization was significantly lower in the DASE group ($5025 *vs* $6005)[33]. Another study confirmed this data, showing the duration of admission was significantly shorter in the DASE group (10.5 ± 6.6 d) than in the EST group (14.9 ± 7.8 d)[34]. Concerning the average cost of the devices used during endoscopic procedures, Karsenti *et al*[12] did not show substantial differences between the DASE group (€449) and the EST alone group (€447)[12]. Finally, an observational study by Itoi *et al*[35] showed in a group of 101 patients that total procedure time and fluoroscopy time in the DASE group were significantly shorter than those of the EST group (32 and 13 min *vs* 40 and 22 min)[35].

The limitations of most of these data are heterogeneity in cost evaluation and variation in study populations, trial design, and operator techniques; therefore, their clinical impact must be considered with caution.

COMPLICATIONS

Bleeding

Literature review shows that DASE-related bleeding is statistically less frequent than occurs in patients treated with EST alone[13,17]. This was confirmed in a recent meta-analysis, which highlighted how post-ERCP bleeding is significantly more frequent in patients treated with complete EST compared to DASE (3.4% *vs* 1.9%, $P = 0.02$)[28]. Of note, the systematic review by Kim and colleagues published in 2013 showed that bleeding related to maximal EST and papillary large balloon dilatation was slightly higher in respect to patients treated with EST alone, whereas there were no differences between patients treated with papillary dilation combined with partial or no EST[27]; these data proved once again that bleeding is strictly related to sphincterotomy and its extension. Many studies have established that liver cirrhosis, uncontrolled coagulopathies, ongoing anti-platelet drugs, stones larger than 16 mm and maximal EST are risk factors for bleeding in patients undergoing to DASE[2,4,15]. In case of DASE-related bleeding, hemostasis can be achieved using standard techniques (adrenaline, clips, SEMS) or inflating again the balloon across the papilla up to 60-180 s, in order to obtain vessel compression and stop blood flow[36-40].

Perforation

Although it has been demonstrated that patients undergoing DASE are not at increased risk of perforation[15,41], a strict and careful radiological evaluation is necessary before and during ERCP procedure. The most serious AE after EPLBD is perforation. Fortunately, this complication is rare, and most cases were described as Stapfer type II (papillary) and type III (bile duct) perforations[15,42,43]. Expert opinion and published studies underlie the presence of unrevealed distal CBD stricture as well as the use of balloons larger than 15 mm are associated with an increased risk of perforation[15,18,42]. Fluoroscopic evaluation of pre-papillary tract during ERCP could be

extremely tricky. Many factors can mask a short and hidden stricture like the overlapping of endoscope and distal CBD, the inability to obtain a high-pressure cholangiography with Fogarty catheter of the distal CBD tract, and the physiological narrowing of its intrapancreatic tract. To overcome these issues, it may be useful to move the radiological arch to obtain images in different projections, eventually pushing the instrument in long position or inflating the balloon toward the papillary orifice before contrast injection (Figure 2). The incidence of perforation has been reported in patients undergoing DASE ranging from 0.4 to 1.4%[15,40,43]. If the injury is promptly recognized, conservative management should be undertaken placing SEMS (with anti-migration shape) across the leak and naso-biliary drainage, minimizing the contact between bile fluid and the damaged wall.

Acute pancreatitis

Historically, PEP is considered the most frequent complication in patients undergoing sphincteroplasty (also named endoscopic papillary balloon dilation -EPBD) even more than EST. The most likely explanation is that papillary oedema, due to pneumatic trans-papillary dilation and tissue stress, causes local compartment syndrome and subsequent outflow obstruction of pancreatic fluids. Nevertheless, a systematic review by Liao *et al*[22] showed that only short EPBD duration (< 60 s) was associated with a higher PEP incidence compared with EST (OR: 3.87, 95% confidence interval [CI]: 1.08–13.84), while long (> 60 s) EPBD was not (OR: 1.14, 95%CI: 0.56–2.35)[23]. Also, the latest ESGE guidelines recommend performing EPBD using an 8 mm balloon after limited EST, keeping it inflated for at least 2 min after waist disappearance. Moreover, the placement of pancreatic stent should be considered in case of papillary balloon dilation not preceded by limited EST[23,44]. While severe pancreatitis was an early concern with DASE, afterward the rates have proven to be low; the hypothesis is that the sphincterotomy with partial section of Oddi's muscle fibers on the biliary side, could direct the tension caused by the inflated pneumatic balloon toward the top, reducing tissue stress on pancreatic side[44-46]. Additional PEP prevention should include the use of NSAIDs (*i.e.* rectal Indomethacin) and adequate intravenous fluids administration, especially in those with virgin papilla[11,46]. Prophylactic pancreatic stent should also be placed in selected patients at high risk for PEP, and in case of difficult biliary cannulation or inadvertent guidewire insertion/ opacification of the pancreatic duct[23,44].

PARTICULAR CASES

Paravaterian diverticulum

The presence of PAD, especially when the papilla is located inside or on the edge of it (PAD types I and II), increases the difficulty to perform a wide EST required for stone passage through the papillary orifice. Some factors that limit the extension of biliary sphincterotomy in presence of a PAD are: The duodenal sprain, the dislocation of the papillary sphincter, and the thin diverticular wall. In these cases, DASE has proven to be a safe and effective technique, as reported in a large cohort of patients by Zulli *et al*[47] in which a complete clearance of the biliary tract was obtained in 96% of cases and with mild or moderate complication in 10%[47]. Due to diverticular compression of the distal bile duct, the balloon choice should be carefully done (not greater than diverticular neck in case of PAD type 1) and the balloon should be inflated progressively, under fluoroscopic and endoscopic view, until the first target is reached.

Altered anatomy

Treatment of choledocolithiasis is challenging in patients with surgically altered anatomy of the bilio-digestive system. A step-by-step approach is necessary for successful endoscopic management of bile duct stones[48]. The most complex phases of ERCP procedure are the intubation to the afferent limb, biliary cannulation, ampullary intervention, and stone extraction. In the case of Billroth II reconstruction, the major papilla (usually located in the reverse position) could be reached using a duodenoscope as first option, then either therapeutic gastroscope, pediatric colonoscope or device-assisted enteroscope as second choices. For biliary sphincterotomy, different techniques could be adopted using rotatable sphincterotome, free hand kindle knife or stent assisted kindle knife, but all these increases the risk of adverse events even in experienced hands. Although data are still limited, some research and patient series report that DASE has proved to be easy, safe and effective,

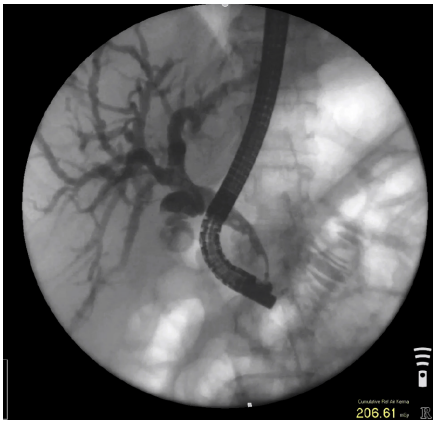

Figure 2 Complex lithiasis with common bile duct distal stricture not suitable for dilation assisted stone extraction treatment.

with complication rates comparable to those found in patients with preserved anatomy[11,49,50] (Figure 3). DASE treatment has also been used in patients with Roux-en-Y reconstruction; nevertheless, considerable technical expertise is often required especially to reach the papilla of Vater using enteroscopes or laparoscopic assistance[48]. Due to the small number of patients studied in this group, there is not enough evidence in the literature to consider DASE procedure the standard practice. This may change in the coming years due to the greater number of Roux-en-Y reconstructions performed after gastric surgery.

CONCLUSION

Currently, DASE represents the first line technique in the treatment of macrolithiasis of the CBD. Its global effectiveness has been reported as comparable or superior to EST for retrieval of CBD stones. In addition, DASE resulted in a reduced need for mechanical lithotripsy, a lower incidence of morbidity rate, and adverse events. Furthermore, procedural duration and cost in endotherapy devices used for ERCP tends to be significantly lower. This treatment is also reproducible, and does not compromise any further therapeutic attempts. To maximize its effectiveness and to reduce complications, the essential aspects are a careful evaluation of the biliary tree, the choice of the balloon size, and the respect of inflation times.

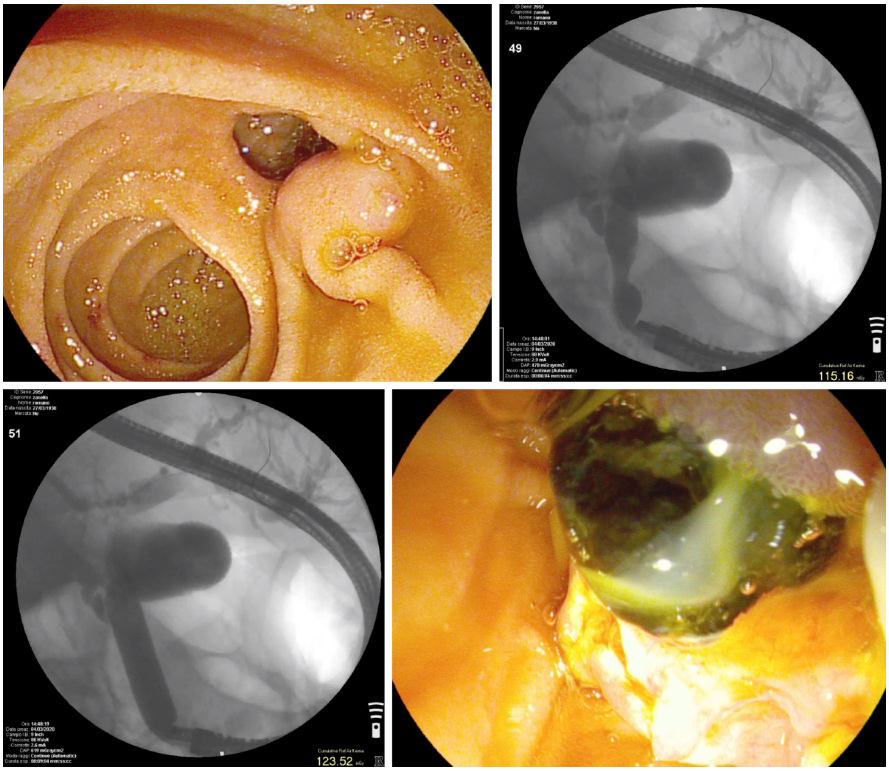

Figure 3 Dilation assisted stone extraction in patient with type II peri-ampullary diverticulum and Billroth-II reconstruction.

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ORIGINAL ARTICLE

Retrospective Study

Complication rates in emergent endoscopy for foreign bodies under different sedation modalities: A large single-center retrospective review

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Author contributions: Razik R and Cha MH conceived and planned the retrospective chart review; Cha MH, Sandooja R, Khalid S, Lim J and Lao N carried out the chart review process; Cha MH and Razik R contributed to the interpretation of the results from the chart review; Cha MH took lead in the writing of manuscript, with all other authors provided critical feedback that helped finalized the manuscript; Razik R supervised the entire project.

Institutional review board statement: The study was reviewed and approved by the Cleveland Clinic Akron General Institutional Review Board (Approval No. 19007).

Informed consent statement: A waiver of informed consent is granted by the Institutional Review Board at Cleveland Clinic Akron General as this study may not be practicably conducted due to the number of patients lost to follow

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Abstract

BACKGROUND

Foreign object ingestion (FOI) and food bolus impaction (FBI) are common causes of emergent endoscopic intervention. The choice of sedation used is often dictated by physician experience. Many endoscopists frequently prefer to use monitored anesthesia care (MAC) and general anesthesia (GA) as opposed to conscious sedation (CS) due to the concern for inadequate airway protection. However, there is insufficient data examining the safety of different sedation modalities in emergent endoscopic management of FOI and FBI.

AIM

To investigate the complication rates of emergent endoscopic extraction performed under different sedation modalities.

METHODS

We conducted a retrospective chart review of patients presenting with acute FBI and FOI between 2010 and 2018 in two hospitals. A standardized questionnaire was utilized to collect data on demographics, endoscopic details, sedation practices, hospital stay and adverse events. Complications recognized during and within 24 h of the procedure were considered early, whereas patients presenting with a procedure-related adverse event within two weeks of the index event were considered delayed complications. Complication rates of patients who underwent emergent endoscopic retrieval were compared based on sedation types, namely CS, MAC and GA. Chi-square analysis and multiple logistic regression were used to compare complication rate based on sedation type.

up and/or expired since the procedure. Please refer to IRB approval letter for further details.

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RESULTS

Among the 929 procedures analyzed, 353 procedures (38.0%) were performed under CS, 278 procedures (29.9%) under MAC and the rest (32.1%) under GA. The median age of the subjects was 52 years old, with 57.4% being male. The majority of the procedures (64.3%) were FBI with the rest being FOI (35.7%). A total of 132 subjects (14.2%) had chronic comorbidities while 29.0% had psychiatric disorders. The most commonly observed early complications were mucosal laceration (3.8%) and bleeding (2.6%). The most common delayed complication was aspiration pneumonia (1.8%). A total of 20 patients (5.6%) could not adequately be sedated with CS and had to be converted to MAC or GA. Patient sedated with MAC and GA were more likely to require hospitalization, $P < 0.0001$. Analysis revealed no statistically significant difference in the complication rate between patients sedated under CS (14.7%), MAC (14.7%) and GA (19.5%), $P = 0.19$.

CONCLUSION

For patients who present with FOI or FBI and undergo emergent endoscopic treatment, there is no significant difference in adverse event rates between CS, MAC and GA.

Key Words: Foreign body; Food bolus impaction; Endoscopy; Sedation; Anesthesia; Complications

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Core Tip: There is insufficient data examining the safety of different sedation modalities in emergent endoscopic management of food bolus impaction or foreign object ingestion. Many endoscopists frequently perform emergent endoscopy under monitored anesthesia care or general anesthesia instead of conscious sedation. This retrospective study aims to investigate the complication rate of emergent endoscopic extraction performed under different sedation modalities. Analysis revealed no significant difference in the complication rate among patients sedated under different sedation modalities. These findings can potentially lead to sedation practices that allow more timely access to emergent endoscopy and further cost savings to the health care system.

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INTRODUCTION

Foreign object ingestion (FOI) and food bolus impaction (FBI) represent the second most common endoscopic emergency after gastrointestinal bleeding[1]. FOI occurs more commonly in the pediatric population but can also affect the adult population[2,3]. Adults presenting with FOI frequently have underlying psychiatric disorders and may occasionally be found to be trafficking illegal drugs[4-7]. Meanwhile, pathologies in esophageal structure or motility predispose adult patients to FBI[8-10]. Flexible endoscopy is preferred compared to rigid endoscopy while performing endoscopic retrieval of foreign objects or food bolus due to lower adverse event rates along with other advantages like avoidance of surgery, reduced cost, ease of access, improved visualization, reduced morbidity, and high removal success rate[11-13]. In general, all FOI and FBI require urgent or emergent endoscopic intervention. Foreign bodies and FBIs in the esophagus have the highest incidence of adverse events with the adverse event rate directly proportional to the dwell time in the esophagus[14-16]. Perforation is most common with sharp objects[17,18]. Thus, they should be removed within 24 h, preferably within 6 to 12 h after presentation[19-21].

Traditionally, low risk flexible endoscopy among adults is performed under

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conscious sedation (CS), which is more time and cost effective compared to general anesthesia (GA)[22]. Meanwhile, GA is recommended in patients who are unable to protect their airway, uncooperative or have a long estimated duration of procedure[21,23]. However, GA is associated with various adverse events including cardiovascular adverse events such as hypotension, cardiac arrhythmias and myocardial infarction, and respiratory adverse events such as respiratory depression, hypoxia and aspiration pneumonia[24].

Currently, there are no standard guidelines in the United States recommending the modality of anesthesia to use for emergent or urgent endoscopy[23]. Often times, the clinician's preference to use monitored anesthesia care (MAC) and GA for emergent endoscopic procedures is due to the concern for airway protection. Some institutions have also enforced policies to mandate the use of GA for endoscopic intervention of FOI and FBI for similar reasons. Despite no substantial evidence that supports the practice, many physicians frequently perform emergent endoscopic retrieval of foreign object/food bolus under MAC and GA. Recognizing the gap in knowledge, our study aims to compare the adverse event rates among patients who underwent flexible endoscopy for FOI or FBI when performed under CS, MAC and GA.

MATERIALS AND METHODS

Subjects recruitment

A retrospective chart review was performed examining all subjects presenting with FBI or FOI who subsequently underwent emergent endoscopy, between January 1st, 2011 to December 31st, 2018 in Cleveland Clinic Main Campus and Cleveland Clinic Akron General. This study was approved by the local institutional review boards of all participating centers with a waiver of informed consent because of the minimal risk to participants. A total of 2664 subjects with the relevant current procedural terminology codes and International Classification of Diseases codes were reviewed. Endoscopic procedures were excluded if subjects presented with a rectal foreign body, were less than 18 years of age or were pregnant. Subjects undergoing removal of stents, pH probes, PEG (percutaneous endoscopic gastrostomy) tubes, sutures and food bezoars were similarly excluded. After excluding subjects mentioned above, a total of 929 endoscopic procedures were included for analysis.

Materials

For this study, a standardized questionnaire was utilized by investigators to collect demographic, clinical and endoscopic data. This included age, sex, comorbidities, use of anticoagulation, type of impaction, location of impaction, sedation modality, instruments (*e.g.*, Roth net, forceps, snare, talon grasper) used for foreign object or food bolus removal and adverse events related to the endoscopic procedure. CS is defined as a "light" sedation modality which does not typically compromise patient's respiratory function. The common medications used are midazolam, fentanyl and diphenhydramine. It is administered by the endoscopist, and the endoscopist typically assumes the dual role of performing the procedure and supervising the sedation. Meanwhile, MAC is a "deeper" sedation modality that is commonly administered by a qualified anesthesia provider, such as an anesthesiologist or certified registered nurse anesthetist, who also monitors the patient's airway and hemodynamics continuously. Although MAC includes sedatives that are frequently used in CS, propofol is exclusively used in MAC. Lastly, GA is solely administered by a qualified anesthesia provider and involves using a variety of medications to induce loss of consciousness and often impairs patient's respiratory function. Patients who undergo GA are almost always placed on mechanical ventilation.

Outcomes

The primary outcome of this study is the adverse event rate for endoscopic removal of foreign object or food bolus under different sedation modalities. Adverse events within 24 h post-procedure were recorded as early adverse events whereas delayed adverse events included those occurring between 1 and 14 d after the procedure. The secondary outcomes include hospitalization rate and success rate among endoscopic procedures using different sedation modalities. Additionally, we also compared the demographic data and outcomes between patients with FOI and FBI.

Statistical analysis

Descriptive statistics as well as inferential statistics were performed. Categorical variables were described using frequencies and percentages, whereas continuous variables were described using medians and interquartile range. Pearson's chi-square test was used to assess the association between type of anesthesia and whether a patient developed an adverse event during or after the procedure. Subsequently, multiple logistic regression analysis was used to estimate the effect of different variables on adverse event rates and hospitalization rates. Analyses were performed using SAS® Software (version 9.4; Cary, NC, United States). A significance level of 0.05 was assumed. The statistical analysis of this study is performed by Mangira C, biostatistician from department of research, Cleveland Clinic.

RESULTS

Baseline patient characteristics

A total of 929 procedures were included for analysis, with demographic and clinical characteristics shown in Table 1. Among these cases, male patients (57.37%) were slightly more common compared to female patients. The median age was 52, with range between 18 and 103 years. Chronic co-morbidities were recorded in 14.21% of patients, while mental health disorders were present in 28.96% of the patients. Only 13 cases (1.40%) presented with airway compromise.

Endoscopy and anesthesia management

All the patients that were recruited underwent endoscopy for food bolus or foreign object extraction performed by gastroenterology, otolaryngology and/or the general surgery service. A total of 597 patients presented with FBI (64.26%) and the rest with FOI (n = 332, 35.74%). The most common site of FBI and FOI was the esophagus (n = 699, 75.24%), followed by the stomach (n = 186, 20.02%). Food bolus or foreign objects were seen in the oropharynx in only 11 cases (1.18%). Endoscopic instruments were commonly used, with 646 procedures (69.54%) requiring use of one or more instruments. Instruments that were frequently utilized include Roth net (n = 299, 32.18%), snare (n = 233, 25.08%) and forceps (n = 188, 20.24%). As some procedures required multiple endoscopic devices, the aggregate data presented may exceed 100%. Meanwhile, a total of 283 (30.46%) endoscopy procedures required only push method without the use of any instruments.

To investigate the association between sedation modality and adverse event rate, patients in the present study were divided into three groups following the sedation modalities used during endoscopy. The most commonly used sedation modality was CS (n = 353, 38.0%), followed by GA (n = 298, 32.08%) and MAC (n = 278, 29.92%). Of the 353 patients who underwent CS, midazolam (n = 322, 91.22%) and fentanyl (n = 241, 68.27%) were the most commonly used sedatives. Patients with FBI more frequently underwent CS (n = 292, 82.72%) compared to MAC (n = 138, 49.64%) and GA (n = 167, 56.04%), $P < 0.001$. Conversely, mental health disorders were more commonly seen in patients undergoing MAC (n = 131, 47.12%) and GA (n = 108, 36.24%), compared to CS (n = 30, 8.50%), $P < 0.001$. The majority of patients that presented with airway compromise due to their FBI/FOI, underwent endoscopy with either MAC (n = 5, 1.80%) or GA (n = 6, 2.01%).

Comparison between FOI and FBI

Patients with FOI were found to be younger (median age 33) compared to FBI patients (median age 61), $P < 0.001$. They also had less co-morbidities (n = 32, 9.64%) compared to patients with FBI (n = 100, 16.75%), $P = 0.0029$. However, prevalence of psychiatric disorder was higher among FOI patients (n = 235, 70.78%) compared to FBI patients (n = 34, 5.70%), $P < 0.0001$. When comparing between the two groups, the FOI group (n = 67, 20.18%) was found to have a higher total adverse event rate compared to the FBI group (n = 84, 14.07%), $P = 0.0156$.

Outcomes and adverse events of endoscopy

In total, 151 adverse events (16.3%) were recorded, with the majority of adverse events reported within 24 h of endoscopy (n = 110). Types of adverse events are shown in Table 2. The most common early adverse events included mucosal laceration (n = 35, 3.77%), bleeding (n = 24, 2.58%), and hypoxia (n = 12, 1.29%). A total of 53 cases of delayed adverse events were recorded, which primarily included aspiration

Table 1 Comparison of baseline characteristics among different sedation modalities (*n* = 929)

	Conscious sedation (*n* = 353), *n* (%)	Monitored anesthesia care (*n* = 278), *n* (%)	General anesthesia (*n* = 298), *n* (%)	Total (*n* = 929), *n* (%)	*P* value
Gender					
Male	226 (64.02)	131 (47.12)	176 (59.06)	533 (57.37)	< 0.0001
Median age	58 (45-74)	39 (33-64)	46 (33-67)	52 (33-69)	< 0.0001
Type of impaction					
Food bolus	292 (82.72)	138 (49.64)	167 (56.04)	597 (64.26)	< 0.0001
Foreign object	61 (17.28)	140 (50.36)	131 (43.96)	332 (35.74)	
Presence of chronic co-morbidities	58 (16.43)	45 (16.19)	29 (9.73)	132 (14.21)	0.0270
Patient with mental health disorder	30 (8.50)	131 (47.12)	108 (36.24)	269 (28.96)	< 0.0001
Periprocedural airway compromise	2 (0.57)	5 (1.80)	6 (2.01)	13 (1.40)	0.2449
Overtube used	16 (4.53)	41 (14.75)	45 (15.10)	102 (10.98)	< 0.001

Table 2 Types of adverse events encountered during/after emergent endoscopy

Endoscopic adverse events	*n* (%)
Early adverse events (*n* = 110)	
Local adverse events	
Bleeding	24 (2.58)
Mucosal Lacerations	35 (3.77)
Perforation	4 (0.43)
Respiratory associated adverse events	
Failure to extubate	3 (0.32)
Hypoxia	12 (1.29)
Aspiration	10 (1.08)
Pain	
Chest pain	4 (0.43)
Abdominal pain	10 (1.08)
Delayed Adverse events (*n* = 53)	
Aspiration pneumonia/hypoxia	17 (1.83)
Abdominal pain	15 (1.61)
Bleeding	4 (0.43)
Fever	7 (0.75)
Perforation	3 (0.32)
Chest pain	6 (0.65)

pneumonia (*n* = 17, 1.83%) and abdominal pain (*n* = 15, 1.61%). Some endoscopy procedures were complicated by both early and delayed adverse events (*n* = 12, 1.29%). Most of the adverse events were monitored and managed with supportive care with less than half of the cases requiring directed treatments (*n* = 62, 41.05%), including antibiotics (*n* = 34) and pain medications (*n* = 17). The vast majority of endoscopic extraction procedures were successful, with only 45 procedures (4.84%)

resulting in inability to remove some or any of the food bolus or foreign object. Only one endoscopic procedure (0.11%) needed conversion to surgical intervention for foreign body removal.

When comparing among the sedation modalities, there was no significant difference in the overall adverse event rate observed among CS (n = 52, 14.73%), MAC (n = 41, 14.75%) and GA (n = 58, 19.46%), P = 0.1902. Comparison of adverse event rates and hospitalization rates among different sedation modalities and other patient characteristics are shown in Table 3. Patients presenting with FOI and procedures requiring the use of instruments were found to have higher rates of adverse events. Conversely, the presence of chronic comorbidities was not associated with a significant difference in adverse event rates. Although adverse event rates did not differ significantly among different sedation modalities, patients who required hospitalization were significantly more common among patients who underwent MAC (51.45%) and GA (50.35%) when compared to CS (25.44%), P < 0.001. Similarly, a significantly higher number of patients who needed hospitalization were seen among patients that presented with FOI and endoscopic procedures that required instrumentation for extraction (P < 0.001).

Among 353 patients who underwent CS, 20 patients (5.67%) needed escalation of sedation modalities to either MAC or GA. However, only 6 patients (2.16%) who underwent MAC needed conversion to GA during endoscopic removal of foreign object or food bolus.

After controlling for potential confounding factors including type of impaction, presence of chronic comorbidities and use of instruments, there was no difference in complication rates between the three sedation modalities. However, subjects who underwent GA were 2.43 times more likely to be admitted to the hospital as compared to those underwent CS. Similarly, subjects who underwent MAC were 2.22 times more likely to be hospitalized as compared to those who underwent CS after controlling for potential confounding variables. Lastly, success rate of endoscopic removal of foreign object and food bolus was significantly higher in patients who underwent CS (n = 344, 97.45%) compared to MAC (n = 259, 93.17%) and GA (n = 281, 94.30%), P = 0.0317.

DISCUSSION

FOI and FBI remain a common clinical problem faced by gastroenterologists worldwide. The most frequently ingested foreign bodies in the pediatric population include coins, toys, jewelry and batteries[25]. In adults, most impactions occur during eating, leading to impaction of either bone and/or meat. Adult patients who intentionally swallow a true foreign body are typically younger, and more likely to have a history of psychiatric illness or possibly drug trafficking[7,26,27]. Unintentional FOI, however, is more commonly seen in the elderly[28]. It has been estimated that the annual incidence of FBI is 13 per 100000 in the United States[9].

FBI and FOI can be associated with serious complications including, but not limited to, mucosal ulceration, esophageal perforation, mediastinitis, vascular trauma, pneumothorax, pericarditis and aorto-esophageal or tracheo-esophageal fistula[15,16,29]. In an early review of cases, an algorithm for management of these patients was developed depending upon the location of the ingested body. Per this algorithm, patients either underwent spontaneous passage, endoscopic removal or operative management based on the location of the obstruction[30]. Ultimately, the choice of treatment modality is largely dependent on several factors including the patient's age, clinical condition, comorbidities, type of ingested body, location of the ingested body, anatomical considerations, physician/institutional experience/preference and availability of resources. For example, sharper objects like toothpicks or chicken bones had the highest risk of perforation and favored early endoscopic removal. Furthermore, Zhang *et al*[15] also observed lower rates of complications in patients presenting with esophageal FBI or FOI within the first 24 h of ingestion. This emphasizes the importance of early endoscopic removal of retained objects, preferably within the first 24 h.

Present guidelines, however, make no recommendations on the modality of anesthesia for emergent endoscopic management of FOI and FBI. Endoscopic removal, like all other endoscopic procedures, needs pre-procedural patient evaluation to assess the risk of sedation on a case-by-case basis. This includes a good medical history to determine relevant risk factors like history of obstructive sleep apnea, specific allergies or potential drug interactions, history of adverse reaction to various sedatives, history of drug or alcohol abuse and time of last oral intake[23]. Although endoscopic removal

Table 3 Comparison of adverse event rates and hospitalization rates

Variable	Adverse event (*n* = 151), *n* (%)	*P* value	Hospitalization (*n* = 374), *n* (%)	*P* value
Type of anesthesia				
Conscious sedation	52 (14.73)	0.1902	87 (25.44)	< 0.0001
MAC	41 (14.75)		142 (51.45)	
General anesthesia	58 (19.46)		145 (50.35)	
Type of Impaction				
Foreign object	67 (20.18)	0.0156	199 (60.86)	< 0.0001
Food bolus	84 (14.07)		175 (30.22)	
Severe comorbidity				
Yes	29 (21.97)	0.0547	63 (49.61)	0.0399
No	122 (15.31)		311 (39.92)	
Use of instrument				
Yes	117 (18.11)	0.0204	288 (45.93)	< 0.0001
No (push method only)	34 (12.01)		86 (30.82)	

of foreign bodies or food boluses under CS may prove to be similarly effective and less time consuming, many clinicians may prefer performing these procedures under MAC or GA. However, no study has shown conclusive benefit of using GA or MAC as compared to CS. In fact, the frequent use of GA, can potentially prolong the duration of foreign object or FBI especially in resource-limited hospitals or due to the absence of in-house anesthesia service during night shifts in smaller community hospitals. This is clinically important as previous studies have shown that early endoscopic intervention increases the rate of successful esophageal foreign object/food bolus removal[14-16,31].

Another factor to be considered in choosing the sedation modality for such patients is the cost. Currently the cost of MAC, which necessitates formal anesthesia assistance can range from an additional $150-$1500 per endoscopic case. This increased cost, however, is not associated with significant increase in safety profile of most procedures as compared to endoscopist-directed sedation or CS[23].

In the current study, a total of 929 emergent endoscopy procedures for FOI and FBI were reviewed and analyzed. The choice of sedation modality was clinician-directed, based on individual preference and clinical judgements. Most of the emergent endoscopies reviewed were performed under CS administered by the endoscopist (38.0%), while the remaining procedures were performed under MAC or GA, with the assistance of a dedicated anesthesia provider. This study found fewer patients underwent GA compared to a previous case series conducted in a Chinese university hospital by Geng *et al*[14], where approximately 50% of patients who underwent foreign object or food bolus retrieval had GA. In the case series, endoscopic foreign object removal under GA was associated with neither higher success rate nor lower adverse event rate as compared to topical pharyngeal anesthesia only. However, unlike the study by Geng *et al*[14], where 10.6% of the patients were children less than 14 years old, our study excluded patients less than 18 years of age. This could potentially explain the lower percentage of patients undergoing GA in our study. Interestingly, the aforementioned study observed almost 65.3% of impacted cases being bony foreign body, indicating a potential cultural and geographical variation in these cases.

Meanwhile, two published case series in Italy reported only 0% to 13.2% of the food bolus and foreign object removals were performed with GA[1,22]. These studies also reported low rates of adverse events ranging between none to 7%. Conversely, in our current study, more than double that number of patients with FOI and FBI, underwent GA. When including only patients with FOI, a case series in a US-based university hospital found that GA and MAC were used in 86% of patients[32]. This finding is similar to our study as more than 80% of examined patients with FOI also underwent GA or MAC. The vast difference in the sedation practices for emergent endoscopic removal of foreign object and food bolus seen in various studies reflected the lack of research and guidelines in this area. This further highlights the need for more studies in order to understand the benefits and risks of different sedation modalities in these settings.

In the present study, the majority of emergent endoscopic interventions were performed for FBI. FBI in adults are most common at sites of narrowing or angulation due to an underlying esophageal pathology. This disrupts the normal anatomy and may cause impaction of food. These pathologies may include but are not limited to benign and malignant strictures, eosinophilic esophagitis, lymphocytic esophagitis, hiatal hernias, Schatzki's rings and esophageal webs[33]. In patients without structural abnormalities, seasonal variation has been reported in patients with FBI in previous studies. This may be attributed to seasonal variation of eosinophilic esophagitis especially in patients with concomitant atopic diathesis[34].

In the present study, patients who presented with FBI were older and had more medical co-morbidities compared to patients with FOI. This could be attributed to poorly chewed food, esophageal narrowing or dysmotility, which are more commonly seen in the older population. Interestingly, patients with FBI who underwent emergent endoscopy were found to have lower adverse event rates compared to patients with FOI despite being in an older age group and having multiple co-morbidities. In contrast, patients who presented with FOI were younger and frequently had underlying psychiatric disorders. The higher adverse event rate among FOI patients may be explained by the sharp nature of many ingested foreign bodies. In addition, they also contributed to frequent re-admission, with one of the patients undergoing a total of 93 endoscopies for foreign object extraction between 2011 and 2018. Unlike FBI, many patients with FOI have underlying psychiatric conditions that are frequently irreversible[26]. Patients with pica do not have effective treatment and frequently have the urge to swallow foreign objects despite support from multidisciplinary teams. As psychiatric patients frequently also have underlying anxiety and can be uncooperative during endoscopy, GA is frequently used in this population.

The most common early adverse events observed in this study were mucosal laceration and bleeding. Theoretically, patients undergoing endoscopy under CS may be at higher risk of laceration due to patient movements due to use of "lighter" anesthesia. However, this study did not show higher complication rates in this patient population, possibly due to proper use of rubber hoods and overtubes. Also, the majority of sedation-related complications can be minimized through a detailed pre-operative assessment, preparation, intraoperative monitoring and support, and post-sedation management[35]. In a similar vein, patients who underwent GA and MAC were more likely to be hospitalized. This is in part due to longer inpatient psychiatric monitoring as many patients who underwent emergent endoscopy under GA frequently presented with FOI with underlying psychiatric disorder. Interestingly, incidence of failure or incomplete removal of foreign object or food bolus is significantly lower in patients who underwent CS compared to other sedation modalities. The higher success rate observed in the CS group may be attributed to the higher proportion of patients with FBI in that group, which may present with lesser technical challenges compared to FOI removal. Although patients who underwent CS had higher success rates and no significant difference in adverse event rates compared to other sedation modalities, up to 5.67% of patients who underwent CS needed escalation of sedation modality to MAC or GA. This is often caused by inadequate sedation or prolonged procedure time due to difficult extraction. This is an important factor that may influence clinicians' decision to perform emergent endoscopy under CS or wait for support from anesthesia service.

Our study has several limitations. First, the retrospective nature of the study limits the control over selection bias. Retrospective chart review also lacks the ability to detect adverse events that were not appropriately documented. Second, patients who presented with FOI often have high readmission rates for the same chief complaint due to an underlying psychiatric condition. This may have led to over-representation of FOI procedures in this study. Third, patients that presented with FBI and FOI were analyzed together. The nature of the impaction may contribute as a confounding factor which affects the measured outcome. Fourth, patients presenting with FBI or FOI may be hospitalized for various reasons, including psychiatric assessments and behavioral monitoring which are unrelated to the endoscopy. Thus, the high hospitalization rate observed in patient undergoing GA may not have a direct causal relationship with the sedation modalities. Finally, the decision to use a specific sedation modality was usually attributed to endoscopist judgement. However, institutional policy change may affect outcomes. Within the Cleveland Clinic Health System where this study was based, there has been a slow paradigm shift towards favoring GA for all patients with FBI/FOI. This may lead to confounding of the results as the decision on sedation modality may not be entirely at the discretion of the endoscopist.

CONCLUSION

In the setting of increasingly common use of GA for emergent endoscopy, this study has shed some light on the outcomes of emergent endoscopic removal of food bolus or foreign objects in the upper gastrointestinal tract under different sedation modalities. In conclusion, patients who underwent emergent endoscopic foreign object or food bolus retrieval under CS were not associated with higher adverse event rates when compared to MAC or GA. Patients presenting with FOI and those who underwent endoscopic removal with the use of instruments were associated with high adverse events rate. However, the hospitalization rate was higher among patients who underwent endoscopy with MAC and GA, patients with FOI, patients with chronic comorbidities, and endoscopies requiring instrumentation. These findings can potentially lead to sedation practices that allow more timely access to emergent endoscopy and further cost savings to the health care system.

ARTICLE HIGHLIGHTS

Research background

Foreign object ingestion (FOI) and food bolus impaction (FBI) are common causes of emergent endoscopic intervention. However, the choice of sedation used during emergent endoscopy for foreign bodies is often dictated by physician experience.

Research motivation

Currently, there is insufficient data examining the safety of different sedation modalities in emergent endoscopy for removal of ingested foreign objects or FBI.

Research objectives

To investigate the complication rates of emergent endoscopic extraction performed under different sedation modalities, namely conscious sedation (CS), monitored anesthesia care (MAC) and general anesthesia (GA).

Research methods

A standardized questionnaire was utilized to collect data on demographics, endoscopic details, sedation practices, hospital stay and adverse events of endoscopic procedures for foreign body removal. Subsequently, complication rates of patients who underwent emergent endoscopic retrieval were compared based on sedation modalities.

Research results

Among the 929 procedures analyzed, 353 procedures (38.0%) were performed under CS, 278 procedures (29.9%) under MAC and the rest (32.1%) under GA. Analysis revealed no statistically significant difference in the complication rate between patients sedated under CS (14.7%), MAC (14.7%) and GA (19.5%), $P = 0.19$. However, patients that underwent MAC and GA were found to be more likely to require hospitalization. This may be due to longer inpatient psychiatric monitoring as many patients who underwent MAC and GA presented with FOI due to underlying psychiatric disorder.

Research conclusions

Emergent endoscopy for foreign body removal under CS is not associated with significantly higher complication rates compared to MAC and GA.

Research perspectives

Future prospective studies are needed to identify various clinical factors that contributes to higher risk for endoscopy-related adverse events.

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ORIGINAL ARTICLE

Observational Study

Molecular analysis of pancreatic cystic neoplasm in routine clinical practice

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Abstract

BACKGROUND

Cystic pancreatic lesions consist of a wide variety of lesions that are becoming increasingly diagnosed with the growing use of imaging techniques. Of these, mucinous cysts are especially relevant due to their risk of malignancy. However, morphological findings are often suboptimal for their differentiation. Endoscopic ultrasound fine-needle aspiration (EUS-FNA) with molecular analysis has been suggested to improve the diagnosis of pancreatic cysts.

AIM

To determine the impact of molecular analysis on the detection of mucinous cysts and malignancy.

METHODS

Informed consent statement: Informed consent was obtained from all patients prior to study inclusion.

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An 18-month prospective observational study of consecutive patients with pancreatic cystic lesions and an indication for EUS-FNA following European clinical practice guidelines was conducted. These cysts included those > 15 mm with unclear diagnosis, and a change in follow-up or with concerning features in which results might change clinical management. EUS-FNA with cytological, biochemical and glucose and molecular analyses with next-generation sequencing were performed in 36 pancreatic cysts. The cysts were classified as mucinous and non-mucinous by the combination of morphological, cytological and biochemical analyses when surgery was not performed. Malignancy was defined as cytology positive for malignancy, high-grade dysplasia or invasive carcinoma on surgical specimen, clinical or morphological progression, metastasis or death related to neoplastic complications during the 6-mo follow-up period. Next-generation sequencing results were compared for cyst type and malignancy.

RESULTS

Of the 36 lesions included, 28 (82.4%) were classified as mucinous and 6 (17.6%) as non-mucinous. Furthermore, 5 (13.9%) lesions were classified as malignant. The amount of deoxyribonucleic acid obtained was sufficient for molecular analysis in 25 (69.4%) pancreatic cysts. The amount of intracystic deoxyribonucleic acid was not statistically related to the cyst fluid volume obtained from the lesions. Analysis of *KRAS* and/or *GNAS* showed 83.33% [95% confidence interval (CI): 63.34-100] sensitivity, 60% (95%CI: 7.06-100) specificity, 88.24% (95%CI: 69.98-100) positive predictive value and 50% (95%CI: 1.66-98.34) negative predictive value (P = 0.086) for the diagnosis of mucinous cystic lesions. Mutations in *KRAS* and *GNAS* were found in 2/5 (40%) of the lesions classified as non-mucinous, thus recategorizing those lesions as mucinous neoplasms, which would have led to a modification of the follow-up plan in 8% of the cysts in which molecular analysis was successfully performed. All 4 (100%) malignant cysts in which molecular analysis could be performed had mutations in *KRAS* and/or *GNAS*, although they were not related to malignancy (P > 0.05). None of the other mutations analyzed could detect mucinous or malignant cysts with statistical significance (P > 0.05).

CONCLUSION

Molecular analysis can improve the classification of pancreatic cysts as mucinous or non-mucinous. Mutations were not able to detect malignant lesions.

Key Words: Pancreatic cysts; Molecular analysis; Next-generation sequencing; Mucinous cyst; Pancreatic cyst fluid; Pancreatic cancer

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Core Tip: Pancreatic cystic lesions are frequently found on imaging studies performed for other reasons, but differentiation between the different types and the detection of malignancy is often suboptimal with morphological features. Molecular analysis has been proposed to optimize cyst classification and the detection of malignancy. However, there is little evidence of its feasibility and usefulness in daily practice. The aim of this study was to evaluate the diagnostic yield of molecular analysis for the detection of mucinous and malignant cysts in routine clinical practice.

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INTRODUCTION

Pancreatic cysts are increasingly diagnosed as a consequence of both incidental

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findings on computed tomography (CT) and magnetic resonance imaging (MRI)[1], and longer life expectancy of the population[2,3]. Their diagnosis can generate a high degree of concern for both patients and physicians leading sometimes to the performance of multiple examinations, associated with an increase in diagnostic costs, and even unnecessary resections.

There are many different types of pancreatic cysts, including both neoplastic and non-neoplastic lesions. Their accurate diagnosis is important as some of them, such as mucinous cystic lesions or solid pseudopapillary tumors, are associated with a risk of malignancy, whereas others, such as serous cystic neoplasms and pseudocysts, are considered benign cysts. Mucinous cysts have a higher risk of malignant transformation. They can be divided into mucinous cystic neoplasm (MCN) and intraductal papillary mucinous neoplasm (IPMN), which can be branch-duct IPMN, mixed-type IPMN or main-duct IPMN (MD-IPMN). However, not all of them have the same risk of malignancy. According to recent publications, MCN have a 10%-17% risk of malignancy[4,5], MD-IPMN 38%-68%[2,6,7], branch-duct IPMN 12%-47%[2,6], and solid pseudopapillary neoplasms 8%-20%[6]. Furthermore, it is also important to note that the presence of an IPMN is associated with a higher risk of developing concomitant pancreatic adenocarcinoma[8,9].

Pancreatic neoplasia is one of the most frequent causes of cancer-related death, with a 5-year survival lower than 10%[9]. Only 20%-25% of pancreatic neoplasms are candidates for surgical treatment at diagnosis, and 80% of these will recur despite surgical intervention. Precursor lesions of pancreatic adenocarcinoma are pancreatic intraepithelial neoplasia and pancreatic cystic neoplasm (PCN)[10], and their identification is crucial for early diagnosis and treatment, thus increasing survival of these patients.

Hence, the main diagnostic challenge for these lesions is the early detection of preneoplastic and malignant lesions, thereby avoiding unnecessary surgeries and establishing an adequate follow-up due to the risk of degeneration and the development of pancreatic adenocarcinoma. Therefore, an accurate diagnosis has prognostic, therapeutic and follow-up implications. Most PCN are incidentally detected in radiological tests performed for other reasons. However, in many cases it is difficult to differentiate between the different types of cysts and their risk of malignancy only by morphological characteristics, with an accuracy for adequate identification of the type of cyst of 40%-95% for MRI and 40%-81% for CT[11].

Endoscopic ultrasound (EUS) is currently the diagnostic technique of choice for PCN as it allows not only assessment of morphological criteria, but also the performance of fine needle aspiration (FNA) and fluid analysis[12]. Usually, cyst fluid analysis includes cytological and biochemical [carcinoembryonic antigen (CEA), and recently glucose] evaluation[13-16]. However, accuracy for the diagnosis of mucinous cysts and malignancy detection remains suboptimal[14,17]. There are different clinical practice guidelines for the diagnosis and treatment of PCN. The most commonly used are the International Association of Pancreatology guideline (IAP), the European guideline and the American Gastroenterological Association (AGA) guideline[3,11,18]. However, the IAP and the European guidelines lead to unnecessary surgeries and the AGA to a decrease in sensitivity for the detection of malignancy[5]. Therefore, multiple authors have evaluated the possibility of incorporating molecular analysis of cyst fluid for the diagnosis of pancreatic cysts, which has shown promising results[14,19,20].

The aim of the current study was to determine the impact of molecular analysis on the detection of mucinous cysts and malignancy in routine clinical practice.

MATERIALS AND METHODS

This prospective trial was conducted in patients from a single center (Hospital Universitario de La Princesa, Madrid, Spain) over an 18-mo period.

Case selection

Consecutive patients over 18 years old referred to the Endoscopy Unit of Hospital Universitario de La Princesa with PCN and an indication for EUS-FNA following current clinical practice guidelines were recruited for the study. Inclusion criteria were: Lesions ≥ 15 mm in size, the need to confirm the diagnosis prior to surgical treatment, presence of worrisome features on imaging (wall thickening, main pancreatic duct > 5 mm, non-enhanced mural nodule, abrupt change in the size of the main pancreatic duct), changes on imaging during follow-up or an increase in serum CA 19.9. Patients were excluded from enrolment according to the following criteria:

Pregnancy, cysts with extra-pancreatic location or outside the scope of EUS, previous study with EUS-FNA, active treatment with anticoagulants or antiplatelets, thrombopenia (< 50.000 platelets/μL) or coagulopathy (INR < 1.5), or refusal to participate in the study. All participants enrolled in the study provided informed consent prior to the procedure. The study was approved by the Research Ethics Committee and prospectively registered on Clinical Trials (NCT03740360).

Imaging features prior to cyst fluid analysis

Radiological imaging impression was obtained by reviewing the radiological reports, and cysts were classified as malignant or without malignant features. A single endoscopist and anesthetist, both experts in their fields, performed the respective procedures in all study participants. All EUS were performed with a linear endoscopic ultrasound device (GF-UCT 180; Olympus Co., Japan). EUS features were described and recorded during the procedure, and lesions were classified as with or without worrisome features, and as malignant, mucinous or serous. After examination of the lesions contrast-enhanced EUS with Sonovue® (sulfur hexafluoride-filled microbubbles) was performed and the examination was recorded for later detailed re-evaluation. We defined three contrast patterns based on the cyst wall and septal enhancement: Hyper-enhanced, hypo-/iso-enhanced and mixed pattern.

Cyst fluid analysis

After antibiotic prophylaxis with 400 mg iv ciprofloxacin or 2 g ceftriaxone in the case of allergy to quinolones, cyst fluid was obtained by EUS-FNA with a 22 G needle (Expert Slimline, Boston®), and sent for cytologic, biochemical and molecular analysis. Both immediate and delayed (after 72 h) complications were registered.

Cytological evaluation: Smears were prepared on glass slides, 2/3 air-dried and 1/3 fixed in ethanol. Mucin staining with Alcian blue was performed on ethanol-fixed slides, and mucin detection was performed with the automatic Dakocitomation system (AR160). Lesions were categorized under Papanicolau classification and as mucin-staining positive or negative.

Biochemical analysis: At least 1 mL of cyst fluid was sent for analysis. We determined CEA levels in our laboratory with the Architect system by chemiluminescent immunoassay. Following prior studies, the CEA cut-off point was established as 192 ng/mL to differentiate mucinous (< 192 ng/mL) from non-mucinous. From the 16th lesion included in the study, intracystic glucose determination was added to the protocol, as recent evidence indicates that glucose levels < 50 mg/dL are suggestive of mucinous cysts[15,16]. Glucose determination was performed in our Hospital laboratory (using calibration for the determination of glucose in biological fluids).

Molecular analysis: After cytological and biochemical analysis, the excess fluid was frozen and stored at -80^{o}C until all patients were recruited. The range of volumes available for molecular analysis was 0.3-5 mL. The collection was registered in the Spanish National Register of Biobanks of the Carlos III Health Institute. The genomic deoxyribonucleic acid (DNA) present in the pancreatic cyst fluid was manually purified using the NZY Blood gDNa Isolation kit (NZYtech) following the manufacturer's recommendations. The extracted DNA was fluorimetrically quantified using the Quantus (Promega) system. The integrity of the DNA obtained was determined in the Agilent 2100 Bioanalyzer (Agilent) using the Agilent High Sensitivity DNA (Agilent) kit. Due to the low concentrations obtained in some samples, DNA was concentrated up to a concentration of 30 ng/uL, using magnetic beads (AMPure XP beads, Beckman Coulter). Although cyst fluid was initially obtained from the 36 pancreatic cysts, only 25 of them yielded the amount of DNA needed to perform sequencing (100 ng of DNA at a concentration of 30 ng/uL). The targeted Next-Generation Sequencing (tNGS) was performed in the MiSeqTM platform (Illumina) using a panel designed specifically for this project (Roche).

Gene panel bioinformatic design

All exons of the following genes were included and sequenced by tNGS: *AKT1, ALK, APC, BRAF, CDKN2A, CDH1, CTNNB1, DDR2, EGFR, ERBB2, ESR1, FBXW7, FGFR1, FGFR2, FGFR3, FOXL2, GNA11, GNAQ, GNAS, HRAS, IDH1, IDH2, KIT, KRAS, MAP2K1, MET, NOTCH1, NRAS, PDGFRA, PIK3CA, PIK3R1, PTEN, RET, RNF43, ROS1, SMAD4, TGFBR2, TP53, VHL*. Therefore, coverage was complete.

tNGS data analysis

Coverage analysis showed that nearly 100% of the regions were covered at a depth of 100 × or more in all the samples, reaching 400 × in a very high percentage of them. The search for variants was carried out with the VarScan software (http://varscan.sourceforge.net/). Among the variants identified, approximately 400, those present in more than 75% of the samples which did not appear as mutations noted in the databases were excluded as they were not likely to participate in the development of the disease. Variants with very low frequency (< 1 reading) were eliminated from the study since these could be due to errors in sequencing. For the final analysis, the variants detected with a frequency between 1%-33% were included. A total of 78 variants were detected in the 25 samples analyzed (mean of 3 mutations per sample). Comparisons between samples and identification of the pathogenicity of variants were carried out using the PredictSNP2tool (https://Loschmidt.chemi.muni.cz/predictsnp2/referencia). In addition, the information from the predictive tools was combined with the results of the search in the ClinVar database, which contains the interpretation of the relationship between variants and their significance for human health.

Diagnostic criteria for malignant/benign cysts

We defined as malignant those PCN that met any of the following criteria[21]: EUS-FNA cytology suspicious or compatible with malignancy; High-grade dysplasia or invasive carcinoma in the histology analysis of a surgical specimen; Progression of the PCN and/or metastatic disease in the imaging tests during follow-up; Death related to neoplastic complications up to 6 mo after diagnosis; Clinical follow-up consistent with underlying tumor disease for 6 mo.

In the absence of a definitive histopathological diagnosis, we defined a "pseudo-gold standard" to classify lesions into mucinous and non-mucinous (Figure 1), based on the previous evidence and the recommendations of clinical practice guidelines[3,10,11,22].

Variables

The following data were recorded for each patient: Age, sex, American Society of Anesthesiologist classification, treatment with antiplatelets or anticoagulants, history of pancreatitis, neoplasia, smoking or familial pancreatic cancer, presence of symptoms, radiological diagnosis, date of EUS examination, EUS diagnosis, complications, size and location of the lesions, biochemical, cytological and molecular analysis of cyst fluid, histopathological diagnosis in the case of surgery, follow-up and diagnosis of malignancy following the above-mentioned criteria.

Statistical analysis

Continuous variables are expressed as average ± SD and were compared between groups using the Student's *t*-test or *U* Mann-Whitney test. Categorical variables are expressed as percentage, and comparisons were made with the c^2 or Fisher´s exact test. The level of agreement reached was determined with Cohen's kappa. Sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of diagnostic variables were determined according to the pseudo-gold standard established in the study. *P* values ≤ 0.05 were considered significant. All the statistical analyses were performed with the IBM SPSS 23.0 or Stata v13.0 program.

RESULTS

Patient baseline characteristics

Eighty-seven patients with a total of 95 PCN were included between June 2017 and December 2018. After applying the exclusion criteria, 52 patients with 59 PCN were excluded: 47 lesions < 15 mm in size, 6 patients with 6 PCN did not agree to participate, 4 due to lack of modification of the plan following the results of EUS-FNA, and 2 lesions due to lack of technical safety to reach the lesion. In one of these cases access was limited by interposition of gastric neoplasia. Thus, 35 patients with 36 PCN were initially enrolled. Demographic and clinical characteristics are detailed in Table 1.

Lesion characteristics

Table 2 summarizes the lesion characteristics on radiological (CT and MRI) and EUS examinations. None of the 8 mural nodules detected on EUS were described in the

Table 1 Demographic and clinical data of the study population, *n* (%)

Patients	*n* = 35
Age (yr)	66.7 ± 14.5
Male gender	17 (48.6)
ASA I-II	25 (71.4)
AAS	5 (14.3)
Smoking	12 (34.3)
History of acute pancreatitis	3 (8.6)
History of extrapancreatic neoplasia	10 (28.6)
Family history of pancreatic cancer	3 (8.6)
Symptoms	10 (28.6)

Quantitative variables are expressed as mean and standard deviation. Qualitative variables are expressed as absolute values; percentages are indicated in parentheses. ASA: American Society of Anesthesiologist classification; AAS: Acetylsalicylic acid.

radiological imaging techniques. Table 3 summarizes the results of cyst fluid analysis. CEA levels were not determined in 7/36 (19.4%) PCN due to technical problems associated with the high viscosity of the fluid (*n* = 1; 14.3%) or insufficient sample (*n* = 6; 85.7%). In the case of glucose levels, they could not be determined in 6/22 (27.3%) because of high viscosity (*n* = 1; 16.7%) or insufficient sample (*n* = 5; 83.3%).

Lesion classification

Classification of 2 (5.6%) of the PCN into mucinous or non-mucinous lesions was not possible because the mucin stain was negative and no additional CEA or glucose was available. The remaining 34 lesions were classified following the algorithm described in Figure 1. Twenty-eight (82.4%) were classified as mucinous because they met at least one of the criteria and 6 (17.6%) as non-mucinous.

Molecular analysis for the identification of mucinous cystic lesions and malignant cysts

The mean volume of liquid sent for molecular analysis was 2.1 ± 2.3 mL. Although cyst fluid was initially collected from the 36 PCN, only 25 (69.4%) had the amount of DNA needed to perform sequencing (100 ng of DNA at a concentration of 30 ng/μL). The cyst fluid volume obtained for molecular analysis in the cases with enough DNA was lower (1.8 ± 1.8 mL) compared to those with insufficient DNA (2.7 ± 3.1 mL). No statistically significant relationship was found between cyst fluid volume and the possibility of performing molecular analysis.

The results of molecular analysis are shown in Table 4. Overall, mutations in *KRAS* were found in 16 (64%) cysts, *GNAS* in 13 (52%), *PIK3R1* in 1 (4%), *IDH1* in 1 (4%), *PDGFRA* in 3 (12%), *FGFR3* in 2 (8%), *RET* in 1 (4%), *ERBB2* in 1 (4%), *BRAF* in 1 (4%), TGFBR2 in 1 (4%), *FBXW7* in 1 (4%) and *MAP2K1* in 1 (4%) cyst. No mutations were found in the other genes analyzed.

Molecular analysis was possible in 18/28 (64.3%) of the cysts classified as mucinous and in 5/6 (83.3%) of the lesions classified as non-mucinous. In addition, sufficient DNA was obtained in two lesions that could not be classified as mucinous or non-mucinous using the cytological and biochemical criteria described in the previous section.

Mucinous cystic neoplasms: None of the mutations were associated with mucinous cysts ($P > 0.05$). Mutations in *KRAS* and *GNAS* were found in 13/18 (72.2%) and 10/18 (55.6%) of the cysts classified as mucinous, respectively. *KRAS* had an 81.2% sensitivity (95%CI: 59-100) and 71.4% specificity (95%CI: 30.9-100) ($P = 0.297$), while *GNAS* had a 76.9% sensitivity (95%CI: 50.1-100) and 80% (95%CI: 50.2-100) specificity ($P = 0.640$) for mucinous cyst diagnosis. When combining *KRAS* and *GNAS* mutations, 15/18 (83.3%) of the mucinous cysts presented mutations in *KRAS* and/or *GNAS*, offering an 83.3% sensitivity (95%CI: 63.3-100), 60% specificity (95%CI: 7.06-100), 88.24% PPV (95%CI: 69.98-100) and 50% NPV (95%CI: 1.66-98.34) ($P = 0.086$) for the detection of mucinous cysts.

Table 2 Morphological characteristics

Radiological imaging tests	*n* (%)
Malignant	7 (19.4)
Non-malignant	29 (80.6)
Worrisome features on EUS	18 (50)
EUS diagnosis	
Malignant	4 (11.1)
BD-IPMN	9 (25)
MD-IPMN	14 (38.9)
MCN	5 (13.9)
SCN	4 (11.1)
Location	
Head	21 (58.3)
Body	15 (41.7)
Tail	0
Multifocal	8 (22.9)
Size (mm)	27 ± 15.5
Size MPD > 3 mm	11 (30.6)
Mural nodule	8 (22.2)
Contrast enhancement pattern	
Hypo/iso-enhanced walls	18 (54.5)
Hyperenhanced walls	12 (36.4)
Mixed enhancement pattern	3 (9.1)

Quantitative variables are expressed as mean ± standard deviation. Quantitative variables are expressed as absolute values, and their proportions are in bracketed text. EUS: Endoscopic ultrasound; BD-IPMN: Branch duct intraductal papillary mucinous neoplasm; MD-IPMN: Main duct intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SCN: Serous cystic neoplasm; MPD: Main pancreatic duct.

Non-mucinous cystic neoplasms: In a similar manner to mucinous cysts, none of the detected mutations were statistically associated with non-mucinous cyst diagnosis. Mutations in *KRAS* and *GNAS* were found in the same 2/5 (40%) PCN; therefore, the combination of both mutations did not provide different results.

Undetermined cystic lesions: Molecular analysis was also performed in 2 (5.6%) PCN that could not be classified as mucinous or non-mucinous. One of them had mutations in *KRAS* and *GNAS*, while no mutations were found in the other cyst.

Malignant cystic neoplasms: Molecular analysis was carried out in 4/5 (80%) of the malignant lesions and in 21/31 (67.7%) of the non-malignant lesions. Mutations in *KRAS* and/or *GNAS* were found in the 4 (100%) lesions classified as malignant and in 14/21 (66.7%) of the non-malignant lesions. No mutations in *PIK3CA* were found in any of the malignant cysts analyzed. None of the mutations found were related to malignancy ($P > 0.05$).

DISCUSSION

In this study, we evaluated the diagnostic yield of molecular analysis of cyst fluid obtained by EUS-FNA for mucinous cyst diagnosis and the detection of malignancy.

Previous studies have shown that mutations present in the histopathological analysis of pancreatic tissue obtained from surgical specimens are also present in pancreatic cyst fluid, although the amount of DNA obtained from fluid analysis is

Table 3 Cyst fluid analysis

Biochemical	*n* (%)
CEA (*n* = 29)	
< 192 ng/mL	14 (48.3)
≥ 192 ng/mL	15 (51.7)
Glucose (*n* = 16)	
< 50 mg/dL	10 (62.5)
≥ 50 mg/dL	6 (37.5)
Cytological	
Papanicolau classification (*n* = 36)	
II	13 (36.1)
IV	22 (61.1)
VI	1 (2.8)
Mucin staining (*n* = 36)	
Positive	22 (61.1)
Negative	14 (38.9)
Molecular	
Possible	25 (69.4)
Not possible	11 (30.6)

Quantitative variables are expressed as absolute values, and their proportions are in parentheses. CEA: Carcinoembryonic antigen.

lower and sometimes insufficient for molecular analysis[23,24]. In our series, we obtained enough material to perform the molecular analysis (100 ng of DNA at a concentration of 30 ng/μL) in 69.4% of included PCN. An insufficient amount of intracystic DNA was not associated with a lower volume of fluid obtained. These results are similar to those reported in previous studies, which described that the volume required to perform molecular analysis ranges between 0.2-0.5 mL, although in some samples the amount of DNA is insufficient to perform the analysis[23,25,26]. Therefore, we assume that the amount of intracystic DNA is low, and in some cases it may be insufficient to perform molecular analysis, providing negative results regardless of cyst fluid volume.

tNGS detected the following mutations: *KRAS* in 16 (64%) cysts, *GNAS* in 13 (52%), *PIK3R1* in 1 (4%), *IDH1* in 1 (4%), *PDGFRA* in 3 (12%), *FGFR3* in 2 (8%), *RET* in 1 (4%), *ERBB2* in 1 (4%), *BRAF* in 1 (4%), *TGFBR2* in 1 (4%), *FBXW7* in 1 (4%) and *MAP2K1* in 1 (4%) cyst. No mutations were found in the rest of the evaluated genes. These results are in accordance with those of Jones *et al*[19], who evaluated 92 pancreatic cysts by tNGS for the presence of mutations in 39 genes; they found no mutations in 43% of the included cysts and the most frequently detected mutations, as in our series, were *KRAS* and *GNAS*. In order of decreasing frequency, mutations were found in the following genes: *KRAS* (47%), *GNAS* (24%), *CDKN2A* (6%), *VHL* (2%), *SMAD4* (1%) and *TP53* (1%). We found mutations in *KRAS* in 72.2% and *GNAS* in 55.6% of mucinous lesions. When combining these results, 83.3% of mucinous cysts harbored a mutation in one or both genes. However, neither *KRAS* nor *GNAS* or other genes were related to mucinous cyst diagnosis ($P > 0.05$). Regarding the lesions classified as non-mucinous, mutations were found in *KRAS* in 40% of these lesions and in *GNAS* in the same 40%. Similar to mucinous cysts, none of the mutations were related to non-mucinous cyst diagnosis ($P > 0.05$). We did not find any mutations in *VHL*. However, although its presence has been related to serous cystic neoplasms with high specificity, the frequency of this mutation is low. Jones *et al*[19] analyzed fluid from 92 PCN using NSG and found *VHL* mutations in 2% of them. Springer *et al*[20] found mutations in 42% of histopathologically confirmed serous cystadenomas, although they carried out their determination in cyst fluid obtained from surgical specimens and therefore, the percentage could be higher.

Some authors have raised the possibility of incorporating molecular analysis of PCN due to the high specificity of *KRAS* and *GNAS* for mucinous cysts diagnosis found in

Table 4 Molecular analysis

	Non-mucinous					Mucinous																
	PCN5	PCN15	PCN18	PCN20	PCN33	PCN0	PCN1	PCN2	PCN3	PCN4	PCN7	PCN11	PCN13	PCN14	PCN16	PCN17	PCN19	PCN21	PCN24	PCN25	PCN29	PCN30	PCN34
KRAS	M	M	N	N	M	M	N	N	N	N	M	N	N	N	N	M	N	N	N	M	M	N	N
GNAS	M	M	N	N	M	N	N	N	N	N	N	N	M	N	N	M	M	N	M	M	M	M	M
VHL	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
P53	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PIK3R1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	N	M	M	M
EGFR	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
ALK	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
NOTCH1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
GNA11	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
CDKN2A	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
APC	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
FGFR2	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
IDH1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	N	M	M	M	M	M	M	M
PIK3CA	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
KIT	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
MET	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
FGFR1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
ROS1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
GNAQ	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PDGFRA	M	M	M	M	M	M	M	M	N	M	M	M	M	M	M	M	M	M	M	M	N	M	N
FGFR3	N	M	M	M	M	M	M	M	M	M	M	M	M	N	M	M	M	M	M	M	M	M	M
RNF43	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
RET	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	N
ERBB2	M	M	M	M	M	M	M	M	N	M	M	M	M	M	M	M	M	M	M	M	M	M	M
DDR2	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M

BRAF	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	N	M
ESR1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
FGFBR2	M	M	M	M	M	M	N	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
FBXW7	M	M	N	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
FOXL2	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
MAP2K1	M	M	M	M	M	M	M	N	M	M	M	M	M	M	M	M	M	M	M	M	M	M
AKT1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
CTNNB1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
SMAD4	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
PTEN	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
NRAS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
IDH2	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
HRAS	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M
CDH1	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M	M

PCN: Pancreatic cystic neoplasm. M: Mutated; N: Not-mutated.

previous studies with histopathological correlation, and the small volume required for their determination[12,19,27,28]. Nikiforova *et al*[26] performed molecular analysis of cyst fluid obtained by EUS-FNA and found that the presence of a *KRAS* mutation offered a sensitivity of 54% and specificity of 100% for mucinous cyst diagnosis[29]. Similarly, Amato *et al*[24] described that *KRAS* and/or *GNAS* were mutated in 92% of *IPMN*, *GNAS* in 79%, *KRAS* in 50% and both in 37.5%[30]; Singhi *et al*[23] found mutations in *GNAS* in 39%, *KRAS* in 68% and both in 83% of IPMN, although only 6% of the MCN had mutations in *KRAS* and/or *GNAS*[31]. Al-Haddad *et al*[32] found that the presence of a mutation in *KRAS* and/or ≥ 2 loss of heterozygosity in cyst fluid obtained by EUS-FNA demonstrated 50% sensitivity and 80% specificity for the diagnosis of mucinous cysts. In their study, 58% of the mucinous cysts with histopathological diagnosis did not present *KRAS* mutations. However, molecular analysis allowed adequate classification of 24% of the mucinous cysts that could not be classified by CEA and cytological analysis. In this study, *KRAS* offered 81.2% sensitivity and 71.4% specificity, *GNAS* 76.9% sensitivity and 80% specificity, and the combination of *KRAS* with *GNAS* 83.3% sensitivity and 60% specificity for the diagnosis of mucinous cysts. Our sensitivity is close to or higher than that of the studies described above, even in those where the fluid was obtained by aspiration of the surgical specimen. On the

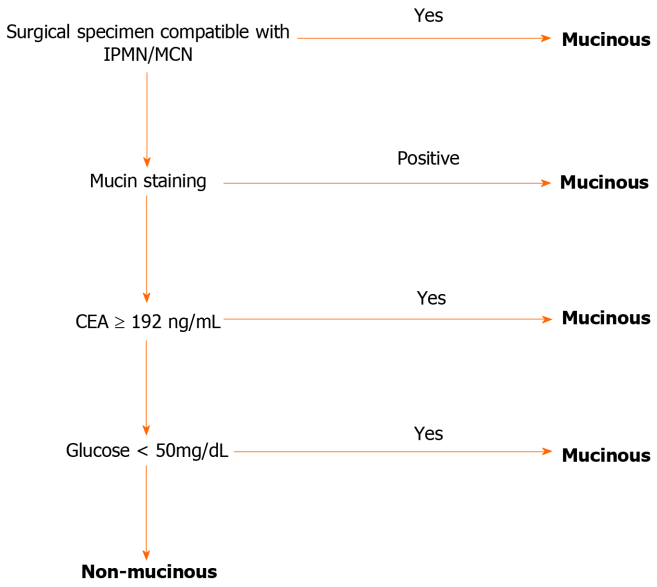

Figure 1 Diagnostic algorithm for mucinous and non-mucinous cysts. Pseudogold standard was considered positive (mucinous) if: Mucinous histology and/or positive mucin staining and/or biochemical > 192 ng/dL and/or glucose < 50 mg/dL, whereas it was considered negative (non-mucinous) if: Non-mucinous histology, negative mucin staining, biochemical < 192 ng/dL and glucose > 50 mg/dL. IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; CEA: Carcinoembryonic antigen.

other hand, our specificity was lower due to the absence of histopathological correlation in some lesions, which could have modified the final diagnosis, and the smaller population of our series.

Taking into consideration the high specificity of *KRAS* and *GNAS* in previous studies for the diagnosis of mucinous cysts[26], the 2 (40%) lesions without histopathological diagnosis classified as non-mucinous would have been recategorized as mucinous after molecular analysis due to the presence of mutations in both *KRAS* and *GNAS*. This would have led to a modification of the follow-up plan in 8% of the cysts in which molecular analysis was successfully performed. Additionally, of the 2 indeterminate cysts in our study, one showed mutation in both *KRAS* and *GNAS* so it could have been classified as mucinous. Therefore, we agree that performing molecular analysis, at least in selected cases with uncertain diagnosis, could improve diagnosis by adequately categorizing PCN as mucinous. This is important as mucinous cysts are premalignant lesions and have a higher risk of concomitant pancreatic adenocarcinoma, thus implying long-term follow-up. We agree with the statement made by other authors about the usefulness of associating the determinations of CEA (more sensitive) and *KRAS*/*GNAS* (more specific)[24,33]. However, further prospective studies with histopathological correlation are needed.

Another area of interest in molecular analysis is the detection of malignancy given the low diagnostic accuracy of other diagnostic methods for early detection of malignant PCN and the morbimortality associated with pancreatic surgery. In our case we were able to evaluate the presence of mutations in 80% of malignant lesions. We found mutations in *KRAS* and/or *GNAS* in all (100%) malignant lesions, but none of these lesions showed mutations in *PIK3CA*. Additionally, we found mutations in IDH1 (n = 1) and *TGFBR2* (n = 1). In our series no mutations were statistically related to malignancy (P > 0.05). Similarly, in previous studies *KRAS* and *GNAS* have not been related to malignancy and have been described as mutations that occur in the early stages of pancreatic carcinogenesis[10,19,25]. In contrast, other mutations such as *TP53*, *PIK3CA*, *PTEN* or loss of *SMAD4* have been associated with malignancy[10,19,23,34]. Our results, similar to those obtained in the study by Singhi *et al*[23], show that *KRAS* and *GNAS* are mutations that occur in the early stages of carcinogenesis and are therefore present in 100% of malignant mucinous cystic neoplasms. However, they found that 50% of the IPMNs with high grade dysplasia and 100% of the IPMNs with adenocarcinoma had, in addition to the *KRAS* and/or *GNAS* mutations, mutations in *TP53*, *PIK3CA* and/or *PTEN*. In our study we found no mutations in *TP53*, *PIK3CA* or *PTEN*. These differences could be justified by the low incidence of malignancy in our sample, differences in the time from extraction to the performance of the molecular analysis and differences in the process of molecular analysis.

There are several clinical practice guidelines focused on diagnosis, treatment and

follow-up of PCN, with differences in the indication of EUS-FNA, surgery and follow-up[2,3,11,18,22,35-37]. These differences show the lack of agreement regarding the role and indication of this technique, probably due to the challenge of early detection of malignancy combined with avoiding unnecessary surgeries. They also reflect disagreement in establishing cost-effective follow-up strategies. The AGA guideline has been widely criticized for its low diagnostic accuracy for detection of malignant cystic lesions, and for its recommendation to discontinue long-term follow-up in the absence of significant findings or changes[12,38,39]. In addition, the European guideline and the IAP guideline have also been criticized mainly for the high number of unnecessary surgeries related to their recommendations[5,40]. Therefore, several authors have proposed alternative algorithms based mainly on lowering the threshold for the indication of EUS-FNA and on performing molecular analysis[12,41,42].

According to the European guideline[11], we believe it is advisable to continue follow-up in mucinous lesions, while it could be discontinued in serous cysts. However, differentiation between serous and mucinous PCN is difficult, so the European guideline advises performing EUS-FNA with cytological analysis, CEA and molecular analysis (NGS) with determination of *KRAS* and *GNAS* when the diagnosis is unclear[11]. In contrast, the IAP guideline considers that molecular analysis is experimental and should only be considered in centers with experience in this technique[3]. We have proven that the performance of molecular analysis is a complex procedure, with high cost and requires an experienced team; thus, we consider, in line with IAP guidelines, that the technique should be standardized before recommending its widespread use.

The main strengths of our study are its prospective nature with a cohort of patients with different types of PCN (82.4% mucinous and 17.6% non-mucinous cysts) and malignancy (13.8%), which shows the standard clinical practice in the study and therapeutic decision on PCN, and therefore our experience is applicable to clinical practice in any other center with access to pancreatic study techniques. Additionally, we performed molecular analysis providing additional information on PCN diagnosis.

However, our study has several limitations. First of all, it is a unicentric study based on the experience of a single endoscopist. Second, it should be noted that the diagnosis using morphological, cytological and biochemical criteria is suboptimal and we only have anatomopathological diagnosis in 5 (13.9%) of the lesions. In fact, as we have already discussed, in 2 lesions classified as non-mucinous, initial diagnosis would have been modified after performing molecular analysis. We consider that our system of classifying the PCN is a good option in clinical practice, where the diagnosis is made with the available data in the absence of a surgical specimen. Third, the absence of malignancy was defined as the absence of progression in imaging tests or clinical deterioration after a follow-up of no less than 6 mo, being the median follow-up in our study of 472 (IQR: 271-619) d. However, the follow-up period could be considered short and it is uncertain if patients could have developed malignancy over a longer follow-up period. Fourth, the small sample size of the study, which was due to the short temporal frame of the study and inclusion criteria, resulted in the absence of statistical significance. Only lesions ≥ 15 mm were included following the recommendations of the European guideline[11], excluding those < 15 mm, even though the presence of malignancy was described in up to 39% of the symptomatic cysts < 2 cm[43]. Finally, we emphasize that, although we consider that molecular analysis is highly specific for the diagnosis of mucinous cysts, the high cost of this technique precludes its universal implementation.

CONCLUSION

In conclusion, molecular cyst fluid analysis obtained by EUS-FNA helped in our study by recategorizing 40% of serous lesions as mucinous cysts. However, the mutations detected in our sample did not reach statistical significance for the diagnosis of mucinous or malignant cysts. Further studies with larger sample sizes and more sensitive techniques could change these results.

ARTICLE HIGHLIGHTS

Research background

Pancreatic cysts are a common finding on imaging tests performed for other reasons.

Adequate characterization is important considering the risk of malignancy of some of these cysts. However, differentiation between different types of cysts and detection of malignancy just with morphological criteria is suboptimal.

Research motivation

Endoscopic ultrasound-guided fine-needle aspiration (EUS-FNA) and molecular analysis could improve the detection of mucinous (premalignant) and malignant cysts.

Research objectives

To determine the diagnostic yield of molecular analysis for the detection of mucinous and malignant cysts in clinical practice.

Research methods

A single center, prospective observational study of consecutive patients over an 18-mo period with pancreatic cystic lesions and an indication for EUS-FNA following European clinical practice guidelines was conducted. EUS-FNA with cytological, biochemical with CEA and glucose, and molecular analysis with next-generation sequencing were performed in 36 pancreatic cysts. Next-generation sequencing results were compared for cyst type and malignancy.

Research results

Of the 36 lesions included, 28 (82.4%) were classified as mucinous and 5 (13.9%) lesions as malignant. The amount of DNA obtained was sufficient for molecular analysis in 25 (69.4%) pancreatic cysts. *KRAS* and/or *GNAS* showed 83.33% sensitivity, 60% specificity, 88.24% PPV and 50% NPV (P = 0.086) for the diagnosis of mucinous cystic lesions. Mutations in *KRAS* and *GNAS* changed the follow-up plan in 8% of the cysts. None of the mutations analyzed were related to malignancy (P > 0.05).

Research conclusions

Molecular cyst fluid analysis obtained by EUS-FNA improved mucinous cyst diagnosis by recategorizing 40% of serous lesions as mucinous cysts. However, the mutations detected in our cohort did not reach statistical significance to confirm the diagnosis of mucinous or malignant cysts.

Research perspectives

Further prospective studies with larger sample sizes are needed to determine the clinical benefit of adding molecular cyst fluid analysis for pancreatic cyst evaluation.

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AIMS AND SCOPE

The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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OPINION REVIEW

Computed tomography colonography and radiation risk: How low can we go?

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Abstract

Computed tomography colonography (CTC) has become a key examination in detecting colonic polyps and colorectal carcinoma (CRC). It is particularly useful after incomplete optical colonoscopy (OC) for patients with sedation risks and patients anxious about the risks or potential discomfort associated with OC. CTC's main advantages compared with OC are its non-invasive nature, better patient compliance, and the ability to assess the extracolonic disease. Despite these advantages, ionizing radiation remains the most significant burden of CTC. This opinion review comprehensively addresses the radiation risk of CTC, incorporating imaging technology refinements such as automatic tube current modulation, filtered back projections, lowering the tube voltage, and iterative reconstructions as tools for optimizing low and ultra-low dose protocols of CTC. Future perspectives arise from integrating artificial intelligence in computed tomography machines for the screening of CRC.

Key Words: Computed tomography colonography; Colorectal cancer; Radiation risk; Image quality; Image noise; Iterative reconstruction

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Core Tip: Computed tomography colonography (CTC) is an important imaging technique with significant advantages over optical colonoscopy in terms of less invasiveness, better compliance, and assessment of extracolonic structures. Ionizing radiation is the most significant burden of this technique. This opinion review comprehensively addresses the radiation risk in CTC with imaging technology refinements that should be used to lower radiation doses.

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INTRODUCTION

Computed tomography colonography (CTC), also referred to as a virtual colonoscopy (VC), was introduced in 1994 by Vining *et al*[1]. They were the first to describe this modified computed tomography (CT) examination of the large intestine as a diagnostic test for colorectal carcinoma (CRC) and polyps[2]. Since then, CTC has become an examination of crucial importance in imaging polyps and potential CRC in patients not amenable to optical colonoscopy (OC). CTC has advantages over OC because of its less invasive nature, better patient compliance, and the ability to detect extracolonic disease[3]. Hence, CTC is an accepted screening test for CRC and is growing in its utilization. We have to be aware that no CTC findings allow us to distinguish adenomas from non-neoplastic polypoid lesions such as hyperplastic or inflammatory polyps, making the histological study necessary in all instances. One of the drawbacks of CTC is usually missed flat lesions such as a flat polyp. Images that can be misinterpreted and can mimic polyps include untagged stool, partially distended haustra, or focally thickened folds[4].

On the other hand, OC is often associated with anxiety, fear, and discomfort compared to CTC, and carries a risk of being incomplete, especially in elderly patients[5]. Despite these advantages of CTC, ionizing radiation is the most significant burden of this technique (Table 1). However, imaging technology refinements, favorable cost analyses, and the impact of extracolonic findings make this method a suitable alternative to OC for CRC screening[3].

CTC FOLLOWING INCOMPLETE OPTICAL COLONOSCOPY

One of the unanimously accepted CTC indications is to complete a colonic workup after an incomplete OC. Some 10% of colonoscopies cannot be completed for different causes: Neoplastic stenosis, diverticulosis, adhesions, loops, or redundant colon[6-9]. A study revealed that 4.3% of neoplasms were missed by incomplete colonoscopy and were found in additional imaging studies[6]. Moreover, the proximal colon study is particularly important in neoplastic stenosis, as the percentage of synchronous cancer is high (4%-5%)[10]. In some patients, OC can be technically challenging, with the inability to achieve cecal intubation, resulting in inadequate visualization of the entire colon, hence a potential risk of undetected colon cancer and polyps[11,12] Except radiology practices with an active screening program, incomplete OC examinations likely account for the vast majority of CTC requests[13]. Factors previously shown to contribute to the risk of incomplete OC include; increasing patient age, low body mass index, female gender, history of prior abdominal and pelvic surgeries, presence of severe diverticular disease, poor bowel preparation, the experience of the endoscopist, tumorous obstruction of the entire lumen and anesthesia-related complications[7].

There are two primary strategies regarding the timing of CTC following incomplete OC. The first and most common is same-day CTC utilizing the prior OC prep, often supplemented with oral contrast after recovery from OC[14]. This is often the more convenient option for the patient as they do not have to undergo further bowel preparation (assuming bowel prep for OC was adequate) and return on a separate day. CTC is usually performed 2–3 h later. Another option is to have the patient return for CTC at a later date utilizing a standard CTC bowel regimen with an osmotic

Table 1 Advantages and limitations of computed tomography colonography

Advantage	Limitation
Minimally invasive procedure	Exclusively diagnostic method
Safe procedure	Ionizing radiation
No need for sedation	Fecal residue simulate pathology
Short examination time	Laxative residue simulate pathology
Assess to extracolonic disease	Flat lesions
Three dimensional view	
View of the entire colonic surface	
Access to post-obstructed bowel	
"Second look"	

cathartic and dual agent tagging protocol. CTC should be delayed if an endoscopic resection has been performed during OC[15].

SCREENING FOR CRC

Most population-based screening programs for CRC target the age range from 50 to 74 years old and include indirect screening, such as fecal occult blood testing or direct visualization with flexible sigmoidoscopy or OC[16]. The most common is the stool test-based screening [guaiac fecal occult blood test (FOBt) or fecal immunochemical test (FIT)] due to its low cost, availability, safety, and easy transport (*via* post). If positive, FOBt and FIT are usually followed by OC to confirm neoplasia or suspect polyps[5].

Since CTC has become an available alternative option to OC, more patients choose CTC as a more desirable option. In a multicenter survey of 1417 individuals, 68% chose CTC over OC due to its less invasive nature, and 47% chose CTC to avoid the risks associated with OC[17]. Another Dutch study showed that 93% of patients would choose another CTC after the initial one[18].

The CRC screening potential of CTC has been investigated in three European randomized trials: COCOS study in the Netherlands (CTC *vs* OC)[19], SAVE[20], and PROTEUS[21] studies in Italy.

The SAVE study compared reduced preparation and full-preparation CTC, FIT, and OC, while the PROTEUS study compared CTC *vs* sigmoidoscopy. The participation rates, positivity rate, and CTC detection rates were similar amongst the studies. The participation rate for screening CTC was higher than that for an OC, with a slightly lower detection rate, but with comparable yield per invitee. The participation rate for screening CTC was much lower than that for FIT, but its detection rate was three-fold that of one FIT round. CTC and sigmoidoscopy showed similar participation and detection rate. These results encourage CTC implementation in screening programs for CRC[22].

RADIATION INDUCED RISKS

CTC's main disadvantage is ionizing radiation, especially since CTC has been considered a CRC screening tool. Radiation dose significantly determines CT image quality, its diagnostic accuracy, and clinical utility. Strategies for lowering radiation dose are utilized to maintain and improve image quality. The dose should only be reduced if one can preserve the diagnostic image quality for the specific pathology. It is essential to understand the relation between image quality and radiation dose to optimize the radiation dose in CTC[23].

CTC dose is lower than the conventional CT examination, about one half of the dose, because of high natural contrast between the soft tissue of the colonic wall, luminal gas, and tagged fecal residue and fluids[6].

To give the proper insight, it is meaningful to compare the doses of different diagnostic procedures with the chest X-ray dose or years of exposure to natural background radiation, ranging from 1 to 3 mSv/year, depending on the geographical

region. Thus, mammography has a dose of 0.13 mSv, which corresponds to 6 chest X-rays or 14 days of background radiation. An average abdominal CT has 5-25 mSv, which corresponds to 250-1250 chest X–rays or 2-11.5 years of background radiation, depending on the number of phases that have to be scanned to confirm the suspect diagnosis[24] (Table 2).

During the last few decades, physicists, radiologists, and technologists have studied CT technology to find ways to reduce radiation doses for specific "diagnosis-related" CT examinations. Currently, we have well-established "diagnosis-related" protocols such as "low-dose" kidney stone dedicated protocol, "low-dose" lung cancer screening protocol, *etc*.

Dose reduction can be achieved in two ways. Firstly it is crucial to appropriately target image quality for a specific diagnostic test, not demanding lower noise or higher spatial resolution than necessary. For instance, in a high-contrast setting, as in the detection of colon polyps from a background of air and contrast-tagged stool[25,26], it allows high noise level and relatively low radiation dose without sacrificing the diagnostic confidence. Detection and characterization of low-contrast lesions present in CT imaging of hepatobiliary and brain pathology require a relatively low noise level and higher radiation dose. Consensus agreement on image quality requirements exists in guidelines and standards[27], but precise quantitative requirements exist only for several examinations[28].

There are many ways to adjust scanning parameters in order to lower the dose. One way to reduce the dose is to change the technical exposure parameters of scanning: The tube current or the voltage depending on the tissue density and contrast, scanning region, and the patients' body shape and size[29].

Modern CT equipment can automatically modulate the X-ray tube current after obtaining a scanned region's initial topogram, known as automatic tube current modulation (ATCM). ATCM adjusts the X-ray tube current (mAs) according to the size and the attenuation of the examined body part. It has been recommended to use ATCM for CTC[5,20,21].

Each time the scanning parameters are changed, it influences the image's quality, namely spatial and/or contrast resolution, which are important for detecting specific pathologies. Spatial resolution relates to sharp boundaries of the tissues, organs, or structures, while contrast resolution involves the difference in contrast of various tissues (*e.g.*, normal or pathologically altered). Low dose protocols have a higher image noise due to altered (lower) electrical conditions. Spatial or contrast resolution is sacrificed, and the radiologist has to get the same information from granulated images. Therefore, it is important to balance the dose by adjusting electrical conditions and maintaining image quality. The image quality needs to be good enough to distinguish pathologic lesions from normal structures. Thus, it is crucial to find a delicate balance between the lowest dose and acceptable image quality, making it possible for a radiologist to discern pathologic structures[5]. This is also referred to as the As Low As Reasonably Achievable principle, well established in the area of radiation protection[23]. In addition to altering exposure parameters, software options have been developed to make less image noise by keeping the tube current as low as possible. These software reconstructions techniques are Sinogram-Affirmed Iterative Reconstruction (SAFIRE) and a conventional filtered back projection. These techniques allowed the use of even lower doses of radiation than the conventional low dose (LD) protocol named ultra-low dose (ULD) with maintained image quality[5,24,30]. In 2018, a study evaluating the ULD protocol's diagnostic value in detecting polyps[31] showed that the ULD protocol lowers the effective dose up to 63.2% compared to LD protocol (0.98 mSv for ULD and 2.69 mSv for LD). Image noise measurements with ULD were slightly lower (28.6) than with LD (29.8) (P = 0.09). Image quality was not different between 2D and 3D with either ULD and LD. A special 3D software option must be used to navigate the large bowel and when interpreting CTC to help detect intraluminal lesions. In contrast, the 2D option is the routine CT examination technique. Polyp detection was also comparable, with no significant difference in detection rate and polyp measurement for LD and ULD protocols[30]. Therefore if iterative reconstruction methods (the software option in almost all modern CT scanners) were included during the scanning, there was no significant image quality degradation with ULD-CTC compared with LD-CTC.

Advantages of specific computer software for CTC interpretation, which enables dynamic viewing of two-dimensional axial images, multi-planar reformats, and three-dimensional renderings, require radiologists' interactive training. The radiologist can use either 2D axial images or 3D renderings for CTC's primary interpretation, with the alternate method reserved for problem-solving specific questions related to a potential lesion. 3D reading is an additional software option that enhances polyp detection and

Table 2 Comparison of different ionizing radiation doses for different examinations

Examination	Ionizing radiation dose [mSv]
X-ray lung	0, 1
X-ray abdomen	1
Barium enema fluoroscopy exam	9
CT abdomen and pelvis (w/o contrast)	10
CTC (2 series)	20
CTC ultra low-dose protocol	2

CT: Computed tomography; CTC: Computed tomography colonography.

decreases the interpretation time without increasing the patient dose (Figure 1).

Skilled usage of these techniques acquired by comprehensive training correlate with polyp detection sensitivity[31]. Primary 2D interpretation is rendered from magnified colonic axial images gained in supine and prone positions. Compared to primary 3D interpretation, it shortens the assessment time of lesion density and homogeneity.

Sessile polyps have round or ovoid morphology and are of soft tissue density. They remain fixed in location on the colon wall in both the supine and prone images. The stool can be differentiated from polyps since it is typically mixed density and shifts location when the patient changes position. Pedunculated polyps can shift in location when the patient moves from supine to prone positions, but the stalk is typically easily identified on 2D and 3D images. Multiplanar reformats and 3D images are useful for evaluating lesion morphology and confirming polyps[32].

In addition to widely used techniques of lowering radiation dose such as automatic tube dose modulation (automatic adjustment after the initial topogram), lowering the tube current, and applying iterative reconstruction (IR), lowering tube voltage can be useful. This option is rarely used for routine CT scanning because it impairs X-ray penetration through the scanned region. However, during the CTC, the bowel has a high contrast due to intraluminal gas; therefore, high voltage is not needed. If there is an option for IR, we can lower the voltage and turn on IR. The iterative reconstruction software option will fix the image noise which arises from the lower voltage[29].

The data suggest that low tube voltage with IR results in a 27 % radiation reduction while maintaining the image quality and detection (100kVp *vs* 80kVp)[33]. In addition, new IR such as SAFIRE could lower the voltage even more[30].

Recent studies show that both hybrid and iterative model reconstruction techniques are suitable for sub-milliSievert ultralow-dose CTC without sacrificing the study's diagnostic performance[34].

Several operational factors typically result in higher doses. Repeated CT scanning, such as multiphase examinations, increases the radiation dose. For example, suppose diagnostic CTC is being performed in a patient with suspected colorectal carcinoma. In that case, intravenous contrast may be necessary, and CT acquisition parameters will typically require higher mAs. If the patient is undergoing CTC as a screening examination, then intravenous contrast is not routinely used.

Patient's hight and/or length also influences the radiation dose. Longer scan length results in radiation exposure to a greater anatomic region and hence higher radiation dose. For some reason, for a detailed analysis, radiologist could request thinner images that provide better image resolution and improved visibility of small objects. However, beam intensity needs to be increased to reduce the noise in these thinner images, which concurrently increases the radiation dose[35].

Since the whole abdomen is visible during CTC screening, many abnormalities outside of the colon can be picked up. Several US screening studies collected the data on clinically significant extracolonic findings that required further imaging. The proportion of patients with follow-up CT scans to investigate these findings was in the range of 5-10%[36,37]. The most common follow-up scan were; an abdomen CT scan and abdomen/pelvis and chest CT scans. The dose from an abdomen/pelvis CT scan performed with and without contrast is about 20 mSv[38], which will result in a radiation risk that is about twice as high as the risk from CTC. However, as only a small proportion (*e.g.*, 10%) of the screening population will receive these additional scans, it is unlikely that they will increase the average risk to the whole screening population by more than 20%.

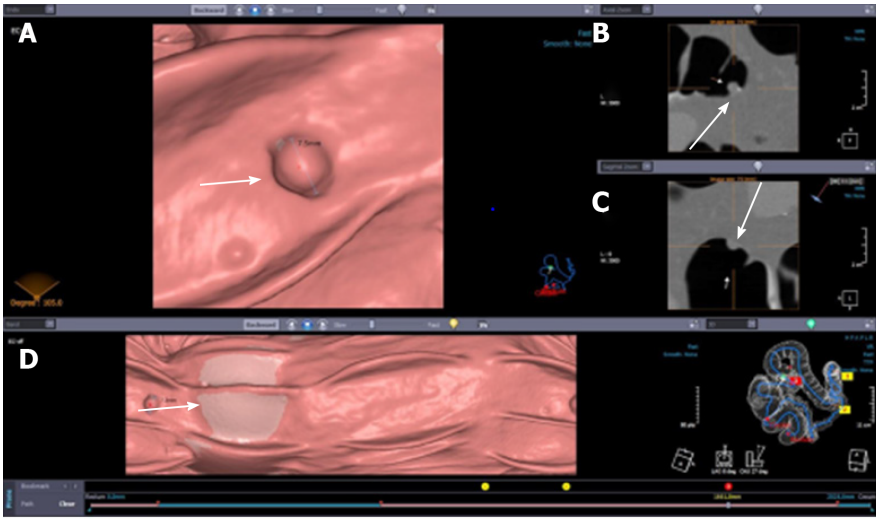

Figure 1 Computed tomography colonography: Two- and three-dimensional view of the polyp (arrows). A: Polyp 3D view; B: Polyp 2D view; C: Polyp 2D view; D: Tagged stool.

The standard American College of Radiology (ACR) CTC protocol[39-42] specifies that the patient be scanned in both the supine and prone positions to allow complete evaluation of the colon with the dependent shifting of luminal fluid and complementary distention of non-dependent colonic segments. In a minority of cases, the same colonic segments will be collapsed on the standard positions, necessitating a third series to achieve full diagnostic evaluation. The sigmoid and/or descending colon account for most non-diagnostic segments, necessitating a right lateral decubitus series to complete the examination[43,44].

The frequency for performing a decubitus series at CTC varies considerably according to study indication, practice site, patient age, BMI, and over time. It is critical to note that the CT technologist is primarily responsible for determining the need for a decubitus series–not the radiologist. These results have important implications for clinical practice, including the need for improved training and feedback for CT technologists[45].

Furthermore, practice regarding ancillary imaging before a CTC and after incomplete OC should be discussed as this can also increase radiation dose; for example, some centers perform a scout/topogram or non-contrast CT abdomen following incomplete OC, in order to exclude a perforation; although there is evidence to suggest this is unnecessary.

Perforation is a recognized complication of colonoscopy. Reported perforation rates range from one case in 3115 procedures (0.032%) to one case in 510 procedures (0.196%)[46-49]. The short time between incomplete colonoscopy and same-day or next-day CTC may not be adequate to allow some perforations to become clinically apparent. Because of the risk of exacerbating a clinically unsuspected perforation during insufflation at CTC, which can increase sepsis risk, screening for the presence of extraluminal gas before insufflation for CTC may benefit occult perforation among these patients. Colonic perforation after colonoscopy can be clinically occult. Recent studies have shown that some findings justify performing low-dose diagnostic CT before rectal tube insertion and gas insufflation in all patients referred for same-day or next-day CTC after incomplete colonoscopy to minimize the risks associated with exacerbating perforation[50].

RADIATION DOSE AND CANCER RISK

Effects of radiation and its risk are usually estimations based on the linear extrapolation of the cancer risks associated with ultra-high doses from Hiroshima and Nagasaki atomic bomb survivor studies[51]. Still, there is no unambiguous evidence of cancer induction at low dose levels, and the issue remains highly controversial.

In 2016, the Health Physics society published that radiation lower than 100mSv did not impact the human body[52]. Assuming that the CTC dose is on average 5mSv, that means that the theoretical cancer risk would be 0.04% in 50-year-old patients and

0.02% in 70-year-old patients after initial screening[51]. Keeping in mind that a lifetime risk for developing colon cancer is around 5%, CTC's benefits outweigh its estimated radiation risk. CTC doses are, currently, in many institutions, even lower than 3mSv, the dose which is comparable to annual radiation exposure in some countries such as the United States[53].

Since the age for screening for CRC is above the age of 50, exposure is decreased significantly, and therefore the radiation-related cancer risk is even lower. Since the proportion of dividing human cells decreases with age, this further raises CTC's safety in the older population it mainly serves[54].

It is important to consider the average frequency of each examination in the population and the average radiation dose with each technique to understand the radiation dose of CTC in the context of other ionizing techniques. However, all examination-based techniques (radiography, fluoroscopy, CT, positron emission tomography-CT, scintigraphy, and interventional cardiology) constitute 34 % of the total annual population dose[53,55].

It is important to emphasize that CTC is quite different from the usual CT examination. Inherently high contrast between the air-filled lumen of the colon and the soft-tissue attenuation of the colonic wall allows a relevant dose reduction without loss of diagnostic accuracy[54].

CONCLUSION

In addition to CTC's high safety profile, slightly better patient compliance, ability to detect extracolonic disease and comparable polyp and cancer detection rate to OC, CTC can be performed with a minimal radiation dose that poses no risk of cancer to the patient.

CTC "good practice" should include individualizing the scanning technique according to the patient's attenuation level and using suitable tube potential selected by advanced automatic exposure control techniques that adjust the tube current. Implementation of iterative reconstruction in everyday clinical practice can bring significant image quality improvement and radiation dose reduction over conventional filtered back-projection-based reconstruction algorithms.

Modern CT equipment allows us to scan CTC at much lower doses ranging from 1 to 5 mSv. These doses are comparable with 1-2 Lung radiograms and are on the annual radiation background level in some countries. Since screening programs mostly include two readers (two experienced radiologists) and "double-blinded" reading, the new perspectives arise from the integration of artificial intelligence in CT machines, which could be used for screening CTC instead of a "second reader".

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SYSTEMATIC REVIEWS

Post-colonoscopy diverticulitis: A systematic review

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Abstract

BACKGROUND

Post-colonoscopy diverticulitis is increasingly recognized as a potential complication. However, the evidence is sparse in the literature.

AIM

To systematically review all available evidence to describe the incidence, clinical course with management and propose a definition.

METHODS

The databases PubMed, EMBASE and Cochrane databases were searched using with the keywords up to June 2020. Additional manual search was performed and cross-checked for additional references. Data collected included demographics, reason for colonoscopy, time to diagnosis, method of diagnosis (clinical *vs* imaging) and management outcomes.

RESULTS

A total of nine studies were included in the final systematic review with a total of 339 cases. The time to diagnosis post-colonoscopy ranged from 2 h to 30 d. Clinical presentation for these patients were non-specific including abdominal pain, nausea/vomiting, per rectal bleeding and chills/fever. Majority of the cases were diagnosed based on computed tomography scan. The management for these patients were similar to the usual patients presenting with diverticulitis where most resolve with non-operative intervention (*i.e.*, antibiotics and bowel rest).

CONCLUSION

The entity of post-colonoscopy diverticulitis remains contentious where there is a wide duration post-procedure included. Regardless of whether this is a true complication post-colonoscopy or a *de novo* event, early diagnosis is vital to guide

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appropriate treatment. Further prospective studies especially registries should include this as a complication to try to capture the true incidence.

Key Words: Colonoscopy; Diverticulitis; Complication; Management; Antibiotics; Surgery

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Core Tip: The entity of post-colonoscopy diverticulitis is a rare complication. However, there is no consensus on its definition especially on the duration included post-procedure. It could well represent a de novo event or exacerbation of subacute condition. Regardless, it should be considered as a differential in patients presenting with abdominal pain post-colonoscopy and managed according to the usual treatment of patients presenting with diverticulitis.

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INTRODUCTION

Colonoscopy is usually performed for the purpose of screening, diagnostic or surveillance. It is a relatively safe procedure with complication rate between 0.1%-0.3%[1,2]. Most large studies report mainly on complications such as bleeding, perforation and post-polypectomy syndrome[1,2]. Other rarer complications such as splenic injury and pancreatitis have also been reported[2,3]. In recent years, the entity of post-colonoscopy diverticulitis has emerged as a potential complication. Its exact incidence is not known but estimated to be around 0.04%-0.08%[1]. The underlying pathogenesis is not known as a few theories have been hypothesized.

This entity is likely to be progressively more significant due to the exponential increase in number of colonoscopies performed worldwide from colorectal screening programmes and the improved life expectancy of the global population which coincides with higher incidence of diverticular disease[4]. This is evident in the study from Guertin *et al*[5] where there were 4066 more screening and surveillance colonoscopies in the last 2 years of the study period as compared with the first 2 years (13841 in 2015-2016 *vs* 9755 in 2013-2014, $P = 0.005$).

With no uniform and clear definition of this entity, the aim of this study was to systematically review all available evidence of post-colonoscopy diverticulitis and described its incidence, clinical course and to propose a definition.

MATERIALS AND METHODS

A systematic review of the literature from the January 1990 to June 2020 was performed by searching PubMed, EMBASE and Cochrane databases. The medical subject headings (MeSH) and keywords used individually or in combination were: "diverticulitis", "colonoscopy", "post-colonoscopy", "colonoscopy-induced", "perforation" and "complication". All references were searched and cross-checked. All foreign language articles if available were translated by medical personnel with proficiency in both foreign language and English. Ethics approval was not required from the institution's ethics committee for this study.

The search pathway is described as per the PRISMA flowchart as shown in Figure 1.

Inclusion and exclusion criteria

A data proforma was designed prior to the collection of data for uniformity. The investigators (Ng ZQ, Tan JH and Tan HCL) individually collected the data. Any difference in opinion was resolved through discussion with the other author (Theophilus M) but was not required. The data collected included author, journal, year, country, demographics, reason for colonoscopy, time to diagnosis, diagnosis

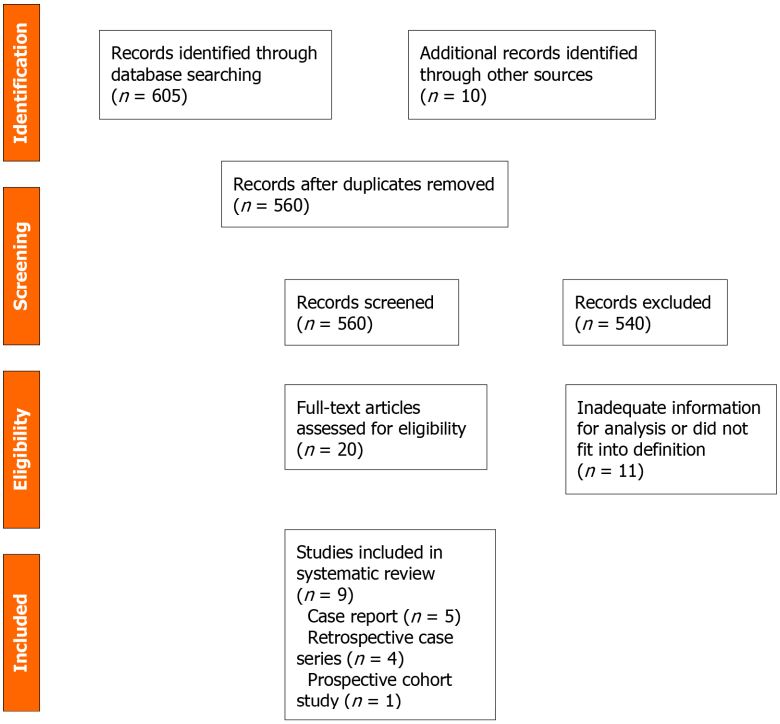

Figure 1 PRISMA flowchart of the search pathway for post-colonoscopy diverticulitis.

method (clinical or radiological), management (outpatient or inpatient, oral or intravenous antibiotics and radiological or surgical intervention) and recurrence of diverticulitis. Data were analyzed using descriptive statistics.

RESULTS

One prospective study[6], four retrospective cohort studies[7-10] and four case reports[11-14] were included in the final analysis, with a total of 339 cases reported in the literature.

The estimated incidence of post-colonoscopy diverticulitis from the four retrospective and one prospective study in this review was 1.3%.

Of the nine studies, only one was published before 2010[8]. Majority of the literature originated from the United States (n = 5)[6-8,10,11]. The rest were from Asia Pacific (n = 4)[9,12-14].

Definition and timeframe

None of the studies have a definition for the entity of post-colonoscopy diverticulitis. Two large studies considered the episode of diverticulitis induced by colonoscopy up to 30 d post-procedure. The other case reports considered it from 2 h to 16 d post-colonoscopy. Two studies did not specify the timeframe.

Demographics, clinical presentation and management (Table 1)

The larger studies did not report the mean or median age and gender distribution of the patients with post-colonoscopy diverticulitis. Only the individual cases reported them.

Only four case reports described the individual case presentations that were not completely typical of the usual presentations[11-14]. There was evidence of raised inflammatory markers (white cell count and c-reactive protein).

Six out of nine studies reported the method of diagnosis[6,7,11-14]. Of those reported, 60 patients were diagnosed with computed tomography (CT) scan and 12 based on clinical judgement. Another reported relied on self-reported symptoms and perceived diagnosis of diverticulitis[6]. The findings of CT scan were reported in six studies where 66 patients were classified as uncomplicated and 6 as complicated diverticulitis.

Six out of nine studies described the management of the patients[7,8,11-14]. Of the six studies, only one patient was managed with outpatient oral antibiotics. Two patients needed percutaneous drainage. Surgical management was required in eight patients on the index presentation, but the type of operation was not specified. In a study of 68

Table 1 All the cases of post-colonoscopy diverticulitis reported in the literature from January 1980 to June 2020

Ref.	Type of study	Number of patient (s)	Age	Gender	Type of colonoscopy	Incomplete (I) *vs* Complete (C)	Reason for colonoscopy	Other concurrent intervention	Diagnosis of Post-colonoscopy diverticulitis	Findings on CT	Duration to diagnosis after scope	Symptoms	Biochemistry	Management
Levin *et al*[8] /United States/2006	Retrospective	6/16318	-	-	C	-	Screening or surveillance	Biopsy (n = 5)	-	-	Within 30 d	-	-	Inpatient antibiotics (n = 4), surgery (n = 2)
Ko *et al*[1]/ United States/2010	Prospective	23/21375	-	-	C	-	Screening and surveillance	-	Self-reported	-	Within 30 d	-	-	-
Rutter *et al*[10]/ United States /2012	Retrospective	82/43456	-	-	C	-	Screening and surveillance	Polypectomy (n = 41)	-	-	-	-	-	-
Park *et al*[13] /Korea/2013	Case report	1	44	M	C	C	Surveillance	Polypectomy and EMR	CT scan	Uncomplicated diverticulitis	2 h	Abdominal pain and fever	Normal WCC	Inpatient intravenous antibiotics
Lin *et al*[9] /Taiwan/2017	Retrospective	156/112543	-	-	C and F	-	Diagnostics and interventional	Biopsy (n = 6)	-	-	-	-	-	-
Park *et al*[14] /Korea/2016	Case report	1	65	M	C	C	Surveillance	Polypectomy	CT scan	Uncomplicated diverticulitis	48 h	Epigastric and left upper quadrant pain	Elevated WCC and CRP	Inpatient intravenous antibiotics
Gorgun *et al*[7]/ United States/2018	Retrospective	68/236377	56 (mean)	M:F = 25:43	C	I:C = 13:55	-	Polypectomy (n = 26)	CT scan	Uncomplicated (n = 62); Complicated diverticulitis (n = 6)	12 ± 8 d	Abdominal pain (n = 26), nausea/vomiting (n = 12), fever (n = 5), diarrhea (n = 5), chills (n = 3), PR bleeding (n = 2)	Elevated WCC	Antibiotics (n = 60), emergency surgery (n = 6), percutaneous drainage (n = 2)
Hudson *et al*[12] /Australia/2019	Case report	1	50	M	C	C	Diagnostics	Polypectomy	CT scan	Uncomplicated diverticulitis	16 d	PR bleeding, generalized abdominal pain	Elevated CRP	Inpatient intravenous antibiotics
Mohan *et al*[11]/ United States/2019	Case report	1	59	F	C	C	Screening	Polypectomy	CT scan	Uncomplicated diverticulitis	48 h	Left lower quadrant abdominal pain	Elevated WCC	Outpatient oral antibiotics

M: Male; F (gender): Female; CT: Computed tomography; C: Colonoscopy; F: Flexible sigmoidoscopy; WCC: White cell count; CRP: C-reactive protein.

cases, six cases subsequently had surgery after non-operative management[7].

Recurrence

Only one study[7] reported the follow-up of patients in recurrence of diverticulitis (26%).

DISCUSSION

Colonoscopy is a common procedure undertaken and has a relatively safe profile[15]. The common complications post-colonoscopy include bleeding, perforation and post-polypectomy syndrome[2,6,8,16]. Rarer complications reported include splenic injury, pancreatitis, mesenteric ischemia, cholecystitis and small bowel perforation[3]. This systematic review found that the entity of post-colonoscopy diverticulitis is a relatively rare complication with incidence slightly higher than previously estimated 0.11%-0.37%[6-10]. Nonetheless, the true incidence may be clouded due to under-recognition or misdiagnosis, and spontaneous resolution without invasive intervention. This is evident in large studies that this entity was not included in the main study objective[15].

The entity of post-colonoscopy appendicitis is likely to share some similarities in its pathogenesis[17]. Various theories have been postulated for its mechanism: Barotrauma secondary to insufflation, inadvertent intubation of the diverticulum, faecolith introduction or propagation during the procedure leading to inflammation and exacerbation of subclinical/chronic disease. In patients with history of diverticulitis, navigating the colonoscopy through the diseased segment of colon can be challenging and potentially lead to inadvertent intubation of the diverticulum[3]. The choice of gas insufflation (air *vs* carbon dioxide) is not known to be a risk. The pre-procedure mechanical bowel preparation has a potential role in altering the gut microbiome resulting in subtle defects in the mucosal barrier and subsequently leading to an inflammatory cascade following colonoscopy[4].

This entity is envisaged to be increasingly recognised due to the following reasons. The number of screening colonoscopies is expected to increase due to the colorectal screening programme for prevention of colorectal cancer where the screening population age coincides with the increased incidence of diverticular disease (> 50% of Americans older than 60 years of age have diverticular disease[4]). Besides, although the current evidence for follow-up colonoscopy after index episode of diverticulitis is contentious but most centres still do it as a routine 6-8 wk post-diverticulitis to ensure no underlying malignancy has been missed[18,19]. Taking into consideration the lifetime risk of diverticulitis in a person is approximately 10%-25%[20], a substantial number of the population will likely undergo a colonoscopic follow-up.

The clinical presentation of post-colonoscopy diverticulitis reported from the review was considerably variable with symptoms such as generalized abdominal bleeding, per rectal bleeding, nausea/vomiting and chills. The symptoms may be interpreted as non-specific and could overlap with other entities such as post-polypectomy syndrome. However, the main concern remains iatrogenic perforation especially in patients who had interventional procedures such as polypectomy, endoscopic mucosal resection or endoscopic submucosal dissection concurrently. The initial management should include a rapid assessment with resuscitation as required. Biochemistry examination maybe unremarkable initially but leucocytosis and a raised C-reactive protein maybe observed. The mainstay of imaging is CT scan of the abdomen/pelvis to exclude colonoscopic perforation or intra-abdominal organ injuries. It will help to confirm the diagnosis and guide further management.

The principles of management are no different to the usual presentation of diverticulitis[4,19]. In patients with uncomplicated diverticulitis, a short inpatient stay with intravenous antibiotics and bowel rest are usually sufficient. Depending on regional practice, in those that are clinically well, they could potentially be managed as outpatient with or without oral antibiotics[19,21]. The use of antibiotics can even be considered omitted in uncomplicated diverticulitis with no increased risk of complications[19,22]. In patients with localized complicated diverticulitis, non-operative management should be trialed upfront[19,23,24]. If there is evidence of large abscess > 4 cm, percutaneous drainage can be organised if accessible. In the clinically unstable patient, urgent surgical intervention should be undertaken.

This systematic review has been limited by the relatively small number of patients reported to have post-colonoscopy diverticulitis with variable duration reported after the colonoscopy. The entity remains unclear as: (1) It could represent an episode of *de novo* acute diverticulitis rather than a sequelae in those that reported up to 30 days

post-colonoscopy[6,8,12]; (2) It could also be an exacerbation of subclinical diverticulitis especially in those that underwent a colonoscopy 6-8 wk after an attack[4] and the information of history of diverticulosis or diverticulitis was lacking in the studies; (3) The symptoms can be easily overlooked and misdiagnosed if based on clinical grounds without confirmatory CT findings where some symptoms are commonly reported such as abdominal pain (10.5%), bloating (25%), diarrhea (6.3%), nausea (4%)[1] and lastly; and (4) A few studies correlated this entity based on ICD coding of diverticulitis from the database which may not be accurate[9]. This was also evident on a blog discussion post on New England Journal of Medicine Journal Watch in 2011[25].

Based on this systematic review, we propose the definition of post-colonoscopy diverticulitis as the occurrence of diverticulitis confirmed on CT scan within 72 h post-colonoscopy without the colonoscopic findings of acute or chronic diverticulitis and other pathology. The timeframe was chosen based on the definition of post-colonoscopy appendicitis which is believed to share some of the similar mechanism of pathogenesis.

A few key points raised from this systematic review: (1) It should be included in future audit of complications from colonoscopy; (2) The patients should be explained of this potential complication during the consenting process; (3) Patients with known history of diverticular disease, a difficult colonoscopy should be anticipated, and other methods should be tried to navigate the colonoscope through the diseased segment to prevent accidental intubation of the diverticula; and (4) The patients that had incomplete colonoscopy due to the abovementioned reason should be warned of the possibility of this complication on discharge.

CONCLUSION

The entity of post-colonoscopy diverticulitis is a relatively rare complication. The clinical presentation can mimic other common symptoms encountered post-colonoscopy. CT scan remains the imaging of choice to diagnose and guide further management. Majority of cases resolve with non-operative management. Endoscopists should be aware of this entity given the increasing number of colonoscopies performed.

ARTICLE HIGHLIGHTS

Research background

The number of colonoscopy performed worldwide is increasing steadily over the past decade for screening, diagnostics and surveillance purposes. Similarly, the incidence of diverticular disease is also increasing in the population.

Research motivation

The entity of post-colonoscopy diverticulitis as a complication of colonoscopy has been reported in the literature without clear description of definition, description, clinical presentation and management strategies.

Research objectives

The aim of this study was to systematically review all available evidence in the literature to propose a definition of post-colonoscopy diverticulitis, describe its incidence, clinical presentation, risk factors and management strategies.

Research methods

The systematic review was performed by searching the PubMed, EMBASE and Cochrane databases up to June 2020 and the references were manually cross-checked for additional references.

Research results

A total of nine studies were included in the final systematic review with a total of 339 cases. The time to diagnosis post-colonoscopy ranged from 2 h to 30 d. Clinical presentation for these patients were non-specific. Diagnosis was made mainly by computed tomography scan. Most of the patients were managed non-operatively with bowel rest and intravenous antibiotics.

Research conclusions

The entity of post-colonoscopy diverticulitis remains debatable due to the variable timeframe included following colonoscopy in the literature. Regardless of whether this is a true complication post-colonoscopy or a *de novo* event, early diagnosis is vital to guide appropriate treatment.

Research perspectives

The results of this systematic review should inform future prospective studies especially registries to record this as a potential complication following colonoscopy to further understand its true incidence and risk factors.

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CASE REPORT

Endoscopic treatment of blue rubber bleb nevus syndrome in a 4-year-old girl with long-term follow-up: A case report

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Author contributions: Marakhouski K, Pataleta A and Sanfirau K conceived of and designed the work; Sharafanovich E contributed to conception of the work; Pataleta A and Svirsky A contributed to design of the work; Marakhouski K, Kolbik U, Nikalayeva K, Pataleta A and Svirsky A collected the literature data; Kolbik U, Sautin A and Nikalayeva K collected the patient's clinical data; Marakhouski K, Sharafanovich E, Kolbik U, Sautin A, Nikalayeva K, Pataleta A, Sanfirau K and Svirsky A performed data analysis; Sharafanovich E and Sanfirau K interpreted the data; Marakhouski K, Sharafanovich E and Sanfirau K performed the patient's diagnostic tests; Kolbik U and Sautin A plotted the hemoglobin dynamics; Sautin A generated a visual table for enteroscopy; Sharafanovich E provided the final diagnosis; Marakhouski K treated the patient; Marakhouski K, Sharafanovich E,

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Abstract

BACKGROUND

Blue rubber bleb nevus syndrome (BRBNS) is a rare vascular disease, difficult to diagnose and choose a treatment method, especially in young children. There are several limiting factors to the use of enteroscopy for diagnostics and treatment in pediatric patients, in general. The literature on BRBNS cases is limited and presents various therapeutic approaches.

CASE SUMMARY

We present here a case of BRBNS involving a 4-year-old female, whose intestinal venous lesions were successfully treated by endoscopic sclerotherapy and aethoxysklerol foam. Skin lesions, typical for BRBNS, appeared on the 8th d of the child's life and their number increased over the next several months. The child also experienced episodes of critical decrease in hemoglobin level (by as much as 52 g/L) for several years, requiring iron supplementation and several blood transfusions. Video capsule endoscopy revealed numerous vascular formations in the small bowel. The combined findings of gastrointestinal venous formations and skin lesions prompted BRBNS diagnosis. Single-balloon enteroscopy was used to perform sclerotherapy, with aethoxysklerol foam. A positive effect was observed within 19 mo of follow-up. We continue to monitor the patient's hemoglobin level, every 2 wk, and it has remained satisfactory (> 120 g/L).

CONCLUSION

Endoscopic sclerotherapy can be effective in the clinical management of gastrointestinal manifestations of BRBNS in young children.

Sanfirau K and Svirsky A drafted and critically revised the manuscript for important intellectual content; Kolbik U contributed to drafting of the manuscript; Sautin A performed text structuring and critical revision of the manuscript for important intellectual content; Nikalayeva K drafted the manuscript and performed text structuring and critical revision of the manuscript; all authors gave final approval for the version to be published.

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Core Tip: In blue rubber bleb nevus syndrome (BRBNS), vascular malformations can affect any organ in the body but skin and gastrointestinal tract are the most frequent. Skin venous malformations have been observed in patients with BRBNS since childhood, with number and size of lesions increasing through time. Gastrointestinal lesions also occur at an early age and provoke gastrointestinal bleeding, leading to anemia. Treatment of the clinical manifestations of BRBNS can be carried out by endoscopic, pharmacological or surgical approaches. We present here a BRBNS case in a young child, treated by sclerotherapy with aethoxysklerol foam applied during single-balloon enteroscopy.

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INTRODUCTION

Blue rubber bleb nevus syndrome (BRBNS), or bean syndrome, is a rare congenital vascular disease, eliciting predominant damage of the skin and digestive tract[1,2] . The clinical spectrum of BRBNS is very heterogeneous, with various phenotypic patterns. Patients may experience single lesions of the skin and gastrointestinal (GI) tract or multiple lesions affecting the skin, GI tract, and other organs[3-5].

The pathogenesis of BRBNS has not been studied extensively. There is an assumption of autosomal dominant inheritance, based upon a change in the 9p chromosome locus and observations of this syndrome among blood relatives[6,7]; although, most cases appear to be sporadic[3,8].

Cutaneous venous formations are observed in 78% of patients and vascular lesions of the GI tract in 89%[9,10]. While BRBNS-related venous malformations can occur throughout the GI tract, they most often involve the small bowel (100%), followed by the colon (74%) and the stomach (26%); they vary in shape and number, ranging from a few to several hundred lesions[8,11] . The development of BRBNS is associated with GI bleeding, and normally the lesions grow in number and size over the lifetime of an afflicted individual[12]. The skin lesions rarely cause serious clinical problems-in contrast to the GI vascular malformations, which can cause acute or chronic bleeding and subsequent anemia, and in some cases fatality[13,14].

We present, herein, a case of BRBNS in a 4-year-old female with skin and GI manifestations.

CASE PRESENTATION

Chief complaints

A 4-year-old female was hospitalized in the Republican Center of Pediatric Surgery (Minsk, Belarus) in 2017 with the signs of chronic GI bleeding, iron deficiency anemia, episodes of melena, and a rapid deterioration in her general condition.

History of present illness

During the first year of observation in our clinic, the child underwent seven procedures of blood transfusions due to low hemoglobin levels before the first sclerotherapy was performed.

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History of past illness

The patient's birth (per *via* naturalis) had resulted from the mother's first pregnancy, which was also full-term. Her birth weight was 3760 g and length was 51 cm. The patient's mother noticed a roundish dark blue, soft-elastic formation on the skin of the child's thigh at 8 d after the birth. A few months later, new formations appeared on the skin of the child's head (at the border of the forehead and parietal ridge) and lumbar, perianal and plantar areas.

Anamnesis vitae yielded report of venous malformations involving the gluteo-femoral region, which had been partly excised at the age of 3 mo. Several complaints of melena were also disclosed. In addition, the parents reported that, at the age of 2 years, the child had developed periodic lethargy, drowsiness, and pallor of the skin; clinical assessment at that time yielded the first detection of a significant decrease in hemoglobin levels. Thus, iron supplements were prescribed. Several other episodes of a critical decrease in hemoglobin reportedly occurred over the next few years, all of which required a blood transfusion.

Personal and family history

The patient has no family history of BRBNS.

Physical examination

The patient's skin showed an overall paleness and several vascular skin lesions were found in the lumbar region, the inner part of the left thigh, the lower leg, the forearm (Figure 1), and on the sole of the right foot. The formations were of various sizes but all had a soft, elastic-like consistency and showed a cyanotic coloration.

Laboratory examinations

The patient's blood parameters were low, with hemoglobin of 95 g/L (normal range: 110-140 g/L), mean corpuscular hemoglobin concentration of 32.8 (normal range: 31.9-35.6 g/dL), erythrocytes of 4.4 × 10^{12}/L (normal range: 3.9-5.3 × 10^{12}/L), and hematocrit of 29% (normal range: 34%-40%).

Imaging examinations

Ultrasound showed vascular malformations in the left lobe of the liver, pancreas, bladder, and left ovary. Magnetic resonance imaging of the soft tissues of the lower extremities showed vascular malformations in the upper third of the left thigh. Although gastroscopy and colonoscopy were unsuccessful in detecting the source of GI bleeding, capsule enteroscopy revealed multiple (-10) vascular formations in the wall of the small intestine (Figure 2). All formations appeared round in shape and bluish-purple in color; the largest reached 2 cm in diameter.

FINAL DIAGNOSIS

BRBNS with secondary severe iron deficiency anemia.

TREATMENT

Sclerotherapy was ordered *via* single-balloon enteroscopy (Figure 3). During the first attempt at antegrade enteroscopy, it became clear that a total examination of the small bowel would be technically impossible. Therefore, subsequent enteroscopies were carried out with sequential antegrade and retrograde access guided by a tattoo of the maximum antegrade passage area of the enteroscope and simultaneous sclerotherapy. From December 2017 to March 2020, five total single-balloon enteroscopies were performed (Table 1). During each, foam sclerotherapy was carried out using 10 mL of a 1% aethoxysklerol solution, targeting all of the vascular malformations that had been identified. The sclerotherapy procedure itself was performed according to the Tessari method[15], in which a 1:4 mixture of the sclerosing agent and air [2 mL of 1% aethoxysklerol (10 mg/mL) mixed with 8 mL of air] was pumped in *via* two syringes connected by a 3-way adapter with a tap.

Table 1 Characteristics of the patient's enteroscopies and spread of vascular malformations

	December 20, 2017	March 23, 2018	May 22, 2018	August 31, 2018	March 30, 2020
Enteroscopy					
Antegrade	+	+	+	+	+
Retrograde	-	+	+	+	+
Sclerotherapy	+	+	+	+	+
Malformations					
Stomach	-	+	+ (sclerotherapy)	No new ones	Not visualized
Small bowel	+	+	+	+	+
Large bowel	-	-	-	-	+

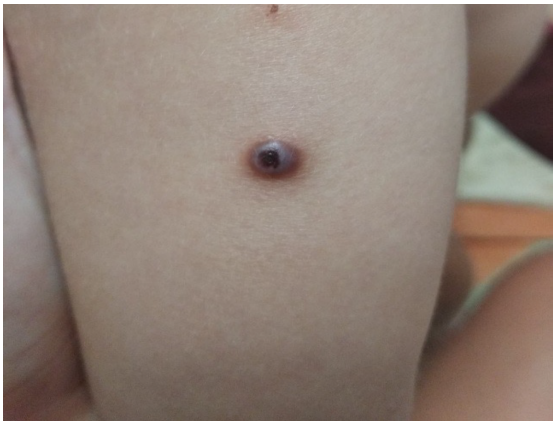

Figure 1 Vascular malformations on the patient's forearm.

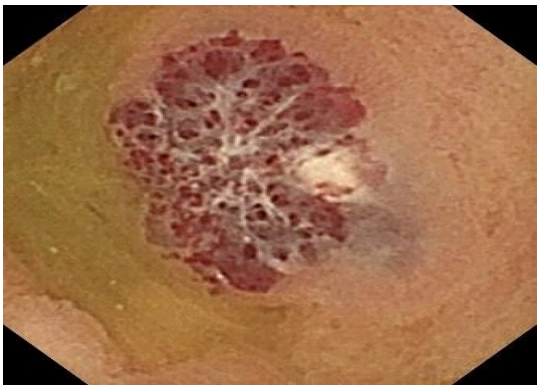

Figure 2 Capsule endoscopy revealed a large vascular formation in the wall of the small bowel.

OUTCOME AND FOLLOW-UP

The total follow-up duration was 33 mo (from December 2017 to September 2020). The first period of remission lasted 15 mo (from October 2018, upon the first detection of hemoglobin > 120 g/L, to January 2020). In February 2020, the patient's hemoglobin level began to fall, reaching a low of 97 g/L in March 2020. At the end of March 2020, single-balloon enteroscopy was reperformed. New vascular malformations were detected in the small bowel and, for the first time, in the colon, and these were considered as the likely cause of the hemoglobin decline. The sequential sclerotherapy was followed by a return of the hemoglobin level to the previous value of 120 g/L in early May 2020. The 2-wk interval follow-ups have shown the level to remain at > 120 g/L since then (Figure 4). It's worth noting that the child has not received iron supplement therapy since November 2018.

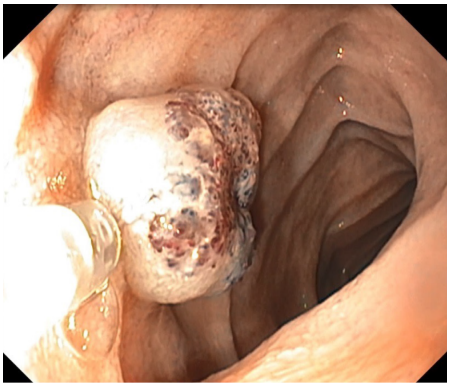

Figure 3 Intraoperative view of sclerotherapy of the vascular formation in the small bowel.

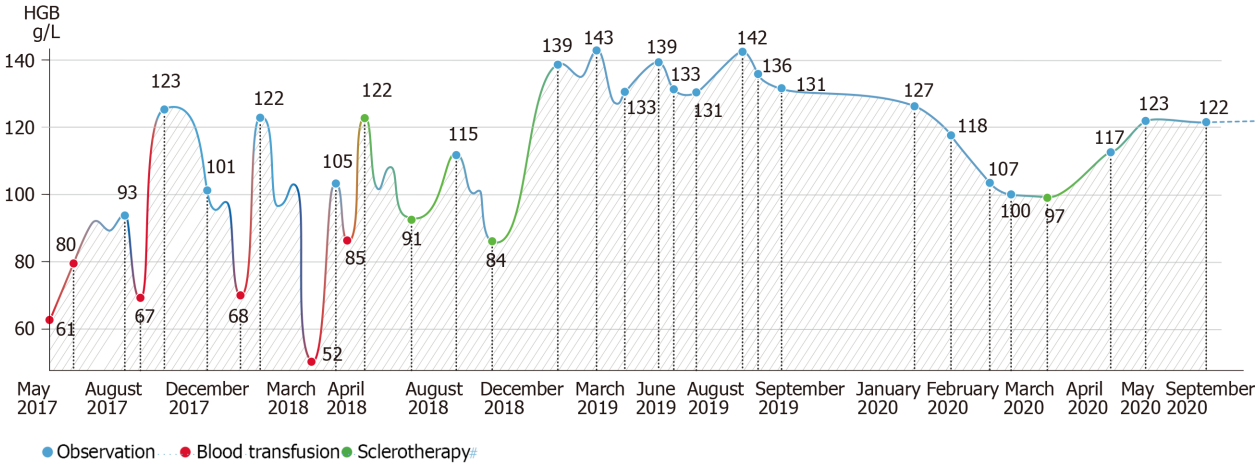

Figure 4 Hemoglobin level dynamics depend on blood transfusions and foam sclerotherapy of venous malformations and follow-up.

DISCUSSION

Treatment of BRBNS is usually based upon the patient's symptomatic profile and depending on degree of GI damage and/or involvement of other organs in the pathological process[10,16]. Choosing the optimal therapy for the manifestation of BRBNS with GI bleeding is a rather difficult task, especially when it comes to a 4-year-old patient. On the one hand, balloon-assisted enteroscopy-while being the gold standard for the diagnosis and treatment of bowel malformations in adult patients with BRBNS-is a relatively unsafe method in young children[17]. Limiting factors in any case are age and weight, especially so for children. Thus, we turned to the literature on pediatric cases of BRBNS.

Chen *et al*[18] reported on the successful performance of two-balloon enteroscopy in 72 pediatric patients, the youngest of whom was 6 years of age. In addition, Isoldi *et al*[10] reported on 18 clinical cases of BRBNS in children; all 4 who underwent balloon-assisted enteroscopy experienced a positive effect that lasted for 4-16 mo. We also chose to treat our patient's illness with balloon-assisted (single) enteroscopies, and the beneficial clinical effect on hemoglobin endured over a total of 19 mo [from October 2018 to September 2020, excepting the 3 mo (February-April 2020) before the last treatment].

Different kinds of GI malformations in BRBNS can be addressed by surgical treatment; although, this approach is rather aggressive, carries risk of postoperative complications, and is probably better justified for patients with few GI malformations located in a limited span of the bowel. There is also the risk of re-manifestation after resection[19], even for the combination method of endoscopic electrocoagulation and surgical removal[20]. The endoscopic interventions themselves, including argon plasma coagulation, electrocautery and histoacryl injection, also carry risk of perforation and rebleeding[11,21]. In our case, the venous malformations detected during enteroscopy numbered more than 15 and were located along the entire length of the hollow organs

of the GI tract. This situation would have required particularly extensive laparoscopic/open resection, posing too great overall risk to the young child. Moreover, the child's young age presented the risk of new lesions forming on the wall of the intestine during the subsequent years of life, adding further reason against the laparoscopic/open resection approach[8] . Endoscopic sclerotherapy was suggested as a less aggressive and less invasive option.

Two studies[15,22] in the literature have suggested systemic medical therapy with sirolimus as highly effective for pediatric patients. Unfortunately, two other studies[23,24] confounded the potential benefit by reporting on substantial negative side effects.

CONCLUSION

The applied method of endoscopic treatment showed its effectiveness in regard to rescue of hemoglobin level for 19 mo, during a 3-year follow-up period. New, clinically significant malformations appeared in the patient's small bowel only at 16 mo after the first application of endoscopic sclerotherapy. In the Republic of Belarus, the patient described herein is, to date, the smallest patient by age and weight to undergo total single-balloon enteroscopy. There were no side effects related to the procedure in our case. Thus, endoscopic sclerotherapy with aethoxysklerol foam can be an appropriate option for BRNBS treatment, even in young children.

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ORIGINAL ARTICLE

Retrospective Study

Identifying who best tolerates moderate sedation: Results from a national database of gastrointestinal endoscopic outcomes

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Author contributions: Koh C is the guarantor of this article; Passi M, Rahman F and Koh C designed the study and were involved in devising the study concept; Passi M, Kumar S and Gurram S were involved in the acquisition of the study data; Passi M and Rahman F were involved in the statistical analysis and interpretation of study results; Passi M, Rahman F, Koh C, and Gurram S were involved in the drafting and revision of the manuscript; all authors have read and approve the final manuscript.

Institutional review board statement: This study is a retrospective analysis of a publicly available, de-identified data repository (Clinical Outcomes Research Initiative National Endoscopic Database) and therefore is IRB-exempt.

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Abstract

BACKGROUND

With increasing volume and cost of gastrointestinal endoscopic procedures, the proper selection of patients for moderate sedation becomes increasingly relevant. The current literature lacks consistent findings that allow for appropriate selection of patients for moderate sedation.

AIM

To analyze a nationwide registry of patients to identify patient and procedural factors associated with lower sedation requirements for endoscopy.

METHODS

The Clinical Outcomes Research Initiative National Endoscopic Database was queried to assess adult patients undergoing moderate sedation for esophago-gastroduodenoscopy (EGD) and colonoscopy from 2008 to 2014. Patients were stratified into two groups [low dose (LD) and high dose sedation] based on sedation requirements. Anthropometric, procedural, and anesthesia data were compared, and multivariable analysis was performed to identify factors associated with LD sedation.

RESULTS

Of the 371102 patients included in the study, 63137 where stratified into the LD

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sedation group and 307965 were in the high dose group. Moderate sedation was managed primarily by endoscopists (50%) and anesthesia providers (47%). Patients undergoing EGDs and procedures performed in the inpatient setting, in ambulatory surgery centers, intensive care units or hospital wards, required less sedation than colonoscopies, outpatient procedures and procedures done in endoscopy suites, respectively ($P < 0.0001$ for all). On multivariable analysis, factors predictive of tolerance with lower sedation requirements for EGDs and colonoscopies were female gender, age ≥ 50, non-White race, Hispanic descent, body mass index ≤ 25 kg/m^2, and higher American Society of Anesthesia Class ($P < 0.0001$ for all).

CONCLUSION
Clinicians should consider these patient profiles in determining which patients will better tolerate moderate sedation *vs* those better suited for alternative sedation methods.

Key Words: Gastrointestinal endoscopy; Anesthesia; Moderate (conscious) sedation; Sedation tolerance

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Core Tip: Limited society guidelines currently exist to aid endoscopists in the selection of the most appropriate sedation method. Rather, it is at the discretion of the endoscopist on a case-by-case basis, with many decisions made based on gut feeling and previous personal experience. With the growing focus on patient satisfaction as a metric for reimbursement and an increased focus on healthcare cost containment initiatives, identifying which patients can safely and effectively undergo endoscopy without anesthesia-administered sedation is becoming exceedingly important. Existing studies on this topic to date have been small scale, single-center data with inconsistent findings. Robust data to drive practice patterns have been lacking. As such, we have capitalized upon nationwide data found in the Clinical Outcomes Research Initiative National Endoscopic Database to clarify these discrepancies and to identify patient and procedure characteristics that may predict better patient tolerance to endoscopy with moderate sedation.

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INTRODUCTION

Adequate sedation and analgesia are considered integral components of a good quality, endoscopic exam[1]. With the adoption of the patient-centered care model, there has been a rise in the use of procedural sedation where 98% of endoscopists in the United States routinely administer sedation during endoscopies[1,2]. The use of procedural sedation is primarily intended to reduce patient anxiety and discomfort, thereby improving tolerability and satisfaction for the procedure[1]. Sedation also provides the endoscopist with an ideal environment for a thorough exam allowing for improved outcomes. The importance of high-quality procedures, and the increasing patient awareness and expectation of a painless examination highlight the need for effective procedural sedation[3].

The use of moderate (conscious) sedation provides adequate control of pain and anxiety, a safety margin when compared with deep sedation and general anesthesia, and provides adequate anesthesia for the majority of routine endoscopies[4]. In the United States, more than 75% of endoscopists use a benzodiazepine plus narcotic regimen, with the combination of midazolam and either fentanyl or meperidine being the most common[2]. These drugs have a predictable pharmacokinetic profile, a rapid

onset of action, analgesic and anxiolytic effects, a short recovery time, and minimal associated risks making them ideal for administration by a non-anesthesia provider[2]. While certain patient characteristics may help predict the dosage needed for adequate sedation, patients differ in their response to sedation and for any given sedative or analgesic, the range of individuals response to a specific drug can be up to 3-5 fold[4,5]. Thus, the ability to seek a balance between patient comfort and drug-related side effects is an art that comes with experience and requires careful consideration of the patient, the endoscopic facility, and the variabilities of the procedure itself[6].

The desire to identify the difficult-to-sedate patient both in terms of safety and patient satisfaction has been the subject of previous research efforts[7]. Certain characteristics that have been associated with higher levels of sedation include younger age, female gender, lower body mass index (BMI), chronic benzodiazepine or opioid use, higher income, higher education, and psychologic distress[5,7-9]. In 2018, the American Society of Gastrointestinal Endoscopy published updated guidelines for sedation in gastrointestinal (GI) endoscopy with acknowledgement that further investigation is needed for the selection of appropriate candidates for various types of sedation[5]. Clearly, certain patient populations require specific sedation strategies based on comorbid factors. Nonetheless, consensus is lacking, and thus the validity of existing studies is limited by inconsistent findings, small-scale, single-institution data, and use of non-standardized, post-procedure patient-administered surveys, introducing potential bias[10-12].

The National Endoscopic Database (NED) contains procedural data collected by the Clinical Outcomes Research Initiative (CORI) from 1995 to 2014. Using this nationwide database, we aimed to evaluate patient tolerance of endoscopy using current sedation practices with the goal of identifying patient and procedure characteristics that may predict better tolerance with moderate sedation.

MATERIALS AND METHODS

National endoscopic database of CORI

We utilized the CORI database – a large national multi-center consortium of 108 sites from 87 practices, created for the means of studying outcomes and utilization of endoscopy in a variety of practice settings. The practice sites consist of 74% community practices, health maintenance organizations and private practices, 15% government agencies (*e.g.*, military and Veterans Affairs Health Services), and 12% academic medical centers. Participating sites use a structured, computerized, report generator to process all endoscopic reports and comply with quality control requirements. Data are subsequently transmitted electronically to a central data repository – the National Endoscopic Database –which is funded by the National Institute of Diabetes and Digestive and Kidney Diseases.

Study population

The CORI version 4 database was queried from 2008 to 2014 to identify all adult patients (≥ 18 years) undergoing moderate sedation for esophagogastroduodenoscopy (EGD) and colonoscopy. After separation into procedure type, patients were stratified into two groups based on sedation requirements: (1) Low dose sedation (LD) (fentanyl ≤ 50 μg or meperidine ≤ 50 mg and/or midazolam ≤ 2 mg), and (2) High dose sedation (HD) (fentanyl ≥ 200 μg or meperidine ≥ 150 mg and/or midazolam ≥ 6 mg and/or the requirement of diphenhydramine at any dose) (Figure 1). These sedation parameters where chosen because the recommended initial dose in the United States for endoscopic sedation for fentanyl is 50 μg, for meperidine is 50 mg and for midazolam is < 2 mg, and the maximum recommended dose for fentanyl is 200 μg, for meperidine is 150 mg and for midazolam is 6 mg. All patients who received any quantity of sedation outside the specified LD and HD sedation ranges (fentanyl > 50 μg to < 200 mg, meperidine > 50 mg to < 150 mg and midazolam > 2 mg to < 6 mg) were excluded from the study. Diphenhydramine is a well-established potentiator of benzodiazepine-narcotic regimens, leading to deeper levels of sedation and decreased pain with minimal hemodynamic side effects in patients undergoing GI endoscopy[2,13-15]. Current American Society of Gastrointestinal Endoscopy guidelines provide a strong recommendation for the use of diphenhydramine as an option in patients who are not adequately sedated with a benzodiazepine and opioid combination for GI endoscopy[16]. As such, patients who received diphenhydramine were considered to fall in the HD sedation group. Patients who received deep sedation or general anesthesia, as recorded in the CORI database, were excluded. In addition, patients < 18

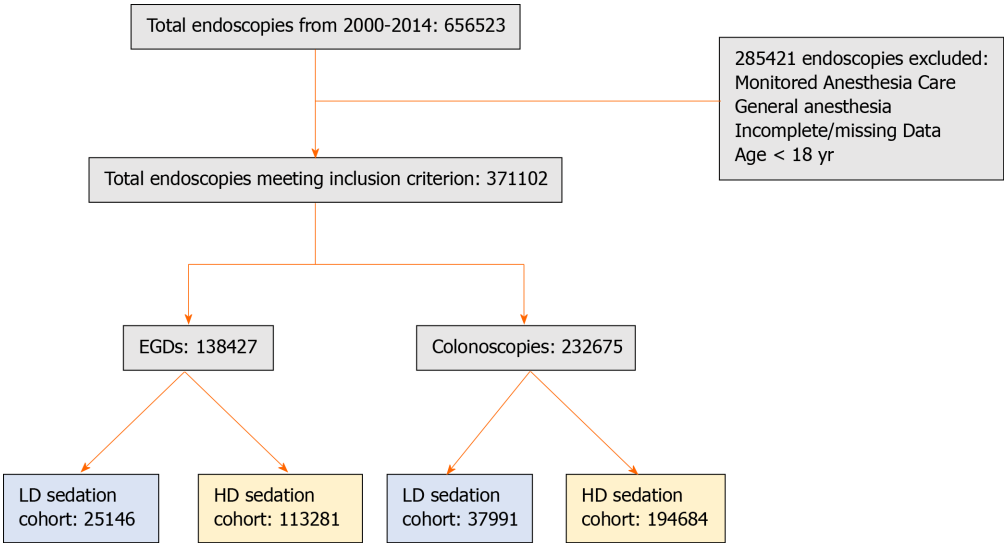

Figure 1 Study flow diagram. Allocation of patients into the "Low dose sedation" group (n = 63154) and "High dose sedation" group (n = 307819). Exclusion of patients based on sedation type/dose, incomplete data, and age (n = 285421). Low dose sedation parameters: Fentanyl ≤ 50 μg or meperidine ≤ 50 mg +/- midazolam ≤ 2 mg. High dose sedation parameters: Fentanyl ≥ 200 μg ormeperidine ≥ 150 mg +/- midazolam ≥ 6 mg +/- diphenhydramine (any dose). Sedation parameters excluded: Fentanyl > 50 μg to < 200 μg, meperidine > 50 mg to < 150 mg, and midazolam > 2 mg to < 6 mg. LD: Low dose; HD: High dose; EGD: Esophagogastroduodenoscopy.

years old and those with incomplete demographic and procedure related data were excluded.

Data collection

Following stratification of patients into groups based on sedation requirements and procedure type, anthropometric, procedural and anesthesia data were compared utilizing a unique procedure identification. Specific data collected on these patients were: Age, sex, type of procedure, American Society of Anesthesia Class (ASA) class, BMI, race, admission status, endoscopy facility type, procedure duration, personnel administering sedation and type/does of conscious sedation administered. Further data on number of aborted procedures and unexpected intubations were recorded. Finally, patient tolerance during endoscopy as perceived by the endoscopist was captured and recorded as one of four categories: "excellent," "good," "fair," and "poor". These demographic and procedure-related variables were selected based on the findings from prior studies suggesting these factors may influence sedation requirements.

Statistical analysis

Although some of the patients included had more than one procedure performed during the study period, quantities observed in different procedures were assumed to constitute statistically independent observations for the purposes of data analysis. Summary statistics of baseline data are presented as either frequencies for categorical data or as means and standard deviations for continuous data, unless otherwise specified. The Student's t-test or the chi-squared test, employing Yates' correction for continuity where appropriate, were performed to understand differences in baseline labs between the LD and HD sedation groups. Univariate logistic regression analysis was performed to calculate an unadjusted odds ratio for factors related to lower sedation requirements. Adjusted odds ratios (aOR) were calculated using multivariate logistic regression. Additional multivariate analyses were done by procedure type (EGD *vs* colonoscopy) to understand factors related to tolerability by procedure. Demographic and procedure related variables that were statistically significant on univariate logistic regression were selected for multivariable analysis. All analysis was done in SAS 9.4. Statistical significance was set at $P < 0.05$. Only complete-case analysis was performed to account for missing values in CORI, as missing values were assumed to be missing at random. Additionally, it is recognized that there was multiple testing of outcome data arising from individual procedures. The multivariable linear regression analyses of factors associated with lower sedation (by type of procedure and overall) are offered as the main, definitive results and for which it is noted that correction for multiple testing by Bonferroni's method would not have

removed statistical significance from any finding. The *P* values for all other statistical tests relating to outcomes should be considered preliminary and exploratory or else secondary; those *P* values are not corrected for multiple testing and are to be taken as descriptive only.

RESULTS

Entire group analysis

Clinical characteristics: During the study period, 656523 procedures were recorded and 371102 (56.5%) met criteria for inclusion. Upon further stratification by procedure type, colonoscopies comprised the majority of cases (63%, *n* = 232675) as compared to EGDs (37%, *n* = 138427) (Figure 1). Amongst the entire group, patients were mostly male (52%), non-Hispanic Whites (84%) with a mean age of 55 ± 18 years and ASA class I or II (88%). The mean BMI amongst the entire group was 28.2 ± 6.3 kg/m^2. Demographic and clinical characteristics of these patients are shown in Table 1. In the LD group, the majority of patients were female (50.1%) whereas in the HD group, the majority were male (52.7%). Among both groups, patients were predominantly non-Hispanic Whites (64.1% in the LD group, 74.8% in the HD group), ≥ 50 years old (85.1% in the LD group, 79.2% in the HD group), and of ASA class I or II (82.4% in the LD group, 88.6% in the HD group).

Among patient characteristics, female gender was a significant predictor of lower sedation requirements [aOR: 1.14, 95% confidence interval (CI): 1.12-1.16, $P < 0.0001$]. Additionally, older age was a predictor of lower sedation requirements when stratifying patients into ages ≥ 50 and < 50 (aOR: 1.61, 95%CI: 1.57-1.65, $P < 0.0001$). The adjusted odds ratios for low dose *vs* high dose sedation by decade of age for the entire study population can be found in Supplementary Table 1. Compared to Whites, African American patients had lower sedation requirements (aOR: 1.51, 95%CI: 1.46-1.57) as did Asians (aOR: 2.29, 95%CI: 2.19-2.39) and Hispanics (aOR: 2.06, 95%CI: 2.01-2.10) ($P < 0.0001$ for all). ASA class was also evaluated as a potential predictor of sedation requirements by comparing patients with an ASA class < III and ≥ III. Higher ASA class (≥ III) was predictive of less sedation requirements for both EGDs and colonoscopies as compared to lower ASA class (< III) (aOR: 1.45, 95%CI: 1.41-1.49, $P < 0.0001$). The adjusted odds ratios for low dose *vs* high dose sedation among each ASA class of patients can be found in Supplementary Table 2. Finally, BMI was evaluated in comparing overweight (BMI ≥ 25 kg/m^2) *vs* normal/underweight (BMI < 25 kg/m^2) patients; normal/underweight BMI was a significant predictor of lower sedation requirements (aOR: 0.81, 95%CI: 0.77-0.86, $P < 0.0001$) (Table 2, Figure 2).

Procedure related outcomes: For all procedures, moderate sedation was managed predominantly by endoscopists (50%) and anesthesia providers (47%). Within the LD group, sedation was primarily performed by anesthesia providers (48.3% *vs* 37.6% by endoscopists) compared to the HD sedation group in which sedation was more often managed by endoscopists than by anesthesia providers (53.3% *vs* 46.4%). The average sedation medication doses for EGDs and colonoscopies among patients in the LD and HD sedation groups are listed in Table 1.

The majority of patients in both the LD and HD groups had endoscopies performed as an outpatient (89.5% and 94.3%, respectively). Similarly, among both groups, cases were more commonly performed in ambulatory surgery centers (62.4% in the LD group, 67.6% in the HD group) followed by the endoscopy suite (35.7% in LD group, 31.4% in HD group). Average procedure duration for patients in the HD group was 2.1 min longer (18.6 ± 20.3 min) as compared to the LD group (mean of 16.5 ± 21.6 min). Unplanned intubations were uncommon among both groups (0.2% incidence in the LD group, 0.08% in the HD groups). Similarly, while the rate of aborted procedures was quite low among both groups, procedures were unexpectedly terminated about four times more often in the LD group (7393 cases) as compared to the HD group (1712 cases) (Table 1).

Admission status was assessed by comparing endoscopies performed as an inpatient *vs* those done as an elective, outpatient procedure. Inpatient procedures required significantly less sedation for both EGDs and colonoscopies as compared to those patients who had endoscopies performed on an outpatient basis (aOR: 0.70, 95%CI: 0.67-0.72, $P < 0.0001$). Additionally, location of procedure was evaluated by comparing cases performed in endoscopy suites *vs* those performed in ambulatory surgery centers, intensive care units (ICUs) and hospital wards. Procedures performed at sites other than the endoscopy suite required significantly less sedation as compared

Table 1 Demographic and clinical characteristics of low dose and high dose sedation groups

Variable	LD EGD (*n* = 25146), *n* (%)	HD EGD (*n* = 113281), *n* (%)	*P* value	LD colonoscopy (*n* = 37991), *n* (%)	HD colonoscopy (*n* = 194684), *n* (%)	*P* value
Age, mean ± SD	51.9 ± 21.9	58.2 ± 19.2	< 0.0001	56.8 ± 14.5	59.7 ± 22.6	< 0.0001
Female gender	13095 (52.1)	55617 (49.1)	< 0.0001	18548 (48.8)	89973 (46.2)	< 0.0001
Hispanic	6091 (24.2)	20479 (18.1)	< 0.0001	9052 (23.8)	22533 (11.6)	< 0.0001
White	19704 (78.4)	91529 (80.8)	< 0.0001	30643 (80.7)	168539 (86.6)	< 0.0001
Black	2084 (8.3)	6427 (5.7)	< 0.0001	2262 (6.0)	8605 (4.4)	< 0.0001
Asian	1284 (5.1)	3985 (3.5)	< 0.0001	2213 (5.8)	5484 (2.8)	< 0.0001
Other race	2025 (8.1)	9697 (8.6)	< 0.0001	3220 (8.5)	10100 (5.2)	< 0.0001
BMI (kg/m^2), mean ± SD	27.8 ± 15.2	28.2 ± 19.8	< 0.0001	28.3 ± 19.9	28.2 ± 17	< 0.0001
Exam duration (min), mean ± SD	9 ± 12	10 ± 8	< 0.0001	20 ± 24	23 ± 23	< 0.0001
Medication dosage, mean ± IQR						
Fentanyl (mcg)	45 ± 8.3	205.6 ± 11.1		47.6 ± 9	255.9 ± 15.3	
Meperidine (μg)	33.9 ± 7.2	170.3 ± 10.4		45.7 ± 12.3	152.8 ± 11.6	
Midazolam (mg)	1.3 ± 9.4	6.3 ± 19.7		1.8 ± 17.4	8.8 ± 21.2	
Diphenhydramine (mg)	N/A	25.2 ± 13.5		N/A	50.3 ± 11.5	
Personnel managing sedation, *n* (%)						
Endoscopist	11522 (45.8)	63187 (55.8)	< 0.0001	15608 (41.1)	96376 (49.5)	< 0.0001
Anesthesiologist	13572 (54.0)	49656 (43.8)	< 0.0001	21288 (56.0)	89120 (45.8)	< 0.0001
Other	9042 (36.0)	216 (0.19)	< 0.0001	1095 (2.9)	46 (0.02)	< 0.0001
Unplanned intubations, *n* (%)	132 (0.5)	239 (0.2)	< 0.0001	5 (0.01)	19 (0.01)	< 0.0001
Aborted procedures, *n* (%)	5791 (23.0)	1371 (1.2)	< 0.0001	1602 (4.2)	341 (0.2)	< 0.0001
Admission status, *n* (%)						
Inpatient	4936 (19.6)	12300 (10.9)	< 0.0001	1642 (4.3)	4894 (2.5)	< 0.0001
Outpatient	20204 (80.3)	100756 (88.9)	< 0.0001	36349 (95.7)	189631 (97.4)	< 0.0001
Location of procedure, *n* (%)						
Ambulatory surgical center	14469 (57.5)	70643 (62.4)	< 0.0001	24967 (65.7%)	137399 (70.6)	< 0.0001
Endoscopy suite	9790 (38.9)	40263 (35.5)	< 0.0001	12735 (33.5)	56352 (28.9)	< 0.0001
Hospital ward	150 (0.6)	205 (0.2)	< 0.0001	24 (0.06)	72 (0.04)	< 0.0001
ICU	668 (2.7)	1678 (1.5)	< 0.0001	114 (0.3)	205 (0.1)	< 0.0001

Operating room	16 (0.1)	66 (0.06)	< 0.0001	4 (0.01)	18 (0.01)	< 0.0001
Other[1]	479 (1.9)	201 (0.2)	< 0.0001	147 (0.4)	47 (0.02)	< 0.0001

[1]Other sites: Includes radiology suites and offices. LD: Low dose sedation group; HD: High dose sedation group; ICU: Intensive care unit; IQR: Interquartile range; SD: Standard deviation.

Table 2 Entire group analysis

Characteristic	Adjusted OR[1] (95%CI)	*P* value
Age ≥ 50 *vs* < 50 (yr)	1.61 (1.57-1.65)	< 0.0001
BMI ≥ 25 *vs* < 25 (kg/m^2)	0.81 (0.77-0.86)	< 0.0001
Females (*vs* males)	1.14 (1.12-1.16)	< 0.0001
African Americans *vs* Whites	1.51 (1.46-1.57)	< 0.0001
Asians *vs* Whites	2.29 (2.19-2.39)	< 0.0001
Hispanics *vs* Whites	2.06 (2.01-2.10)	< 0.0001
Colonoscopy *vs* EGD	0.97 (0.95-0.99)	0.001
Outpatient *vs* inpatient	0.70 (0.67-0.72)	< 0.0001
Completed: No *vs* yes	1.18 (1.12-1.24)	< 0.0001
ASA ≥ III *vs* ASA < III	1.45 (1.41-1.49)	< 0.0001
Location: OR *vs* endoscopy suite	0.97 (0.95-0.99)	0.005
Location: Other site[2] *vs* endoscopy suite	1.25 (1.16-1.34)	< 0.0001
Duration: ≥ 30-60 *vs* < 30 (min)	0.96 (0.93-0.99)	0.02
Duration: > 60 *vs* < 30 (min)	0.52 (0.48-0.57)	< 0.0001

[1]Adjusted odds ratios for all procedures requiring low dose sedation *vs* high dose sedation.
[2]Other site: Ambulatory surgery center, hospital ward, intensive care units, and radiology suite. EGD: Esophagogastroduodenoscopy; ASA: American Society of Anesthesia Class; OR: Odds ratio; CI: Confidence interval.

to those performed in endoscopy suites (aOR: 1.25, 95%CI: 1.16-1.34, P < 0.0001). Conversely, procedures performed in the endoscopy suite required less sedation as compared to those performed in the operating room (OR) (aOR: 0.97, 95%CI: 0.95-0.99, P = 0.005). Procedures that were aborted before completion required significantly less sedation as compared to those that were completed (aOR: 1.18, 95%CI: 1.12- 1.24, P < 0.0001). Procedure duration was assessed by comparing procedures less than 30 min (< 30 min) long, procedures 30 to 60 min (≥ 30–60 min) long, and procedure longer than 60 min (> 60 min). Significantly less sedation was required for all procedures < 30 min long as compared to both those ≥ 30-60 min and those > 60 min long (aOR: 0.96, 95%CI: 0.93-0.99, P = 0.02 and aOR: 0.52, 95%CI: 0.48-0.57, P < 0.0001, respectively) (Table 2, Figure 2).

Regarding patient tolerance as perceived by the endoscopist, patients were deemed to have "good" tolerance the majority of the time (65.9% in the LD sedation group, 60.9% in the HD group). On the other hand, patients in the HD group were 12.6% more likely to be "poorly tolerant" per endoscopist report compared to patients in the LD group.

EGD vs colonoscopy subgroup analysis

Clinical characteristics: Analyzing the data by procedure type provided additional insight into specific factors that affect tolerance for different procedures as shown in Table 3. When stratifying by procedure type, older patients (≥ 50 years old) were more likely to require less sedation compared to younger patients (< 50) for both EGDs (aOR: 2.23, 95%CI: 2.15-2.31) and colonoscopies (aOR: 1.16, 95%CI: 1.13-1.20) (P < 0.0001 for both). Female gender was also predictive of lower sedation requirements as compared to males (EGD: aOR: 1.23, 95%CI: 1.19-1.26; colonoscopy: aOR: 1.08, 95%CI:

Table 3 Comparison of esophagogastroduodenoscopy and colonoscopy groups

Characteristic	EGD group adjusted OR[1] (95%CI)	*P* value	Colonoscopy group adjusted OR[1] (95%CI)	*P* value
Age ≥ 50 *vs* < 50 (yr)	2.23 (2.15-2.31)	< 0.0001	1.16 (1.13-1.20)	< 0.0001
BMI ≥ 25 *vs* < 25 (kg/m^2)	1.18(1.09-1.28)	< 0.0001	0.67 (0.63-0.72)	< 0.0001
Females (*vs* males)	1.23 (1.19-1.26)	< 0.0001	1.08 (1.05-1.10)	< 0.0001
African Americans *vs* Whites	1.43 (1.35-1.51)	< 0.0001	1.54 (1.46-1.62)	< 0.0001
Asians *vs* Whites	1.73 (1.61-1.86)	< 0.0001	2.70 (2.56-2.85)	< 0.0001
Hispanics *vs* Whites	1.58 (1.53-1.64)	< 0.0001	2.49 (2.42-2.56)	< 0.0001
Outpatient *vs* inpatient	0.59 (0.57-0.62)	< 0.0001	0.85 (0.80-0.91)	< 0.0001
Completed: No *vs* yes	1.01 (0.89-1.14)	0.89	1.22 (1.15-1.29)	< 0.0001
ASA ≥ III *vs* ASA < III	1.44 (1.39-1.49)	< 0.0001	1.44 (1.39-1.50)	< 0.0001
Location: OR *vs* endoscopy suite	1.10 (1.06-1.14)	< 0.0001	0.91 (0.89-0.94)	< 0.0001
Location: Other site[2] *vs* endoscopy suite	1.06 (0.97-1.16)	0.20	1.75 (1.51-2.01)	< 0.0001
Duration: ≥ 30-60 *vs* < 30 (min)	1.12 (1.07-1.17)	< 0.0001	0.81 (0.77-0.85)	< 0.0001
Duration: > 60 *vs* < 30 (min)	0.35 (0.27-0.45)	< 0.0001	0.55 (0.50-0.60)	< 0.0001

[1]Adjusted odds ratios for esophagogastroduodenoscopy group and colonoscopy group requiring low dose sedation *vs* high dose sedation.
[2]Other site: Ambulatory surgery center, hospital ward, intensive care units, and radiology suite. EGD: Esophagogastroduodenoscopy; ASA: American Society of Anesthesia Class; OR: Odds ratio; CI: Confidence interval.

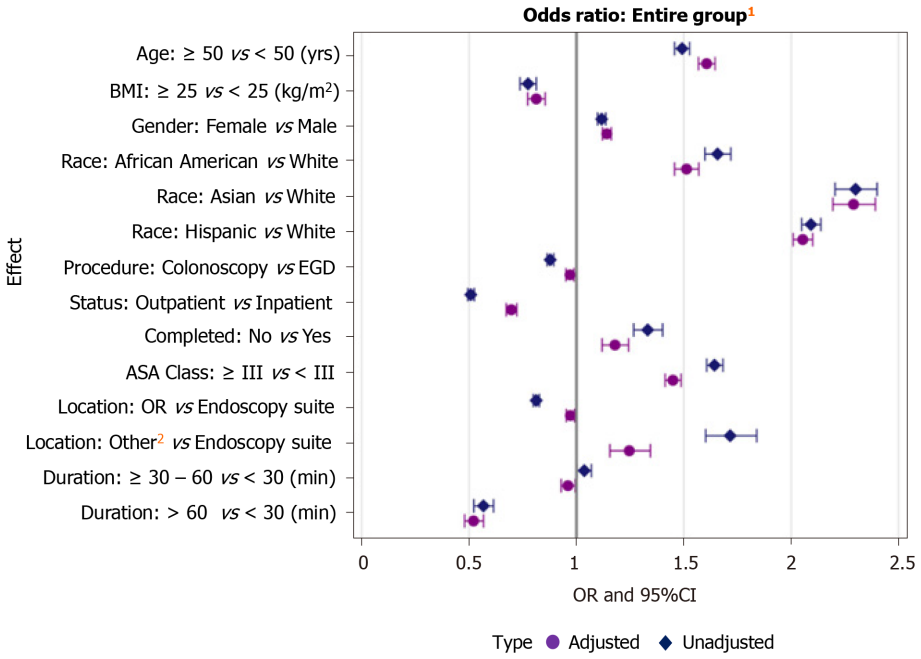

Figure 2 Entire group analysis. Odds ratios based on adjusted and unadjusted analysis comparing "Low dose" sedation group (*n* = 63154) *vs* "High dose" sedation group (*n* = 307819) across all procedures. [1]Adjusted odds ratios and unadjusted odds ratios for all procedures requiring low dose sedation *vs* high dose sedation. [2]Other site: Ambulatory surgery center, hospital ward, intensive care units, and radiology suite. EGD: Esophagogastroduodenoscopy; ASA: American Society of Anesthesia Class; OR: Odds ratio; CI: Confidence interval.

1.05-1.10; $P < 0.0001$ for both). African American, Asian, and Hispanic races all had higher odds of requiring less sedation as compared to Whites for both EGDs and colonoscopies ($P < 0.0001$ for all). While a higher BMI (≥ 25 kg/m^2) was predictive of lower sedation requirement for EGDs (aOR: 1.18, 95%CI: 1.09-1.28), a lower BMI (BMI < 25 kg/m^2) was a significant predictor of lower sedation requirements for colono-

scopies (aOR: 0.67, 95%CI: 0.63-0.72) (P < 0.0001 for both). Interestingly, a higher ASA class (≥ III) was predictive of requiring less sedation for both EGDs (aOR: 1.44, 95%CI: 1.39-1.49) and colonoscopies (aOR: 1.44, 95%CI: 1.39-1.50) (P < 0.0001 for both) as compared to a lower ASA class (ASA I and II) (Table 3, Figure 3).

Procedure related outcomes: Inpatients status was more predictive of lower sedation requirements among patients undergoing EGDs (aOR: 0.59, 95%CI: 0.57-0.62) and colonoscopies (aOR: 0.85, 95%CI: 0.80-0.91) (P < 0.0001 for both). Colonoscopies performed at sites outside the endoscopy suite (*i.e.* in ambulatory surgery center, ICUs, and hospital wards) had a significantly higher odds of requiring less sedation as compared to procedures done in the endoscopy suite (aOR: 1.75, 95%CI: 1.51-2.01, P < 0.0001). On the other hand, for EGDs, there was no significant difference in sedation requirements for procedures performed at sites outside the endoscopy suite as compared to those performed in the endoscopy suite (P = 0.20). On the contrary, while colonoscopies performed in the endoscopy suite was predictive of lower sedation requirements as compared to those performed in the OR (aOR: 0.91, 95%CI: 0.89-0.94), the inverse was true for EGDs (*i.e.* those performed in the OR were predictive of lower sedation requirements compared to the endoscopy suite) (aOR: 1.10, 95%CI: 1.06-1.14), (P < 0.0001 for both). While for colonoscopies, procedures that were aborted prior to completion required significantly less sedation as compared to those that were completed (aOR: 1.01, 95%CI: 0.89-1.14, P < 0.0001), there was no significant difference in sedation requirements for EGDs that were terminated early *vs* completed (P = 0.89). For colonoscopies, significantly less sedation was required for all procedures < 30 min long as compared to both those ≥ 30-60 min and those > 60 min long (aOR: 0.81, 95%CI: 0.77-0.85 and aOR: 0.55, 95%CI: 0.50-0.60, P < 0.0001 for both). On the other hand, for EGDs, while procedures < 30 min long were predictive of lower sedation requirements as compared to those > 60 min long (aOR: 0.35, 95%CI: 0.27-0.45, P < 0.0001), EGDs that were ≥ 30-60 min long were predictive of lower sedation requirements as compared to those < 30 min (aOR: 1.12, 95%CI: 1.07-1.17, P < 0.0001) (Table 3; Figure 3).

DISCUSSION

In this large, multi-center study evaluating a nationwide group spanning academic, government-based, and community practice experiences, we compared two groups of patients stratified by sedation needs, to discern factors associated with lower sedation requirements using moderate sedation. We found that female gender, older age, non-White race, Hispanic descent, higher ASA class, procedures performed as inpatient status and those done at locations other than the endoscopy suites (*i.e.*, ICUs, ambulatory surgery centers, hospital wards), were identified as factors associated with lower sedation requirements for completion. These factors were predictive on entire group analysis and remained predictive upon subgroup analysis when assessing EGD and colonoscopy groups separately, with the exception of BMI. Not only does this study add to the current body of literature, but it also provides definitive evidence informed by nationwide, multi-institutional data to illustrate the profile of the prototypical patient most likely to tolerate endoscopy under moderate sedation *vs* those better suited for an alternative sedation method. Our results should serve as a clinical guide to better inform the appropriate sedation practice utilized during GI endoscopy.

ASA class I and II patients undergoing routine endoscopy are generally deemed suitable for moderate sedation[5]. In low to average risk patients undergoing standard endoscopy, sedation administered by an endoscopist has previously been shown to be safe and offers patient satisfaction comparable with sedation administered by an anesthesia provider[17]. Alternatively, we found that higher ASA class and older age patients have lower sedation requirements. The pharmacokinetics of midazolam, the most widely used sedative in the United States, are influenced by patient age and renal and hepatic clearance, which affect the availability and functioning of cytochrome enzymes responsible for its metabolism[2,18,19]. This may explain the lower sedation requirements among patients of older age and higher ASA class, a surrogate for the presence of comorbidities, as compared to their younger, healthier counterparts. Moreover, with regards to colonoscopy, younger patients often have tighter mesentery tissues, as opposed to elderly patients whose mesenteries are more elastic and therefore, easier to navigate for the endoscopist. As such, older patients are likely more tolerable of colonoscopy with less sedation requirements. Another explanation could be that extra caution was exercised and less sedation was administered to patients of

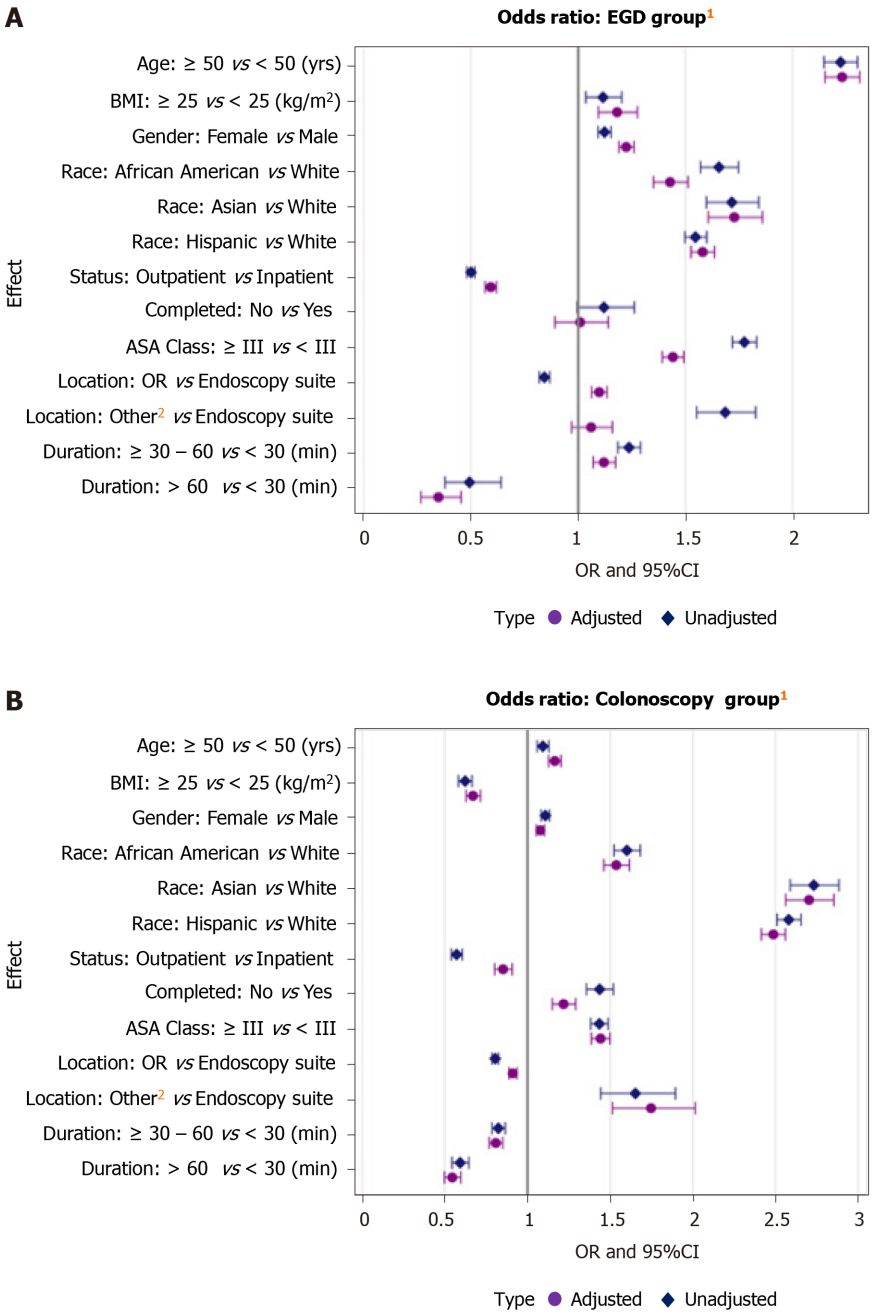

Figure 3 Comparison of esophagogastroduodenoscopy and colonoscopy groups. A: Esophagogastroduodenoscopy; B: Colonoscopy. Odds ratios based on adjusted and unadjusted analysis comparing "High dose" sedation group and "Low dose" sedation group during esophagogastroduodenoscopy (High dose group = 113281; Low dose group = 25146) and during colonoscopy (High dose group = 194684; Low dose group = 37991). [1]Adjusted odds ratios and unadjusted odds ratios for all procedures requiring low dose sedation *vs* high dose sedation; [2]Other site: Ambulatory surgery center, hospital ward, intensive care units, and radiology suite. LD: Low dose; HD: High dose; EGD: Esophagogastroduodenoscopy; OR: Odds ratio; CI: Confidence interval.

higher ASA class due to concern for the risk of sedation-related adverse events.

In our study, African Americans, Asians, and patients of Hispanic ethnicity uniformly had lower sedation requirements as compared to Whites. Previous studies have demonstrated conflicting data with regards to the role of race on pain perception[20,21]. This is largely attributable to the complex interplay among various factors including social and cultural beliefs, expressiveness towards pain, psychological factors, as well as biological factors such as genetics and alterations in the endogenous pain control systems, implicated in pain and tolerance to discomfort[22]. This remains an interesting area for further study on how race affect a patient's perception of the endoscopic experience.

Contrary to other studies, our findings suggest that females have lower sedation requirements as compared to males[7,11,23]. Alternatively, one prospective cohort study found that gender has no impact on sedation requirements during endoscopy[12].

Younger females tend to have longer colons with decreased mobility due to higher organ burden in the abdominopelvic cavity and acute bends in the sigmoid colon[24,25]. This can make colonoscopies in this patient demographic challenging for the endoscopist, creating potential patient discomfort and translating into higher sedation requirements. In our study, however, younger females (*i.e.,* females < 40 years old) were grossly under-represented, comprising only 10% of all female patients included in our study as compared to females between the ages of 50 and 69, which comprised > 50% of our entire female study population (Supplementary Table 1). As such, our findings may be more reflective of the older, female population. Nonetheless, it is worth noting that compared to prior studies, our study had significantly more patients across all age subgroups, and thus, our findings are likely more generalizable[7,11]. Additionally, the inconsistent findings in sedation requirements with regards to BMI among patients undergoing EGD and colonoscopy in our study is unclear. Recent data on midazolam implies that while the peripheral volume of distribution increases with higher BMI, the clearance of the drug with CYP3A is unaffected with higher BMI, challenging the notion that midazolam clearance is influenced by weight[24]. This may help to explain the variable findings regarding BMI in our colonoscopy and EGD groups. Nonetheless, while the effects of benzodiazepine agents are better studied, there remains a paucity of data with regards to the effects of patient demographics on opioid response in the procedure setting, which could be an interesting avenue for further research.

Our study is not without limitations. The CORI database is a clinical database, not an analytical data set, and is subject to human error and misclassification biases. In addition, the database has missing information, thus possibly introducing an inadvertent selection bias. We stratified our study population into two groups with opposite experiences in regard to sedation requirements to help emphasize demographic and procedural factors predictive of procedural sedation needs; however, we acknowledge that there are some patients who may fall into a "gray zone" with moderate sedation requirements. Furthermore, in this study, we assumed that amount of sedation administered was titrated to patient comfort; however, we recognize that practices may differ in their determination of what constitutes a suitable sedation level. This may help to explain our finding of higher ASA class patients "requiring" less sedation; in reality, less sedation may have been given as a result of the comfort level of the personnel administering the sedation. We would also like to recognize the subjective nature of "patient tolerance" during endoscopy as perceived by the endoscopist; since this study includes multi-center data input from different endoscopists, without a means for standardizing this data point, the patient "tolerance" parameter is subject to induce significant heterogeneity. Additionally, due to incomplete data in the CORI database, we could not account for procedural indications; had we done so, we likely would have identified a difference in tolerance of moderate sedation between procedures performed for screening or surveillance purposes and those performed for diagnostic and therapeutic purposes. Finally, due to limitations with the available data in the CORI repository, this study did not reflect upon the endoscopist's experience and its effect on sedation tolerance. It is conceivable that an experienced endoscopist may have a significant effect on patient comfort and tolerance, and this is a potential area for future investigation.

CONCLUSION

In conclusion, younger age, low/normal BMI, female sex, African American and Asian race, Hispanic ethnicity, and higher ASA class were shown to be significant predictors of lower sedation requirements and, thereby, improved tolerance to moderate sedation. This is substantive data to guide sedation practices during GI endoscopy, a source of debate in recent years. The utilization of monitored anesthesia care for endoscopy has been steadily rising. Given the high volume of GI endoscopies, payment for anesthesia services which accounts for 40% of the total overhead cost of an endoscopic exam, could be substantial. The use of anesthesiologist administered sedation for otherwise healthy, low risk patients undergoing routine endoscopy, has no proven benefit with respect to patient safety, satisfaction, and procedure efficacy. Thus, identifying those patients suitable for moderate sedation for GI endoscopy becomes even more critical to decrease discretionary spending and overutilization of anesthesia resources. Mitigation strategies to reduce aerosolized airborne pathogen exposure in the endoscopy suite has come to the forefront of endoscopic practice over the recent months; therefore, it has become increasingly important to identify those

patients who would benefit from conscious sedation *vs* those requiring higher levels of sedation and possible intubation. This study utilizes a nationwide registry, and to our knowledge it is the largest study examining the potential factors predictive of lower sedation requirements for endoscopy with moderate sedation. These findings are novel and increase our understanding of how patients should be assessed prior to undergoing sedation for routine endoscopic procedures.

ARTICLE HIGHLIGHTS

Research background

Moderate (conscious) sedation administered by endoscopists provides adequate sedation and analgesia for the majority of American Society of Anesthesia (ASA) class I and II patients undergoing routine gastrointestinal (GI) endoscopy. Deep sedation and general anesthesia are traditionally reserved for patients at higher risk for sedation-related adverse events.

Research motivation

Currently, there are limited society guidelines and insufficient data to aid endoscopists in the selection of the most appropriate sedation method. Rather, this decision is often based on the endoscopist's personal discretion and prior experience.

Research objectives

The study's main objective was to identify patient and procedure characteristics that may predict better tolerance with moderate sedation for routine GI endoscopy.

Research methods

This was a retrospective cohort study utilizing a nationwide, multi-center repository of endoscopic outcomes. Sedation dose requirements for all adult patients undergoing moderate sedation for esophagogastroduodenoscopy (EGD) and colonoscopy were identified from which patients were stratified into one of two groups based on sedation dose needs (low *vs* high dose). Anthropometric, procedural, and anesthesia-related data were compared between the two sedation groups, and logistic regression analysis was used to identify factors associated with lower sedation requirements.

Research results

Among 371102 patients included, 63137 patients were stratified into the low dose sedation group and 307965 patients were stratified into the high dose sedation group. Patients undergoing EGDs *vs* colonoscopies, procedure performed in the inpatient *vs* outpatient setting, and those performed in ambulatory surgery centers *vs* endoscopy suites were associated with lower moderate sedation requirements. On further multivariable analysis, factors predictive of tolerance with lower sedation requirements for both EGDs and colonoscopies included female gender, older age (≥ 50 years old), non-White race, Hispanic descent, lower BMI (≤ 25 kg/m^2) and higher ASA class.

Research conclusions

We have provided substantive data identifying key demographic and procedure related variables associated with lower sedation requirements during routine GI endoscopy and thereby, improved tolerance with moderate sedation.

Research perspectives

While our findings can help to guide appropriate sedation practices during GI endoscopy, future prospective studies are needed to clarify the effects of patient demographic and procedure related variables on opioid and benzodiazepine response in the procedure setting.

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LETTER TO THE EDITOR

Vinyl bag cover method to avoid droplet-containing aerosol escape from endoscopic forceps channel caps during COVID-19 pandemic (with Video 1 and Video 2)

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Author contributions: Akahoshi K designed the method; Akahoshi K, Tamura S, Akahoshi K, Kaneshiro Y, Sashihara R, Uemura K and Sato K conducted research; Akahoshi K (the first author) wrote the letter.

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Abstract

Endoscopists are at high risk of allowing transmission of coronavirus disease 2019 (COVID-19) during gastrointestinal endoscopy (GIE) procedures under pandemic conditions. The main avenues of droplet-containing aerosol generated during GIE are the mouth, anus, and endoscopic forceps channel. Although the usefulness of personal protective equipment for preventing COVID-19 dissemination has been well reported, measures to address infected aerosol escaping during endoscopic forceps use have been neglected. Pathogen-contaminated aerosol from the endoscopic forceps channel, leading into the gastrointestinal lumen, has been confirmed and is a highly problematic source of infection. We developed a technique that entails covering the forceps entry/exit hole with a vinyl bag, thereby preventing contamination of the endoscopy room by the infected aerosol that escapes from this hole. The technique can be used in daily clinical endoscopic practice. Furthermore, this shielding technique is useful for all patients who undergo GIE, regardless of the purpose of the procedure such as for making a diagnosis, administering therapy, or in an urgent situation. In this letter, we introduce our novel, easily performed, inexpensive method of infection prevention by disallowing infected aerosol to escape from a COVID-19-infected patient into the air during a procedure that requires the use of endoscopic forceps.

Key Words: Vinyl bag; Droplets; Endoscopy; COVID-19; Infection; Contamination

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Core Tip: The world is experiencing a viral pandemic. The main avenues of droplet-containing aerosol generated during gastrointestinal endoscopy are the mouth, anus,

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and endoscopic forceps channel. Although the usefulness of personal protective equipment for preventing coronavirus disease 2019 dissemination has been well reported, measures to address infected aerosol escaping *via* endoscopic forceps use have been neglected. We developed a technique using a vinyl bag to cover the hole through which forceps enter the gastrointestinal lumen. It prevents endoscopy room contamination by disallowing infected aerosol to escape *via* the forceps entrance. It thus protects the endoscopy room and staff during endoscopy.

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TO THE EDITOR

Following the first reports of coronavirus disease 2019 (COVID-19) infections in December 2019 from Wuhan, China[1], the infection rapidly spread worldwide until it reached pandemic proportions. Recently, it has been reported that severe acute respiratory syndrome coronavirus 2 virus has been detected in the oral cavity and fecal samples of COVID-19-infected patients[2,3].

Gastrointestinal endoscopic procedures are performed by inflating the gastrointestinal tract with air or carbon dioxide, thereby inducing belching, vomiting, coughing, and flatus, each of which may generate virus-infected aerosol. The main sources of such aerosol generated during gastrointestinal endoscopy (GIE) are the mouth, anus, and endoscopic forceps channel. Johnston *et al*[4] reported that the endoscopist's face risks bacterial exposure during GIE and recommended the use of universal facial protection during these procedures. Furthermore, bacteria-contaminated aerosol from the endoscopic forceps channel, leading to the gastrointestinal lumen, has been confirmed and is a highly problematic source of infection[5]. The endoscopic forceps channel cap usually loses its sealing ability through repeated insertion of the forceps. Hence, endoscopists are at high risk of COVID-19 transmission while performing GIE procedures.

There are many reports on the effectiveness of personal protective equipment for preventing COVID-19 infection during GIE[6,7]. In addition, several useful protective shielding methods against the infected aerosol escaping from the patient's mouth have been developed, such as aerosol chambers[8] and face shields for the patients[9,10]. However, little attention has been paid to infection control measures against infected aerosols escaping *via* the endoscopic forceps channel[5] that communicates with the lumen of the gastrointestinal tract.

We therefore developed a technique for covering the forceps entrance hole cap with a vinyl bag (Figure 1) to prevent contamination of the endoscopy staff and endoscopy room by aerosols escaping from the "relaxed" forceps cap of the endoscope. We have been using the technique during GIE procedures in our daily practice since May 2020. The materials required include a vinyl bag, a round reinforcement label for marking, transparent adhesive tape, medical tape, and a toothpick, which are inexpensive and easily obtained worldwide (Figure 2).

The first step in preparing the apparatus is to make a small hole at the bottom of a small vinyl bag through which a device such as forceps can be inserted (Video 1). The second step is to cover the endoscopic forceps hole cap using the vinyl bag, which produces space in which to trap the infected droplet-containing aerosol, ultimately leading to reduced COVID-19 transmission. To obtain effective intra-vinyl bag space, there must be several centimeters of separation between the endoscopic forceps hole cap and the insertion hole of the vinyl bag. This separation ensures that the aerosol does not escape from the vinyl bag. We conducted an experiment with rapid retrograde injection of indigo carmine solution through a forceps channel, which showed that no dye-containing droplets had escaped from the vinyl bag (Video 2). Hence, it is extremely important for the endoscopists and assistants to carefully maintain the separation during GIE. Figure 3 shows the liquid from the aerosol

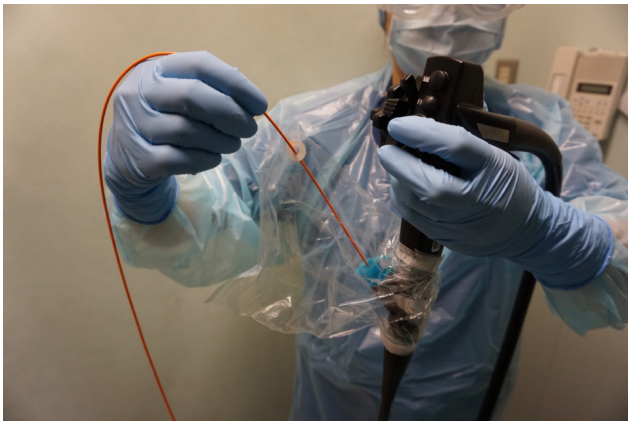

Figure 1 Overview photograph of the vinyl bag cover technique to prevent contamination of the endoscope room by droplet-containing aerosol escaping from the forceps hole of the endoscope.

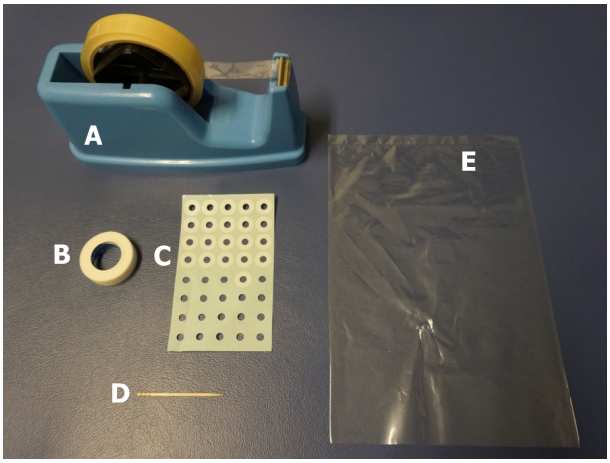

Figure 2 Materials required for constructing the apparatus. A: Transparent adhesive tape (*e.g.*, sellotape, scotch tape); B: Medical tape; C: A round seal; D: Toothpick; E: A transparent vinyl bag (27 cm × 18 cm).

trapped in a vinyl bag during colonic endoscopic submucosal dissection in a patient with a laterally spreading colonic tumor.

After the endoscopic procedure, the contaminated vinyl bag can be easily removed from the endoscope and safely discarded, making the apparatus disposable (Video 2). Furthermore, this shielding technique is useful for all patients who undergo GIE, regardless of the purpose of the procedure (*e.g.*, diagnostic, therapeutic, urgent).

Although wearing full personal protective equipment is the most basic measure of infection control in this COVID-19 pandemic era, further measures to reduce the risk of infection are urgently needed in endoscopy suites. Our newly devised shielding method is thus a promising countermeasure to prevent contamination of the endoscopy staff and room by infected aerosol escaping from the patient's gastrointestinal lumen *via* the entrance/exit hole for endoscopic forceps. The technique is inexpensive, and the apparatus is easily constructed, disposable, and practicable in endoscopy rooms worldwide. However, further aerodynamic study is needed to assess the effectiveness of the method.

Figure 3 Apparatus in use. Liquid formed from droplet-containing aerosol escaping from the endoscopic forceps entrance/exit hole is being trapped in a vinyl bag during colonic endoscopic submucosal dissection.

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The primary aim of *World Journal of Gastrointestinal Endoscopy* (*WJGE*, *World J Gastrointest Endosc*) is to provide scholars and readers from various fields of gastrointestinal endoscopy with a platform to publish high-quality basic and clinical research articles and communicate their research findings online.

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ORIGINAL ARTICLE

Retrospective Study

Impact of intragastric balloon on blood pressure reduction: A retrospective study in Eastern North Carolina

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Author contributions: Samuel GO and Lambert K collected and managed data, communicated with institutional review board, prepared study initiation activities, and helped with the writing of the manuscript; Asagbra E analyzed the data and helped with writing of the manuscript; Harvin G reviewed and helped with writing of the manuscript; Ibegbu E managed and provided data, reviewed and helped with writing of the manuscript; all authors have read and approved the final manuscript.

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Abstract

BACKGROUND

Obesity has evolved into a global pandemic. The prevalence of obesity and hypertension in eastern North Carolina are comparable, if not higher, than the national prevalence. In the United States, an estimated 34% of adults have hypertension, the most modifiable risk factor for heart disease and stroke. Lifestyle and pharmacological interventions often do not provide sustained weight loss in obese patients. Bariatric surgery offers an effective weight reduction with short-and long-term health improvements; however, a higher body mass index is associated with higher surgical morbidity and mortality, longer hospitalization, and increasing rates of 30-day readmission due to co-morbidities. Intragastric balloon may bridge a critical gap in the treatment of obesity. The objective of this paper is to showcase the impact of endoscopic bariatric therapy on blood pressure reduction.

AIM

To investigate the impact of intragastric balloon on blood pressure reduction.

METHODS

A retrospective chart review was conducted from January 1, 2016 to January 31, 2019 of consecutive adults who received intragastric balloon therapy (IGBT) in a gastroenterology private practice in Eastern North Carolina. The balloon was introduced into the stomach under endoscopic guidance, and while in the region of the gastric body, inflation with saline was performed at increments of 50 mL until target volume between 500 to 650 mL of saline was attained depending on

relevant conflicts of interest exist for all authors.

Data sharing statement: Statistical codes, and dataset available from the corresponding author at gbeminiyi.samuel@gmail.com.

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the patient's gastric capacity. No procedural complications were noted during endoscopic placement and removal of the balloon. A cohort study design was used for data analysis. A total of 172 patients had the Orbera® intragastric balloon placed. Of the 172 patients who had IGBT at baseline, 11 patients (6.4%) requested early balloon removal due to foreign body sensation (n = 1), and/or intolerable gastrointestinal adverse events (n = 10). The reported gastrointestinal adverse events were nausea, vomiting, abdominal pain, and diarrhea. Eventually, 6-mo follow-up data were available for only 140 patients. As a result, only the 140 available at the 6-mo follow-up were included in the analysis. Univariate, bivariate, and multivariate statistical analyses were performed. Specifically, scatterplots were created to show the relationship between weight and blood pressure, and paired two-sample t-test was carried out to determine if there was a significant reduction in weight before and after the IGBT. Multiple regressions were also performed to examine the association between participants' total body weight and blood pressure. The outcome variables for the multiple regression were systolic and diastolic blood pressure measured as continuous variables. This was followed by logistic regression analyses to determine the association between total body weight and hypertension at 6-mo post-implantation. The outcome variables for the logistic regression were systolic blood pressure–non-hypertensive (140 mmHg or less) or hypertensive (greater than 140 mmHg), and diastolic blood pressure–non-hypertensive (90 mmHg or less) or hypertensive (greater than 90 mmHg). All authors had access to the study data and reviewed and approved the final manuscript. All statistical analyses were done using STATA 14®.

RESULTS

The study included 15% males and 85% females. 50% of the patients were white and just over 22% were non-white, and about 27% declined to give their race. The average baseline patients' weight prior to IGBT was 231.61 Lbs. (SD = 46.53 Lbs.). However, the average patients' weight after IGBT at the 6-mo follow-up was 203.88 Lbs. (SD = 41.04 Lbs.). Hence, on average, the percent total body weight loss at 6-mo is 11.97 after IGBT. The logistic regression performed revealed that weight ($\beta = 0.0140$, $P < 0.000$) and age ($\beta = 0.0534$, $P < 0.000$) are important factors in determining systolic blood pressure after IGBT. None of the other demographic characteristics or indicated comorbidities were found to be significant.

CONCLUSION

IGBT can be an effective short-term weight reduction modality with a relatively little risk of adverse event. Due to its improvement on systolic blood pressure, IGBT may help reduce cardiovascular risk.

Key Words: Intragastric balloon; Orbera®; Obesity; Hypertension; Systolic blood pressure; Diastolic blood pressure

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Core Tip: Obesity is one of the leading causes of preventable life-years lost among Americans. Adults who have obesity compared with adults at a healthy weight have an increased risk of developing serious health conditions including hypertension. The treatment of hypertension in obesity is complicated by a high prevalence of resistant hypertension, as well as unpredictable hemodynamic effects of many medications. Weight loss stabilizes neurohormonal activity and causes clinically significant reductions in blood pressure. While lifestyle interventions can improve blood pressure, they fail to consistently yield sustained weight loss and have not demonstrated long-term benefits. Weight loss promotes dramatic declines in blood pressure and attenuation of long-term cardiovascular risk.

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INTRODUCTION

Obesity with its associated devastating consequences has evolved into a global pandemic and a major health concern[1]. In the United States, an estimated 34% of adults have hypertension (approximately 8.7 million people), which is the most modifiable risk factor for heart disease and stroke[2]. Lifestyle interventions often do not provide sustained weight loss for people who are obese[2]. While 4.5%-11% total body weight loss can be achieved with pharmacological agents, some patients cannot achieve enough weight loss with lifestyle modifications and medication alone[3]. The pharmacological agents indicated for weight reduction often have limited data for long term effects or intolerable side effect profile[4]. Bariatric surgery is the most effective weight reduction intervention with short- and long-term health improvements; however, a higher body mass index is associated with higher surgical morbidity and mortality, longer hospitalization, and increasing rates of 30-d readmission due to co-morbidities[5-8]. In addition, risks may outweigh the benefits in those with a greater body mass index. While the mortality rates associated with bariatric surgery have decreased, the complication rates remain high with one meta-analysis citing a complication rate of 17% and a reoperation rate of 7%[9]. In addition, only 1% of patients eligible for bariatric surgery ultimately undergo the procedure[3]. Minimally invasive non-surgical options may bridge a critical gap in the treatment of obesity[10,11].

One of the most widely studied of the endoscopic bariatric therapies is Orbera, which is an intragastric balloon approved for a body mass index of 30-40 kg/m^2[11]. It is a spherical silicone device, filled with saline, that is endoscopically implanted and removed with an approved indication of placement for six months[10,11]. It promotes weight loss by its effect as a space occupying device and altering gut hormones, however the mechanism is not quite clear[11]. One study showed that weight loss achieved with Orbera was 11.3% and excess weight loss measured was 25.4%[9]. Comorbidity improvement occurs at a 10% body weight reduction[1,12,13].

Limited studies have evaluated the efficacy of Orbera and its influence on co-morbidities. Genco *et al*[14] demonstrated in an Italian study significant improvement and resolution of pre-operative complications (hypertension, diabetes, respiratory disorders, osteoarthritis, and dyslipidemia) in 89.1% patients. There was a 44.8% resolution of hypertension; yet, there is an insufficient amount of data analyzing the association of weight loss with blood pressure reduction.

MATERIALS AND METHODS

A retrospective chart review was conducted from January 1, 2016 to January 31, 2019 of consecutive adults who received intragastric balloon therapy (IGBT) in a gastroenterology private practice in Eastern North Carolina. The balloon was introduced into the stomach under endoscopic guidance, and while in the region of the gastric body, inflation with saline was performed at increments of 50 mL until target volume between 500 to 650 mL of saline was attained depending on the patient's gastric capacity (see Figure 1 for placement and removal of gastric balloon)[15]. No procedural complications were noted during endoscopic placement and removal of the balloon.

This study was exempt from institutional review board (IRB) review after institutional IRB review (UMCIRB 19-001002). The data collected consisted of patient demographics and other comorbidities. The patient demographic information collected included race, gender, age, and weight. Race was categorized in three groups-white, non-white, and not reported. The comorbidities considered in this study included hyperlipidemia, depression, coronary artery disease, cardiovascular disease, obstructive sleep apnea, and diabetes mellitus.

The unit of analysis was the patient, and the outcome of interest was hypertension. Both systolic and diastolic blood pressure were obtained to determine hypertension. All blood pressure measurements were assessed by a digital blood pressure machine (GE Dinamap Carescape V100 Vitals Monitor). This study examined the impact of

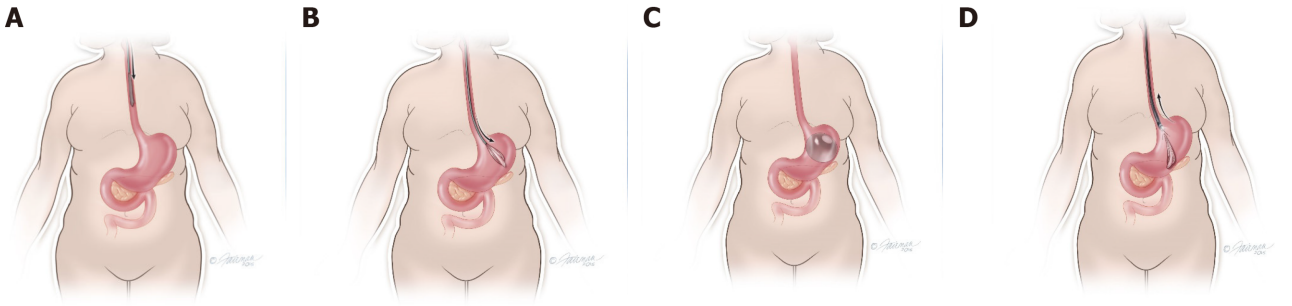

Figure 1 Placement and removal of gastric balloon. A: Showing endoscopic advancement of the balloon in the esophagus; B: Showing endoscopic appearance of deflated balloon in the gastric body; C: Showing endoscopic appearance of inflated balloon in the gastric body; and D: Removal of intragastric balloon after deflation. Citation: Image Library. In: Illustrations [cited 22 March 2021]. Available from: http://apolloresource.wpengine.com/orbera/image-library/. Copyright© The figures 2021. Published by Apollo Endosurgery, Inc.[15].

weight reduction at baseline compared to 6-mo on hypertension. The cut-offs for systolic and diastolic blood pressures were 140 and 90 respectively. This allowed for the creation of binary outcome variables-hypertension and non-hypertension for both systolic and diastolic blood pressures.

A cohort study design was used for data analysis. A total of 172 patients had the Orbera intragastric balloon placed. Of the 172 patients who had IGBT at baseline, 11 patients (6.4%) requested early balloon removal due to foreign body sensation (n = 1), and/or intolerable gastrointestinal adverse events (n = 10). The reported gastrointestinal adverse events were nausea, vomiting, abdominal pain, and diarrhea. Eventually, 6-mo follow-up data were available for only 140 patients. As a result, only the 140 available at the 6-mo follow-up were included in the analysis. Univariate, bivariate, and multivariate statistical analyses were performed. Specifically, scatterplots were created to show the relationship between weight and blood pressure, and paired two-sample t-test was carried out to determine if there was a significant reduction in weight before and after the IGBT. Multiple regressions were also performed to examine the association between participants' total body weight and blood pressure. The outcome variables for the multiple regression were systolic and diastolic blood pressure measured as continuous variables. This was followed by logistic regression analyses to determine the association between total body weight and hypertension at 6-mo post-implantation. The outcome variables for the logistic regression were systolic blood pressure (SBP)–non-hypertensive (140 mmHg or less) or hypertensive (greater than 140 mmHg), and diastolic blood pressure–non-hypertensive (90 mmHg or less) or hypertensive (greater than 90 mmHg). All authors had access to the study data and reviewed and approved the final manuscript. All statistical analyses were done using STATA 14®.

RESULTS

Univariate and bivariate analysis

Of the 172 patients at baseline, follow-up data were available for only 140 patients at 6-mo. Table 1 shows the descriptive statistics for both patient demographic information and presence of comorbidities at baseline unless otherwise stated. The study included 15% males and 85% females. 50% of the patients were white and just over 22% were non-white, and about 27% declined to give their race. Additionally, a few patients were diagnosed with comorbidities including 12.86% patients with hyperlipidemia, 30% with depression, 2.86% with coronary artery disease, 5.71% with cardiovascular disease, 17.86% with obstructive sleep apnea, and 21.43% with Diabetes Mellitus.

The average baseline patients' weight prior to IGBT was 231.61 Lbs. (SD = 46.53 Lbs.). However, the average patients' weight after IGBT at the 6-mo follow-up was 203.88 Lbs. (SD = 41.04 Lbs.). Hence, on average, the percent total body weight loss at 6-mo is 11.97 after IGBT. For comparison, a paired two-sample t-test was performed as shown in Table 2. The result reveals a statistically significant reduction in weight at the 6-mo follow-up after the IGBT. The scatterplot showing the relationship between total body weight and systolic and diastolic blood pressure is presented in Figure 2. The plots reveal a weak but positive correlation between total body weight and systolic blood pressure (r = 0.280), and total body weight and diastolic blood pressure (r =

Table 1 Patient demographical information and comorbidities at baseline

Variables	Description	Frequency	Percent (%)
Race distribution	White	70	50.00
	Non-White	32	22.86
	Declined	38	27.14
Gender distribution	Male	21	15.00
	Female	119	85.00
Age (in year)	mean (SD)	45.56 (10.75)	
Weight in lbs. (At baseline)	mean (SD)	231.61 (46.53)	
Weight in lbs. (At 6-mo)	mean (SD)	203.88 (41.04)	
Systolic blood pressure (At baseline)	Non-hypertensive (140 or less)	76	54.29
	Hypertensive (Greater than 140)	64	45.71
Systolic blood pressure (At 6-mo)	Non-hypertensive (140 or less)	110	78.57
	Hypertensive (Greater than 140)	30	21.43
Diastolic blood pressure (At baseline)	Non-hypertensive (90 or less)	123	87.86
	Hypertensive (Greater than 90)	17	12.14
Diastolic blood pressure (At 6-mo)	Non-hypertensive (90 or less)	125	89.29
	Hypertensive (Greater than 90)	15	10.71
Has hyperlipidemia	No	121	86.43
	Yes	18	12.86
	Missing	1	0.71
Has depression	No	97	69.29
	Yes	42	30.00
	Missing	1	0.71
Has CAD	No	136	97.14
	Yes	4	2.86
Has CVD	No	132	94.29
	Yes	8	5.71
Has OSA	No	115	82.14
	Yes	25	17.86
Has diabetes mellitus	No	110	78.57
	Yes	30	21.43

CAD: Coronary artery disease; CVD: Cardiovascular disease; OSA: Obstructive sleep apnea.

0.132). Given the weak correlation, several cofounders were included in the multivariate analysis as presented below.

Multivariate analysis

This study further analyzed the relationship between weight loss and blood pressure using a multiple regression technique. The findings presented in Table 3 show that after controlling for other cofounders like comorbidities and patient demographic characteristics, weight is an important factor for predicting the systolic blood pressure of the study participants ($\beta = 0.1350$, $P < 0.000$). Conversely, it was revealed that weight was not significantly associated with the diastolic blood pressure of the study participants ($\beta = 0.0295$, $P < 0.138$).

The logistic regression performed revealed that weight ($\beta = 0.0140$, $P < 0.000$) and age ($\beta = 0.0534$, $P < 0.000$) are important factors in determining systolic blood pressure

Table 2 *t*-test: Paired two sample for means

	Weight at baseline	Weight at 6-mo follow-up
Mean	231.61	203.88
t-stat	18.06	
P value	0.0000	

Table 3 Multiple regression showing the association between systolic and diastolic blood pressure and demographics and other comorbidities

	Systolic blood pressure (β)	Diastolic blood pressure (β)
Weight	0.1350[b]	0.0295
Age	0.5135[b]	0.1439
Gender		
Female	-1.1118	-2.9830
Race (White)		
Non-White	-0.9900	1.9809
Declined	0.9093	1.0592
DM	-1.0136	-3.8298
OSA	-1.4531	-0.7374
CVD	-5.5353	-2.4714
Hyperlipidemia	-1.4230	3.5368
CAD	14.9021	-0.4645
Depression	-2.3854	-0.9559

[b]$P < 0.01$. CAD: Coronary artery disease; CVD: Cardiovascular disease; OSA: Obstructive sleep apnea.

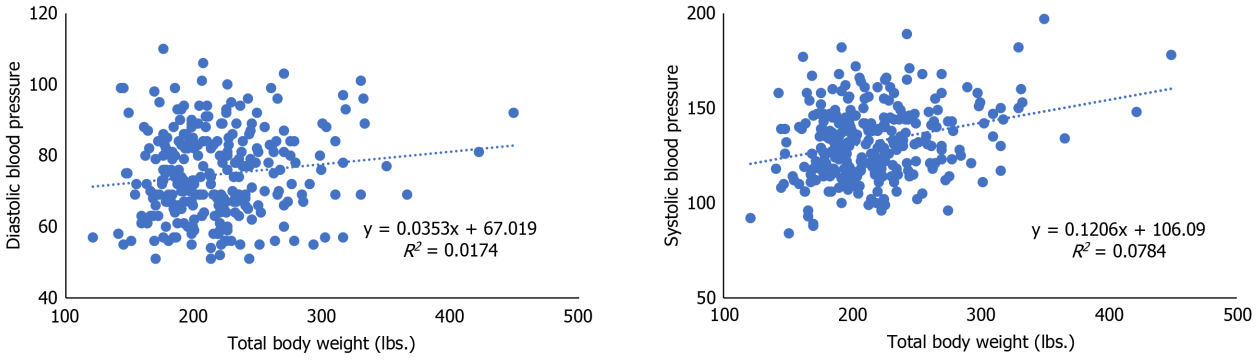

Figure 2 Chart showing the association between total body weight and blood pressure.

after IGBT. None of the other demographic characteristics or indicated comorbidities were found to be significant. The results specifically indicated that for every unit increase in weight, the log odds of SBP will increase by 1.4%. Also, for every unit increase in age, the log odds of SBP will increase by 5.34%. No variable included in the study however showed a significant association with diastolic blood pressure after IGBT. These results are presented in Table 4.

Table 4 Logistic regression showing the association between systolic and diastolic blood pressure and demographics and other comorbidities at 6-mo post-implantation

	Systolic blood pressure (β)	Diastolic blood pressure (β)
Weight	0.0140[b]	0.0081
Age	0.0534[b]	0.0262
Gender		
Female	0.0002	0.2519
Race (White)		
Non-White	-0.3575	0.0558
Declined	0.1795	-0.3747
DM	-0.1462	-0.2354
OSA	-0.4340	-0.3993
CVD	-0.4240	0.3402
Hyperlipidemia	-0.0603	0.4243
CAD	0.3749	0.0000
Depression	-0.3549	-0.3365

[b]$P < 0.01$. CAD: Coronary artery disease; CVD: Cardiovascular disease; OSA: Obstructive sleep apnea.

DISCUSSION

The intragastric balloon is used for those patients who have failed to achieve and maintain the weight loss with conservative measures or prefer a less invasive approach. In addition, it can have a significant role in the preoperative management of morbidly obese patients prior to bariatric surgery to reduce mortality and morbidity.

We observed an average loss of 11.97% from baseline weight at 6-mo post implantation, which is sufficient for comorbidity improvement. The present data indicate that Orbera® intragastric balloon significantly reduced weight, and systolic blood pressure at the time of balloon removal at 6-mo; although there was a decrease in diastolic blood pressure, it was not statistically significant. Furthermore, weight and age appear to be important factors in determining systolic blood pressure after intragastric balloon therapy. The weight reduction observed was analogous to other studies. Yorke *et al*[12] demonstrated a 15 kg and 5.9 ± 1.0 kg/m^2 reduction post-implantation in a systematic review of 26 studies. Herve *at al*[16] demonstrated a 12 kg weight reduction at the time of balloon removal and 8.6 kg reduction at 1 year follow up. A Brazilian multicenter study also cited a significant weight reduction of 15.2 ± 10.5 kg, however, Ganesh *et al*[17] reported a 5.9 kg reduction after 6 mo[18]. While the intragastric balloon can induce short-term weight reduction, the weight loss sustainability is often difficult to achieve. Despite weight regain observed, Crea *et al*[19] reported improvement in metabolic syndrome and the sustained 10% body weight loss.

Obesity plays a key role in metabolic syndrome[20]. The development of hypertension in obesity involves multiple mechanisms such as insulin resistance, increased inflammatory markers, oxidative stress, the sympathetic nervous system, and the renin-angiotensin aldosterone system. The mentioned effects in the setting of obesity induce endothelial dysfunction thus contributing to elevated blood pressure[20]. While patients who undergo lifestyle interventions often have blood pressure improvement, its sustainability on weight loss is limited; therefore, it may fail to decrease long-term adverse cardiovascular effect[20]. While there are conflicting data regarding the influence of pharmacological agents for weight reduction on blood pressure improvement, there is evidence that bariatric surgery improves blood pressure by mechanisms such as decreasing plasma leptin and sympathetic nervous system activity[20]. Given the relatively new field of endoscopic bariatric therapies, there is limited data regarding the influence of intragastric balloon therapy on blood pressure. It is known that the intragastric balloon adopts the gastric restriction mechanism through the space-occupying design, while increasing post-prandial satiety and decreasing pre-prandial hunger. It has also been reported to alter hormone

release, such as leptin and ghrelin, leading to weight loss; however, it appears to be a transitory affect[21,22].

Orbera has a relatively good safety profile with the commonest adverse events being abdominal pain, nausea, vomiting, and gastroesophageal reflux disease[8,12,23]. While there is a cited early balloon removal rate of 9%, in our study, there was a 6.4% early balloon removal rate due to intolerable gastrointestinal adverse events[9].

The study has several limitations. They include the retrospective analysis of a single-center analysis and the absence of a control group. The frequency of the other comorbidities may be an underestimate. In addition, the follow-up period was only at the six-month time period of balloon removal, and therefore, weight loss sustainability cannot be concluded.

CONCLUSION

IGBT can be an effective short-term weight reduction modality with a relatively little risk of adverse event. Due to its improvement on systolic blood pressure, IGBT may help reduce cardiovascular risk.

ARTICLE HIGHLIGHTS

Research background

In the United States, about a third of adults have hypertension, which is the most modifiable risk factor for heart disease and stroke. The prevalence of obesity and hypertension in eastern North Carolina are comparable, with obesity being an established risk factor for hypertension. Lifestyle interventions and pharmacological agents often are not sufficient to achieve enough weight loss. Bariatric surgery offers the most effective weight reduction intervention, however patients with higher body mass index may have higher surgical morbidity and mortality, longer hospitalization, and high rates of 30-d readmission due to co-morbidities. Minimally invasive non-surgical options like the intragastric balloon may bridge a critical gap in the treatment of obesity.

Research motivation

The weight loss mechanism of the intragastric balloon therapy is restrictive, and this leads to weight reduction due to reduced food intake from early post-prandial satiety. Weight loss helps to lower the risk of potentially serious obesity-related health problems like heart disease, stroke, hypertension, diabetes and osteoarthritis. Aside from long-term health benefits, weight reduction is cost-effective and promotes substantial health-care cost savings.

Research objectives

Our study focused on the impact of intragastric balloon therapy (IGBT) on blood pressure reduction. IGBT leads to statistically significant weight and systolic blood pressure reduction at 6-mo. Also, the degree of weight reduction by IGBT is sufficient to effect improvement in comorbidities.

Research methods

A retrospective chart review was conducted from January 1, 2016 to January 31, 2019 of consecutive adults who received IGBT in a gastroenterology private practice in eastern North Carolina. The balloon was introduced into the stomach under endoscopic guidance, and while in the region of the gastric body, inflation with saline was performed at increments of 50 mL until target volume between 500 to 650 mL of saline was attained depending on the patient's gastric capacity. No procedural complications were noted during endoscopic placement and removal of the balloon.

Of the 172 patients who had IGBT at baseline, 11 patients (6.4%) requested early balloon removal due to foreign body sensation (n = 1), and/or intolerable gastrointestinal adverse events (n = 10). The reported gastrointestinal adverse events were nausea, vomiting, abdominal pain, and diarrhea. Eventually, 6-mo follow-up data were available for only 140 patients. As a result, only the 140 available at the 6-mo follow-up were included in the analysis. Univariate, bivariate, and multivariate statistical analyses were performed. Specifically, scatterplots were created to show the

relationship between weight and blood pressure, and paired two-sample *t*-test was carried out to determine if there was a significant reduction in weight before and after the IGBT. Multiple regressions were also performed to examine the association between participants' total body weight and blood pressure. The outcome variables for the multiple regression were systolic and diastolic blood pressure measured as continuous variables. This was followed by logistic regression analyses to determine the association between total body weight and hypertension at 6-mo post-implantation. The outcome variables for the logistic regression were systolic blood pressure–non-hypertensive (140 mmHg or less) or hypertensive (greater than 140 mmHg), and diastolic blood pressure-non-hypertensive (90 mmHg or less) or hypertensive (greater than 90 mmHg). All authors had access to the study data and reviewed and approved the final manuscript. All statistical analyses were done using STATA 14®.

Research results

Weight is an important factor for predicting the systolic blood pressure of the study participants ($\beta = 0.1350$, $P < 0.000$). Conversely, weight was not significantly associated with the diastolic blood pressure of the study participants ($\beta = 0.0295$, $P < 0.138$). On average, the percent total body weight loss at 6-mo is 11.97 after IGBT. The logistic regression performed revealed that weight ($\beta = 0.0140$, $P < 0.000$) and age ($\beta = 0.0534$, $P < 0.000$) are important factors in determining systolic blood pressure after IGBT. The results specifically indicated that for every unit increase in weight, the log odds of SBP will increase by 1.4%. Also, for every unit increase in age, the log odds of SBP will increase by 5.34%.

IGBT can be an effective short-term weight reduction modality with a relatively little risk of adverse event. Due to its improvement on systolic blood pressure, IGBT may help reduce cardiovascular risk. Study limitations include the retrospective analysis of a single-center and the absence of a control group. In addition, the follow-up period was only at the six-month time period of balloon removal, and therefore, weight loss sustainability cannot be concluded.

Research conclusions

IGBT engenders short-term weight reduction modality with a relatively little risk of adverse event. Its improvement on systolic blood pressure may help reduce cardiovascular risk.

Research perspectives

Given the increasing global prevalence of obesity, it is envisioned that bariatric devices such as intragastric balloons will continue to evolve. Though intragastric balloons can bring about short-term morbidity/mortality benefits, the long-term benefits are questionable. Further studies will focus on promoting the long-term weight benefits of intragastric balloons.

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ORIGINAL ARTICLE

Observational Study

Comparison of endoscopic gastritis based on Kyoto classification between diffuse and intestinal gastric cancer

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Abstract

BACKGROUND

Gastric cancers can be categorized into diffuse- and intestinal-type cancers based on the Lauren histopathological classification. These two subtypes show distinct differences in metastasis frequency, treatment application, and prognosis. Therefore, accurately assessing the Lauren classification before treatment is crucial. However, studies on the gastritis endoscopy-based Kyoto classification have recently shown that endoscopic diagnosis has improved.

AIM

To investigate patient characteristics including endoscopic gastritis associated with diffuse- and intestinal-type gastric cancers in *Helicobacter pylori* (*H. pylori*)-infected patients.

METHODS

Patients who underwent esophagogastroduodenoscopy at the Toyoshima

anonymous clinical data that were obtained after each patient agreed to treatment by written consent. For full disclosure, the details of the study are published on the home page of Toyoshima Endoscopy Clinic.

Conflict-of-interest statement: All other authors have nothing to disclose.

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Endoscopy Clinic were enrolled. The Kyoto classification included atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. The effects of age, sex, and Kyoto classification score on gastric cancer according to the Lauren classification were analyzed. We developed the Lauren predictive background score based on the coefficients of a logistic regression model using variables independently associated with the Lauren classification. Area under the receiver operative characteristic curve and diagnostic accuracy of this score were examined.

RESULTS

A total of 499 *H. pylori*-infected patients (49.6% males; average age: 54.9 years) were enrolled; 132 patients with gastric cancer (39 diffuse- and 93 intestinal-type cancers) and 367 cancer-free controls were eligible. Gastric cancer was independently associated with age ≥ 65 years, high atrophy score, high intestinal metaplasia score, and low nodularity score when compared to the control. Factors independently associated with intestinal-type cancer were age ≥ 65 years (coefficient: 1.98), male sex (coefficient: 1.02), high intestinal metaplasia score (coefficient: 0.68), and low enlarged folds score (coefficient: -1.31) when compared to diffuse-type cancer. The Lauren predictive background score was defined as the sum of +2 (age ≥ 65 years), +1 (male sex), +1 (endoscopic intestinal metaplasia), and -1 (endoscopic enlarged folds) points. Area under the receiver operative characteristic curve of the Lauren predictive background score was 0.828 for predicting intestinal-type cancer. With a cut-off value of +2, the sensitivity, specificity, and accuracy of the Lauren predictive background score were 81.7%, 71.8%, and 78.8%, respectively.

CONCLUSION

Patient backgrounds, such as age, sex, endoscopic intestinal metaplasia, and endoscopic enlarged folds are useful for predicting the Lauren type of gastric cancer.

Key Words: Gastric cancer; Lauren classification; Endoscopy; Pathology; Gastritis; Kyoto classification

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Core Tip: Accurately assessing the Lauren classification before the treatment of gastric cancer is crucial. Factors independently associated with intestinal-type cancer were age ≥ 65 years, male sex, high endoscopic intestinal metaplasia score, and low endoscopic enlarged folds score when compared to diffuse-type cancer. The Lauren predictive background score was defined as the sum of +2 (age ≥ 65 years), +1 (male), +1 (intestinal metaplasia), and -1 (enlarged folds) points. Area under the curve of the Lauren predictive background score was 0.828 (cut-off: +2) for predicting intestinal-type cancer. Age, sex, intestinal metaplasia, and enlarged folds are useful for predicting tumor type.

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INTRODUCTION

The International Agency for Research on Cancer reported in GLOBOCAN 2018 that stomach cancer was the third leading cause of mortality worldwide[1]. Gastric cancers are epidemiologically crucial and can be categorized into two types based on the

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Lauren histopathological classification: diffuse and intestinal-types[2]. Intestinal-type cancers are associated with a *Helicobacter pylori (H. pylori)*-induced chronic inflammatory process, known as the Correa pathway, which includes atrophy, metaplasia, dysplasia, and cancer[3], whereas diffuse-type gastric cancers directly undergo a highly active inflammation-based carcinogenesis without having to pass through the Correa pathway[4,5]. The two histological subtypes of gastric tumors proposed by Lauren exhibit several distinct clinical and molecular characteristics[6-8]. Depending on the Lauren type, the frequency of lymph node metastasis[2,9,10] and peritoneal metastasis[11,12], application of endoscopic mucosal dissection[13,14], recommended surgical margin[15], response to chemotherapy[16], and prognosis[2,16,17] differ. The Lauren classification is diagnosed by pathology; however, it would be useful if subtypes could be endoscopically predicted.

In recent years, advancement in endoscopy has enabled diagnosis that is highly consistent with histology[18,19]. In 2013, the endoscopy-based Kyoto classification of gastritis was advocated by the Japan Gastroenterological Endoscopy Society with the aim of unifying the endoscopic diagnosis of gastritis in clinical practice and match it with the pathological diagnosis of gastritis[20]. The Kyoto classification adopted and scored atrophy, intestinal metaplasia, enlarged folds, nodularity, diffuse redness, and the regular arrangement of collecting venules (RAC) as endoscopic findings of gastritis. Among them, the Kyoto score, which is the sum of the scores of these factors, has been vigorously reported to be associated with gastric cancer[21,22], gastric cancer risk[20,23], and *H. pylori* infections[24]. Evaluating the risk of gastric cancer on the basis of endoscopic findings is an important alternative to biopsy.

Since there are few reports regarding the relationship between the Lauren classification and endoscopic findings based on the Kyoto classification[21,22], we investigated the background patient characteristics and endoscopic gastritis of patients with diffuse- and intestinal-type gastric cancers, focusing on *H. pylori* infected patients. Based on these outcomes, a score was created to predict the Lauren classification, and its accuracy was examined.

MATERIALS AND METHODS

Study design and oversight

We conducted a retrospective case-control study at the Toyoshima Endoscopy Clinic, which is an outpatient endoscopy-specialized clinic located in Tokyo, an urban area in Japan. This study was approved by the certificated review board of the Hattori Clinic on September 4, 2020 (approval No. S2009-U04, registration number UMIN000018541). Written informed consent was obtained from all patients. All clinical investigations were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. This study received no financial support.

Study population

Eligibility criteria included patients with gastric cancer and an *H. pylori* infection who underwent esophagogastroduodenoscopy at the Toyoshima Endoscopy Clinic from September 2008 to February 2020. We excluded patients who did not have *H. pylori* infection, patients in whom *H. pylori* was successfully eradicated, and those whose *H. pylori* status was unavailable. Patients with gastric cancer and past gastrectomy were also excluded. As control group, patients with *H. pylori*-positive gastritis and without gastric cancer were enrolled. This criterion included patients who underwent esophagogastroduodenoscopy and initial assessments for an *H. pylori* infection from December 2013 to March 2016 and from January 2018 to February 2019.

Diagnosis of Lauren classification and H. pylori infection

The Lauren classification was diagnosed from resected specimens or, if unresectable, biopsy specimens.

An *H. pylori* infection was diagnosed using pathology (hematoxylin and eosin staining) or the urea breath test.

Endoscopic gastritis based on the Kyoto classification

The Kyoto score for endoscopic gastritis, which ranges from 0 to 8, is based on the total scores of the following five endoscopic findings: atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. A high score represents an increased risk of gastric cancer[20-23] and *H. pylori* infection[24].

Endoscopic atrophy was classified based on the extent of mucosal atrophy (the Kimura Takemoto classification)[26]. Non-atrophy and C1 atrophy were scored as atrophy score 0, C2, and C3 atrophies as atrophy score 1, and O1 to O3 atrophies as atrophy score 2.

Endoscopically, intestinal metaplasia typically appears as grayish-white and slightly elevated plaques surrounded by mixed patchy pink and pale areas of the mucosa, forming an irregular uneven surface. A villous appearance, whitish mucosa, and rough mucosal surface are useful indicators for the endoscopic diagnosis of intestinal metaplasia. Intestinal metaplasia score 0 was defined as the absence of intestinal metaplasia, score 1 as the presence of intestinal metaplasia within the antrum, and score 2 as intestinal metaplasia extending into the corpus. The intestinal metaplasia score was calculated based on the diagnosis of metaplasia using white-light imaging.

An enlarged fold is defined as ≥ 5 mm width that is not flattened or is only partially flattened by stomach insufflation. The absence and presence of enlarged folds were scored as enlarged fold scores of 0 and 1, respectively.

Nodularity is a condition in which a miliary pattern similar to "goosebumps" is mainly located in the antrum. The absence and presence of nodularity were scored as nodularity scores of 0 and 1, respectively.

Diffuse redness refers to uniformly reddish mucosa with continuous expansion located in the non-atrophic mucosa, mainly in the corpus. The RAC is a condition in which collecting venules are arranged in the corpus. From a distance, the venules look like numerous dots; however, up close, the venules appear like a regular pattern of starfish-like shapes. The absence of diffuse redness, presence of mild diffuse redness or diffuse redness with RAC, and severe diffuse redness or diffuse redness without RAC were scored as diffuse redness scores of 0, 1, and 2, respectively.

Data collection and outcomes

We obtained data for cancer and participants background information from the endoscopic database of the Toyoshima Endoscopy Clinic from September 2008 to February 2020. Two expert endoscopists reviewed all images and scored them according to the Kyoto classification.

Clinical data of this study consisted of variables including gastric cancer type according to the Lauren classification, age, sex, and endoscopic gastritis score based on the Kyoto classification (Kyoto score, atrophy score, intestinal metaplasia score, enlarged folds score, nodularity score, and diffuse redness score).

The main outcome of this study was the differences in patient backgrounds and the endoscopic gastritis between patients with diffuse- and intestinal-type gastric cancers. To predict the Lauren type of cancer, this study developed a Lauren predictive background score using variables associated with the Lauren classification. We assessed the discrimination of the Lauren predictive background score using the receiver operating characteristic (ROC) curve, the corresponding area under the ROC curve (AUC), and the diagnostic accuracy of predicting the Lauren type of tumor.

We also compared *H. pylori*-infected patients with cancer (whole, diffuse-, and intestinal-type cancers, respectively) and cancer-free *H. pylori*-infected controls.

Statistical analyses

Univariate and multivariate analyses were conducted using a binomial logistic regression analysis. The multivariate analysis included age, sex, and each score of the Kyoto classification, excluding the Kyoto score. Age was categorized based on the average number of patients with gastric cancer. A multivariate analysis was conducted, using a backward stepwise logistic regression, for variables with P values < 0.1; these values were determined by a univariate analysis. Regarding missing data, we used complete case analysis.

We developed the Lauren predictive background score based on the coefficients of a logistic regression model, using variables with P values < 0.05 in a multivariate analysis. The AUC for predicting intestinal-type cancer and the sensitivity, specificity, and accuracy of the Lauren predictive background score were measured. The optimal cut-off value of the ROC curve was calculated using the Youden index.

A two-sided P value of < 0.05 was considered statistically significant. Statistical analyses were performed using Ekuseru-Toukei 2015 (Social Survey Research Information company, Limited, Tokyo, Japan).

RESULTS

Patient characteristics

A total of 132 patients with *H. pylori*-positive gastric cancers (39 diffuse- and 93 intestinal-type, 105 early, and 27 advanced cancers) were included; 11 patients were excluded as they did not have an *H. pylori* infection, 104 due to successful eradication, and 16 due to an unavailable *H. pylori* status. The control group comprised 367 patients with *H. pylori*-positive gastritis (gastric cancer free controls). A total of 499 patients were enrolled in this study. We show patient flowchart in Figure 1. The mean age in this study was 54.9 ± 14.1 (range: 23-89) years, and 49.6% of patients were male; the Kyoto score was 4.93 ± 1.58, (atrophy: 1.53 ± 0.61; intestinal metaplasia: 0.83 ± 0.92; enlarged folds: 0.42 ± 0.49; nodularity: 0.33 ± 0.47; and diffuse redness: 1.83 ± 0.48).

H. pylori-positive gastritis with vs without gastric cancer

Univariate analysis showed that patients with *H. pylori*-infected cancer patients were older (66.4 *vs* 50.9 years) and had a higher Kyoto score (5.63 *vs* 4.69) than *H. pylori*-infected non-cancer patients. Among the scores of the items of the Kyoto classification, atrophy and intestinal metaplasia scores for gastric cancer were higher than those for cancer-free gastritis; however, nodularity scores for gastric cancer were lower than those for cancer-free gastritis. There was no significant difference in the enlarged folds and diffuse redness scores. Based on the results of a multivariate analysis, *H. pylori*-infected gastric cancer was independently associated with an age of 65 years or more [odds ratio (OR): 4.01], a high atrophy score (OR: 2.80), high intestinal metaplasia score (OR: 1.57), and a low nodularity score (OR: 0.51, Table 1).

H. pylori-infected gastritis with diffuse-type gastric cancer vs without gastric cancer

On comparing *H. pylori*-infected patients with diffuse-type cancer and those without gastric cancer (gastric cancer-free controls), a univariate analysis showed that patients with diffuse-type cancer were older (58.0 *vs* 50.9 years) and had a higher Kyoto score (5.33 *vs* 4.69), higher atrophy score, and higher intestinal metaplasia score than gastric cancer-free patients. In a multivariate analysis, a high atrophy score was independently associated with diffuse-type gastric cancer (Table 2).

H. pylori-infected gastritis with intestinal-type gastric cancer vs without gastric cancer

H. pylori-infected intestinal-type gastric cancer and *H. pylori*-infected non-cancer gastritis were compared. Univariate analysis showed that *H. pylori*-infected patients with intestinal-type gastric cancer were older (69.9 *vs* 50.9 years), comprised more of males (62.4% *vs* 47.7%), and had a higher Kyoto score (5.75 *vs* 4.69), higher atrophy score, higher intestinal metaplasia score, lower enlarged folds score, and lower nodularity score than those with non-cancer gastritis. Similar results were obtained in multivariate analysis (Table 3).

H. pylori-infected gastritis with diffuse- vs intestinal-type gastric cancer

Table 4 shows a comparison of endoscopic background gastritis between *H. pylori*-infected patients with diffuse- and intestinal-type cancers. Univariate analysis showed that patients with intestinal-type cancer were older (69.9 *vs* 58.0 years), comprised more of males (61.5% *vs* 37.6%), had a higher atrophy score (1.95 *vs* 1.69), higher intestinal metaplasia score (1.58 *vs* 0.97), lower enlarged folds score (0.28 *vs* 0.56), and lower nodularity score (0.10 *vs* 0.28). There was no significant difference in the Kyoto and diffuse redness scores. In a multivariate analysis, factors independently associated with intestinal-type cancer were an age of 65 years or more (coefficient: 1.98; OR: 7.26), male sex (coefficient: 1.02; OR: 2.78), high intestinal metaplasia score (coefficient: 0.68; OR: 1.97), and low enlarged folds score (coefficient: -1.31; OR: 0.27).

Based on the coefficients of a multivariate analysis, the equation for the scoring system was calculated based on an assumption that patients receive +2 points if they were aged 65 years or more, +1 point if they were male, +1 point if they had intestinal metaplasia, and -1 point if they had enlarged folds. We defined the Lauren predictive background score as the sum of these points, ranging from -1 to +4.

The ROC curve based on the Lauren predictive background score in 132 patients with diffuse- or intestinal-type cancer is shown in Figure 2. AUC of the Lauren predictive background score for predicting intestinal-type cancer was 0.828 (95% confidence interval: 0.744-0.912). The optimal cut-off value of the Lauren predictive background score for correlation with intestinal-type gastric cancer was +2, based on

Table 1 Endoscopic gastritis based on Kyoto classification of *Helicobacter pylori*-infected patients with *vs* without gastric cancer

	Gastric cancer (+)	Cancer (-)	Univariate analysis			Multivariate analysis		
			Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value
n	132	367						
Age, mean (SD), yr	66.4 (12.4)	50.9 (12.4)	1.099	1.078-1.120	< 0.001			
Age ≥ 65 yr, %	60.6	15.3	8.544	5.446-13.405	< 0.001	4.010	2.436-6.603	< 0.001
Male sex, %	55.3	47.7	1.357	0.910-2.024	0.134			
Atrophy score, mean (SD)	1.871 (0.336)	1.411 (0.642)	6.173	3.635-10.486	< 0.001	2.800	1.583-4.954	< 0.001
Intestinal metaplasia score, mean (SD)	1.402 (0.809)	0.624 (0.878)	2.570	2.031-3.253	< 0.001	1.567	1.188-2.067	0.001
Enlarged folds score, mean (SD)	0.364 (0.483)	0.441 (0.497)	0.723	0.480-1.090	0.121			
Nodularity score, mean (SD)	0.152 (0.360)	0.387 (0.488)	0.283	0.168-0.476	< 0.001	0.508	0.282-0.913	0.024
Diffuse redness score, mean (SD)	1.841 (0.507)	1.823 (0.466)	1.085	0.706-1.667	0.709			
Kyoto score, mean (SD)	5.629 (1.149)	4.687 (1.637)	1.568	1.342-1.831	< 0.001			

P value was calculated using the binomial logistic regression analysis. CI: Confidence interval; SD: Standard deviation.

Table 2 Endoscopic gastritis based on Kyoto classification of *Helicobacter pylori*-infected patients with diffuse-type gastric cancer *vs* without gastric cancer

	Diffuse-type cancer (+)	Cancer (-)	Univariate analysis			Multivariate analysis		
			Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value
n	39	367						
Age, mean (SD), yr	58.00 (13.00)	50.88 (12.41)	1.044	1.018-1.072	0.001			
Age ≥ 65 yr, %	28.2	15.3	2.182	1.027-4.634	0.042	1.434	0.633-3.246	0.388
Male sex, %	38.5	47.7	0.686	0.348-1.349	0.275			
Atrophy score, mean (SD)	1.692 (0.468)	1.411 (0.642)	2.327	1.223-4.428	0.010	2.327	1.223-4.428	0.010
Intestinal metaplasia score, mean (SD)	0.974 (0.903)	0.624 (0.878)	1.516	1.065-2.158	0.021	1.313	0.905-1.906	0.152
Enlarged folds score, mean (SD)	0.564 (0.502)	0.441 (0.497)	1.638	0.842-3.186	0.146			
Nodularity score, mean (SD)	0.282 (0.456)	0.387 (0.488)	0.622	0.300-1.290	0.202			
Diffuse redness score, mean (SD)	1.821 (0.556)	1.823 (0.466)	0.990	0.495-1.978	0.976			
Kyoto score, mean (SD)	5.333 (1.402)	4.687 (1.637)	1.306	1.044-1.632	0.019			

P value was calculated using the binomial logistic regression analysis. CI: Confidence interval; SD: Standard deviation.

the Youden index. The sensitivity, specificity, and accuracy of the Lauren predictive background score were 81.7%, 71.8%, and 78.8%, respectively.

DISCUSSION

This study showed that old age, male sex, the presence of endoscopic intestinal metaplasia, and the absence of endoscopic enlarged folds were independently associated with intestinal-type gastric cancer compared to diffuse-type cancer among *H. pylori*-infected patients. The Lauren predictive background score created based on these variables was good, with AUC of 0.828, sensitivity of 81.7%, and accuracy of 78.8%. It is well known that old age, male sex[2,27], and endoscopic intestinal metaplasia[28] are indicators of intestinal-type cancers and that endoscopic enlarged folds[5,29] are characteristics of diffuse-type tumors. The strength of this study is that

Table 3 Endoscopic gastritis based on Kyoto classification of *Helicobacter pylori*-infected patients with intestinal-type gastric cancer *vs* without gastric cancer

	Intestinal-type cancer (+)	Cancer (-)	Univariate analysis			Multivariate analysis		
			Odds ratio	95%CI	*P* value	Odds ratio	95%CI	*P* value
n	93	367						
Age, mean (SD), yr	69.86 (10.29)	50.88 (12.41)	1.138	1.107-1.169	< 0.001			
Age ≥ 65 yr, %	74.2	15.3	15.967	9.261-27.527	< 0.001	6.220	3.394-11.400	< 0.001
Male sex, %	62.4	47.7	1.818	1.140-2.900	0.012	1.794	0.955-3.372	0.069
Atrophy score, mean (SD)	1.946 (0.227)	1.411 (0.642)	15.312	6.147-38.144	< 0.001	6.167	2.321-16.382	< 0.001
Intestinal metaplasia score, mean (SD)	1.581 (0.697)	0.624 (0.878)	3.368	2.499-4.539	< 0.001	1.683	1.166-2.430	0.005
Enlarged folds score, mean (SD)	0.280 (0.451)	0.441 (0.497)	0.491	0.299-0.808	0.005	0.453	0.237-0.867	0.017
Nodularity score, mean (SD)	0.097 (0.297)	0.387 (0.488)	0.170	0.083-0.348	< 0.001	0.323	0.141-0.742	0.008
Diffuse redness score, mean (SD)	1.849 (0.488)	1.823 (0.466)	1.135	0.681-1.891	0.626			
Kyoto score, mean (SD)	5.753 (1.007)	4.687 (1.637)	1.696	1.407-2.004	< 0.001			

P value was calculated using the binomial logistic regression analysis. CI: Confidence interval; SD: Standard deviation.

independent variables related to cancer type were investigated using the currently vigorously studied endoscopic gastritis evaluation method (Kyoto classification), and Lauren predictive background score was newly created using these variables; moreover, the score was accurate. Predicting cancer types without a biopsy may lead to faster treatment choices. A pathological diagnosis before endoscopic resection, surgery, or chemotherapy is vital to determine the line of treatment of lesions[13-16]. However, cases in which there are differences between the histological diagnoses of biopsy and resected specimens amount to 20%–30% of all cases[30-32]. Biopsy results are supported when the Lauren predictive background score is consistent with the biopsy diagnosis; however, the treatment should be carefully selected when discrepancies are observed. Furthermore, some endoscopic features of cancer are indicated by the Lauren classification. For example, diffuse-type cancers are frequently located in the proximal stomach[33]. The endoscopic gross appearance of an elevated-type cancer predominantly indicated intestinal-type cancer, whereas flat and depressed types of cancers indicated difuse-type cancer[34,35]. In the early stages of gastric cancer, intestinal-type cancer is usually reddish, whereas diffuse-type cancer is pale. While magnifying with narrow-band imaging, a well-demarcated area[36] and a white opaque substance[37] serve as an indicator of intestinal-type cancer, an ill-defined area[36] and a high proportion of the area with an absent microsurface pattern[38] are specific markers for diffuse-type cancer. In contrast, our study is unique in predicting the Lauren classification from background information rather than tumor information. In the future, a combination of both background and tumor information may allow for more accurate predictions, and a diagnosis by artificial intelligence may help.

We previously showed that corpus-predominant gastritis (5.96) has a higher Kyoto score than pangastritis (5.21)[20]. Corpus-predominant gastritis and pangastritis are risk factors for intestinal- and diffuse-type cancers, respectively[39], and a similar tendency was observed in this study.

Next, this study demonstrated that the Kyoto score of gastric cancer patients was higher than that of cancer-free patients among *H. pylori*-infected participants, regardless of whether the cancer was diffuse- or intestinal-type. This result is concordant with that of a previous report by Sugimoto *et al*[21]. While examining each item of the Kyoto classification, atrophy and intestinal metaplasia showed a positive association with gastric cancer; however, nodularity was negatively correlated with gastric cancer. This tendency is also the same as that reported in a previous study[21]. Nodularity has been reported as a risk factor for stomach cancer in young patients[40]; however, our observation might indicate a negative association since it covers all ages. When we previously investigated the association of the ABC classification, which consisted of a combination of serum *H. pylori* antibody and pepsinogen,

Table 4 Endoscopic gastritis based on Kyoto classification of *Helicobacter pylori*-infected patients with diffuse- *vs* intestinal-type gastric cancer

	Diffuse-type	Intestinal-type	Univariate analysis			Multivariate analysis				
			Odds ratio	95%CI	*P* value	Coefficient	95%CI	Odds ratio	95%CI	*P* value
n	39	93								
Age, mean (SD), yr	58.00 (13.00)	69.86 (10.29)	1.091	1.051-1.132	< 0.001					
Age ≥ 65 yr, %	28.2	74.2	7.318	3.166-16.917	< 0.001	1.983	1.045, 2.921	7.263	2.843-18.553	< 0.001
Male sex, %	38.5	62.4	2.651	1.228-5.724	0.013	1.021	0.069, 1.973	2.776	1.071-7.193	0.036
Atrophy score, mean (SD)	1.692 (0.468)	1.946 (0.227)	7.822	2.530-24.188	< 0.001	0.727	-0.927, 2.381	2.069	0.396-10.816	0.389
Intestinal metaplasia score, mean (SD)	0.974 (0.903)	1.581 (0.697)	2.473	1.544-3.959	< 0.001	0.678	0.128, 1.228	1.970	1.136-3.413	0.016
Enlarged folds score, mean (SD)	0.564 (0.502)	0.280 (0.451)	0.300	0.138-0.653	0.002	-1.308	-2.261, -0.356	0.270	0.104-0.701	0.007
Nodularity score, mean (SD)	0.282 (0.456)	0.097 (0.297)	0.273	0.102-0.726	0.009	-0.237	-1.621, 1.147	0.789	0.198-3.149	0.737
Diffuse redness score, mean (SD)	1.821 (0.556)	1.849 (0.488)	1.116	0.545-2.288	0.764					
Kyoto score, mean (SD)	5.333 (1.402)	5.753 (1.007)	1.355	0.987-1.860	0.060					

P value was calculated using the binomial logistic regression analysis. CI: Confidence interval; SD: Standard deviation.

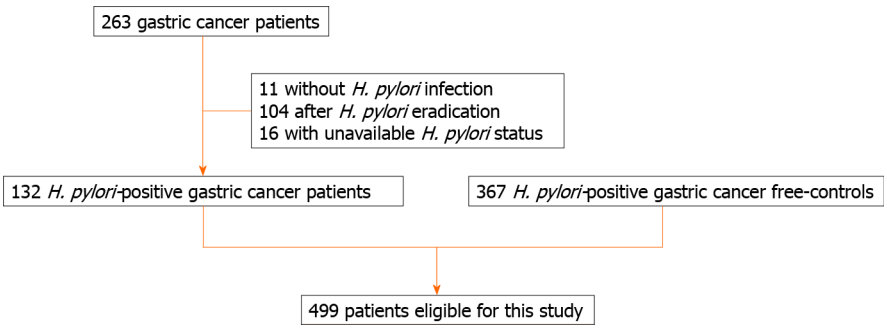

Figure 1 Patient flowchart. *H. pylori: Helicobacter pylori.*

with endoscopic gastritis, the simplified Kyoto score using only atrophy and intestinal metaplasia scores was more dramatically related to the ABC classifi-cation[27]. Combined with the results of this study, we suggest that nodularity and diffuse redness scores be not included in the gastric cancer risk score. Particularly, enlarged folds scores should be excluded from the risk score for intestinal-type cancer. However, further verifications are required for this matter.

This study has some limitations. The subjects of our study were limited to *H. pylori*-infected patients. Gastric cancer is detected even after *H. pylori* eradication[41]. Take *et al*[42] described an increased incidence of diffuse-type cancer more than 10 years after *H. pylori* eradication. Studying subjects after *H. pylori* eradication or *H. pylori*-uninfected subjects in the future is warranted. The gastric cancer-free control group in this study was extracted from a shorter period than the gastric cancer group. In the future, comparisons between the endoscopic background diagnosis of patients with gastric cancer (especially according to the Lauren classification) and that of non-cancer controls during the same period is desired. In addition, further investigations using prospective study designs are needed to evaluate the accuracy of the Lauren predictive

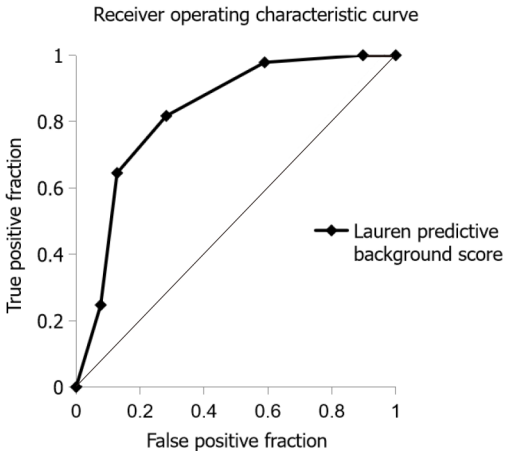

Figure 2 Receiver operating characteristic curve for predicting intestinal-type gastric cancer. Receiver operating characteristics curve was based on the Lauren predictive background score in 132 patients with diffuse- or intestinal-type gastric cancer according to Lauren classification. The Lauren predictive background score was defined as a sum of the following points: +2 points for an age of 65 years or older, +1 point for male sex, +1 point for endoscopic intestinal metaplasia, and -1 point for endoscopic enlarged folds.

background score. The sample size for that study would be 26 (8 patients with diffuse type cancer, and 19 patients with intestinal type cancer).

CONCLUSION

In conclusion, patient backgrounds, such as age, sex, endoscopic intestinal metaplasia, and endoscopic enlarged folds are useful for predicting tumor type.

ARTICLE HIGHLIGHTS

Research background

The accurate diagnosis of gastric cancer using the Lauren classification is crucial.

Research motivation

The relationship between the Lauren classification and endoscopic findings based on the Kyoto classification is not clear.

Research objectives

To investigate the background patient characteristics and endoscopic gastritis of patients with diffuse- and intestinal-type gastric cancers, focusing on *Helicobacter pylori (H. pylori)*-infected patients.

Research methods

This study included participants who underwent esophagogastroduodenoscopy at the Toyoshima Endoscopy Clinic. The endoscopy-based Kyoto classification of gastritis consisted of atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. The effects of age, sex, and Kyoto classification score on gastric cancer according to the Lauren classification were analyzed.

Research results

A total of 499 *H. pylori*-infected patients (49.6% males; average age, 54.9 years) were enrolled. A total of 132 patients with gastric cancer (39 diffuse- and 93 intestinal-type) and 367 cancer-free controls were eligible. Gastric cancer was independently associated with age ≥ 65 years, high atrophy score, high intestinal metaplasia score, and low nodularity score when compared to the control. Factors independently associated with intestinal-type cancer were age ≥ 65 years, male sex, high intestinal metaplasia score, and low enlarged folds score when compared to diffuse-type cancer. The Lauren predictive background score was defined as the sum of the following points: +2 points for an age of ≥ 65 years, +1 point for male sex, +1 point for intestinal

metaplasia, and -1 point for enlarged folds. The area under the curve of the Lauren predictive background score was 0.828 for predicting intestinal-type tumors. With a cut-off of +2, the sensitivity and specificity of the Lauren predictive background score were 81.7% and 71.8%, respectively.

Research conclusions

Patient backgrounds such as age, sex, endoscopic intestinal metaplasia, and endoscopic enlarged folds are useful for predicting tumor type.

Research perspectives

Studying subjects after *H. pylori* eradication or *H. pylori*-uninfected subjects in the future is warranted. Furthermore, comparisons between the endoscopic background diagnosis of patients with gastric cancer (especially according to Lauren classification) and that of non-cancer controls is desired.

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META-ANALYSIS

Meta-analysis and trial sequential analysis of randomized evidence comparing general anesthesia *vs* regional anesthesia for laparoscopic cholecystectomy

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Abstract

BACKGROUND

In an effort to further reduce the morbidity and mortality profile of laparoscopic cholecystectomy, the outcomes of such procedure under regional anesthesia (RA) have been evaluated. In the context of cholecystectomy, combining a minimally invasive surgical procedure with a minimally invasive anesthetic technique can potentially be associated with less postoperative pain and earlier ambulation.

AIM

To evaluate comparative outcomes of RA and general anesthesia (GA) in patients undergoing laparoscopic cholecystectomy.

METHODS

A comprehensive systematic review of randomized controlled trials with subsequent meta-analysis and trial sequential analysis of outcomes were conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards.

RESULTS

Thirteen randomized controlled trials enrolling 1111 patients were included. The study populations in the RA and GA groups were of comparable age (P = 0.41),

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gender (P = 0.98) and body mass index (P = 0.24). The conversion rate from RA to GA was 2.3%. RA was associated with significantly less postoperative pain at 4 h [mean difference (MD): - 2.22, P < 0.00001], 8 h (MD: -1.53, P = 0.0006), 12 h (MD: -2.08, P < 0.00001), and 24 h (MD: -0.90, P < 0.00001) compared to GA. Moreover, it was associated with significantly lower rate of nausea and vomiting [risk ratio (RR): 0.40, P < 0.0001]. However, RA significantly increased postoperative headaches (RR: 4.69, P = 0.03), and urinary retention (RR: 2.73, P = 0.03). The trial sequential analysis demonstrated that the meta-analysis was conclusive for most outcomes, with the exception of a risk of type 1 error for headache and urinary retention and a risk of type 2 error for total procedure time.

CONCLUSION

Our findings indicate that RA may be an attractive anesthetic modality for day-case laparoscopic cholecystectomy considering its associated lower postoperative pain and nausea and vomiting compared to GA. However, its associated risk of urinary retention and headache and lack of knowledge on its impact on procedure-related outcomes do not justify using RA as the first line anesthetic choice for laparoscopic cholecystectomy.

Key Words: Laparoscopic cholecystectomy; Regional anesthesia; General anesthesia; Laparoscopy; Level 1 evidence; Meta-analysis

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Core Tip: Despite the existence of solid level 1 evidence from multiple randomized controlled trials on comparative outcomes of general anesthesia and regional anesthesia (RA) in laparoscopic cholecystectomy and demonstration of feasibility of laparoscopic cholecystectomy under RA, lack of knowledge on the impact of RA on specific procedure related outcomes may discourage surgeons from selecting RA as the first choice of anesthesia for laparoscopic cholecystectomy. Considering our findings, we encourage use of RA in patients who are not fit for general anesthesia but do not hesitate to highlight that available evidence does not justify using RA as the first line anesthetic choice for laparoscopic cholecystectomy.

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INTRODUCTION

Gallstone disease is thought to occur in approximately 15% of the population of whom 20% are symptomatic[1]. Laparoscopic cholecystectomy is the gold standard treatment for symptomatic gallstone disease and one of the most commonly performed general surgical procedures[1]. This minimally invasive procedure results in a shorter length of hospital stay and quicker overall recovery compared with the traditional open approach[2].

Traditionally, laparoscopic cholecystectomy is carried out under general anesthesia (GA). Some argue the endotracheal intubation is required to prevent aspiration or respiratory complications secondary to the induction of pneumoperitoneum[3]. Furthermore, GA is associated with rapid onset of action and reduces the procedure related stress[4].

In an effort to further reduce the morbidity and mortality profile of laparoscopic cholecystectomy, the outcomes of such procedure under regional anesthesia (RA) have been evaluated[5]. RA, including spinal anesthesia (SA) and epidural anesthesia (EA), confers the advantages of avoidance of both paralytic agents and endotracheal intubation[6]. Although combining a minimally invasive surgical procedure with a minimally invasive anesthetic technique would appear attractive, it's use is currently

limited[7]. Nevertheless, it has been demonstrated that the use of neuraxial anesthetics decreases postoperative thromboembolic events, myocardial infarction as well as overall mortality[8]. Moreover, RA has been demonstrated to be associated with less postoperative pain and earlier ambulation in patients undergoing laparoscopic cholecystectomy[7].

The purpose of our study was to conduct a comprehensive review of the current literature and conduct a meta-analysis of randomized trials to evaluate comparative outcomes of RA and GA in patients undergoing laparoscopic cholecystectomy. Furthermore, we aimed to conduct a trial sequential analysis to assess the robustness of our meta-analysis findings.

MATERIALS AND METHODS

Design

We highlighted our eligibility criteria, methods, and evaluated outcomes in a review protocol. Our study was carried out in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards[9].

Inclusion criteria

(1) Randomized controlled trials (RCTs); (2) Including patients aged > 18 years old of any gender; (3) Including patients undergoing laparoscopic cholecystectomy under RA; and (4) Comparing laparoscopic cholecystectomy under GA.

Exclusion criteria

(1) Observational studies, case series, case reports, and letters; (2) Including patients undergoing open cholecystectomy; and (3) Including patients undergoing laparoscopic intraoperative cholangiogram with or without common bile duct exploration.

Outcomes

Primary outcome measures were defined as the post-operative pain intensity assessed on a 10 mm visual analogue scale (VAS) at 4 h, 6 h, 12 h and 24 h. The pain intensity data described by other means than a 10 mm VAS were standardized to such a scale. Operative time, total operative and anesthetic time, urinary retention (defined as inability to urinate spontaneously during the early postoperative period requiring application of heat or urinary catheterization), nausea and vomiting, headache, and hypotension (defined as a reduction of > 30% in mean arterial pressure or systolic blood pressure < 90 mmHg) were the secondary outcome parameters.

Literature search strategy

Three authors independently searched the following electronic databases: MEDLINE, EMBASE, CINAHL, and the Cochrane Central Register of Controlled Trials (CENTRAL). The literature search was performed on 08 March 2019. Our search strategy was adapted according to thesaurus headings, search operators and limits in the aforementioned databases (Supplementary Table 1). Furthermore, we searched World Health Organization International Clinical Trials Registry (http://apps.who.int/trialsearch/), ClinicalTrials.gov (http://clinicaltrials.gov/), and ISRCTN Register (http://www.isrctn.com/) to identify ongoing and unpublished studies. Moreover, the reference lists of identified articles were screened for further potentially eligible trials.

Selection of studies

The yielded search results were evaluated by two reviewers. Following evaluation of their titles, abstracts and full-texts of identified articles, those studies that met the inclusion criteria of our study were selected for inclusion in data synthesis. Disagreements in selection of studies were resolved by discussion between the reviewers. However, if the discrepancies remained unresolved, a third reviewer was involved.

Data extraction and management

We created an electronic data extraction spreadsheet according to the Cochrane's recommendations for intervention reviews. The data extraction spreadsheet was pilot-tested in randomly selected articles and adjusted accordingly. The following information were extracted from the included studies by two independent authors: (1)

Study-related data (first author, publication year, country of origin of the corresponding author, journal in which the study was published, study design, and study size); (2) Baseline demographic and clinical information of the study populations (age, gender, weight, height, body mass index, American Society of Anesthesiologists classification); (3) Type of anesthetic agent used in the RA group or any additional medications used, conversion from SA to GA; (4) Primary and secondary outcome data; and (5) Disagreements during data extraction and management were resolved following consultation with a third independent author.

Assessment of risk of bias

The methodological quality and risk of bias assessment were carried out by two authors using the Cochrane's tool[10]. The Cochrane's tool classifies studies into low, unclear and high risk of bias following evaluating and determining the risk of selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of bias. We resolved discrepancies in risk of bias assessment by discussion between the assessing authors. Nevertheless, if no agreement could be reached, a third reviewer was involved as an adjudicator.

Summary measures and synthesis

For urinary retention, nausea and vomiting, and headache we calculated the risk ratio (RR) as the summary measures. The RR is the risk of an adverse event in the RA group compared to the GA group. An RR of less than one would favor the SA group. For VAS score at 4 h, 6 h, 12 h and 24 h, operative time, and total operative and anesthetic time we calculated the mean difference (MD) between the two groups.

The number of individual patients was used as the unit of analysis for all outcome parameters. Information with regards to dropouts, withdrawals and any other missing data were recorded. We planned to contact authors of the included studies where information about our outcome of interest was not reported. Our final analysis respected the intention-to-treat concept.

One independent review author entered the extracted data into Review Manager 5.3 software for data synthesis[10]. The entered data were subsequently checked by a second independent review author. Random-effects or fixed-effect modelling were used, as appropriate, for analysis. Only when significant between-study heterogeneity existed, random-effects models were applied. This has previously been defined by Higgins *et al*[10]. We reported the results of our analysis for each outcome parameter in a forest plot with 95% confidence intervals (CIs).

Heterogeneity among the studies was assessed using the Cochran Q test (χ^2). We quantified inconsistency by calculating I^2 and interpreted it using the following guide: 0% to 25% might not be important; 25% to 75%: may represent moderate heterogeneity; 75% to 100% may represent substantial heterogeneity. Moreover, where more than 10 studies were available in analysis of an outcome parameter, funnel plots were planned to be constructed in order to assess their symmetry to visually evaluate publication bias.

We conducted sensitivity analyses to explore potential sources of heterogeneity and assess the robustness of our results. For each outcome parameter, we repeated the primary analysis using random-effects or fixed-effect models. Moreover, for each of our defined dichotomous variable, we calculated the pooled odds ratio or risk difference. Finally, we evaluated the effect of each study on the overall effect size and heterogeneity by repeating the analysis following excluding one study at a time.

Trial sequential analysis

Trial sequential analysis was performed for the outcomes reported by at least 5 trials using the trial sequential analysis software 0.9.5.5 Beta (Copenhagen Trial Unit, Copenhagen, Denmark). In order to control the risk of type 1 error, we planned to adjust the thresholds for the *Z* values using O'Brien-Fleming α-spending function; allowing the type I error risk to be restored to the desired maximum risk. Crossing the O'Brien-Fleming α-spending boundaries by a Z-curve would indicate statistical significance. Moreover, we penalised the *Z* values according to the strength of the available evidence and the number of repeated significance tests as defined by the law of the iterated logarithm. The risk of type 2 error was controlled using the β-spending function and futility boundaries. Crossing the futility boundaries by a Z-curve would indicate that the two interventions do not differ more than the anticipated intervention effect. Random or fixed effects modelling were applied as appropriate for the analyses. We handled the zero event trials by constant continuity correction which involved adding a continuity correction factor to the number of events and non-events in each

intervention group. A two-sided CI with 95% confidence level was used to indicate statistical significance. We estimated the information size for the analyses based on achievement of 80% power and 10% relative risk reduction between the two groups.

RESULTS

The literature search identified 1267 articles. After further evaluation of the identified articles, 13 RCTs[4,5,11-21] met our inclusion criteria (Figure 1). The included studies reported the outcomes of 1111 patients of whom 554 patients underwent laparoscopic cholecystectomy under RA and the remaining 557 patients had laparoscopic cholecystectomy under GA.

The date of publication and country of origin, journal, and study design of the included studies are presented in Table 1. Table 2 presents baseline demographic and clinical characteristics of the study populations. There was no significant difference in mean age (P = 0.41), gender (P = 0.98) and body mass index (P = 0.24) between two groups. There were 13 conversion from RA to GA. Table 3 demonstrates details of anesthetic agent used in the RA group in the included studies

Methodological appraisal

Figure 2 presents the risk of bias assessment of the included RCT. Eleven studies had low risk of selection bias and the remaining two had unclear risk of selection bias due to not providing information about the allocation concealment. All included studies had high risk of performance bias due to lack of blinding. Three studies had low risk of detection bias as they blinded the outcome assessor. However, 9 studies had high risk of such bias. All included studies had low risk of attrition and reporting bias.

Data synthesis

Outcomes are summarized in Figure 3.

VAS score at 4 h: Seven studies (539 patients) reported the VAS score at 4 h postoperatively as one of their outcomes. The pooled analysis demonstrated that RA was associated with significantly less postoperative pain at 4 h following surgery (MD: -2.22, 95%CI: -3.10 to -1.34, P < 0.00001). The heterogeneity among the studies was significant (I^2 = 94%, P < 0.00001).

VAS score at 8 h: Five studies reported the VAS score at 8 h as an outcome. The pooled analysis which included 430 patients demonstrated that RA was associated with significantly lower pain 8 h following laparoscopic cholecystectomy (MD: -1.53, 95%CI: -2.41 to -0.66), P = 0.0006). The between-studies heterogeneity was significant (I^2 = 89%, P < 0.00001).

VAS score at 12 h: Five studies including 473 patients reported this outcome. The meta-analysis demonstrated RA was associated with significantly lower postoperative pain at 12 h following surgery when compared to GA (MD: -2.08, 95%CI: -2.58 to -1.58, P < 0.00001). Significant heterogeneity existed among the included studies (I^2 = 84%, P < 0.0001).

VAS score at 24 h: Seven studies (583 patients) reported postoperative VAS score at 24 h in their study groups. The pooled analysis demonstrated that there was a significantly lower postoperative pain at 24 h in favor of RA (MD: -0.90, 95%CI: -1.28 to -0.53, P < 0.00001). The heterogeneity among the included studies was considerable (I^2 = 87%, P < 0.00001).

Nausea and vomiting: Nine studies (811 patients) reported postoperative nausea and vomiting as an outcome in their intervention groups. The nausea and vomiting rates in the RA and GA groups were 6.2% and 15.7%, respectively. There was a significantly lower rate of nausea and vomiting in favor of RA compared to GA (RR: 0.40, 95%CI: 0.26-0.61, P < 0.0001). Low heterogeneity existed among the included studies (I^2 = 0%, P = 0.49).

Headache: Four studies (631 patients) reported post-operative headache as one of their outcomes. The rate of headache in the RA group was 3.2% while it was only 0.3% in the GA group. The pooled analysis demonstrated that RA was associated with significantly higher rate of postoperative headaches compared to GA (RR: 4.69, 95%CI: 1.21-18.21, P = 0.03). The between-study heterogeneity was low (I^2 = 0%, P = 0.98).

Table 1 Summary characteristics of included studies

Ref.	Year	Country	Journal	Design	Total number of patients	GA	RA
Majedi *et al*[15]	2019	Iran	*Advanced Biomedical Research*	RCT	80	40	40
Sharaf *et al*[19]	2018	Pakistan	*Anaesthesia, Pain and Intensive Care*	RCT	120	60	60
Donmez *et al*[11]	2017	Turkey	*Annals of Surgical Treatment and Research*	RCT	49	25	24
Kalaivani *et al*[14]	2014	India	*Journal of Clinical and Diagnostic Research*	RCT	50	25	25
Prasad *et al*[17]	2014	India	*Journal of Evolution of Medical and Dental Sciences*	RCT	60	30	30
Ellakany *et al*[12]	2013	Egypt	*Egyptian Journal of Anaesthesia*	RCT	40	20	20
Tiwari *et al*[20]	2013	India	*Journal of Minimal Access Surgery*	RCT	235	114	110
Bessa *et al*[5]	2012	Egypt	*Journal of Laparoendoscopic and Advanced Surgical Techniques*	RCT	180	90	90
Ross *et al*[18]	2012	United States	*Surgical Endoscopy*	RCT	20	10	10
Mehta *et al*[16]	2010	India	*Anesthesia, Essays and Researches*	RCT	60	30	30
Imbelloni *et al*[13]	2010	Brazil	*Revista Brasileira de Anestesiologia*	RCT	68	33	35
Bessa *et al*[21]	2010	Egypt	*Journal of Laparoendoscopic and Advanced Surgical Techniques*	RCT	60	30	30
Tzovaras *et al*[4]	2008	Greece	*Archives of Surgery*	RCT	100	50	50

RCT: Randomized controlled trial; GA: General anesthesia; RA: Regional anesthesia.

Table 2 Demography and clinical characteristics of the patients

Ref.	Age		Male:female ratio		BMI		ASA I: II: III	
	GA	RA	GA	RA	GA	RA	GA	RA
Majedi *et al*[15]	50.1 ± 9.78	52.06 ± 15.03	14:26	16:24	NR	NR	NR	NR
Sharaf *et al*[19]	44.07 ± 5.62	42.57 ± 5.77	0:60	0:60	25.41 ± 2.36	26 ± 2.31	14:46:0	22:38:0
Donmez *et al*[11]	45 ± 13	45 ± 14	18:07	18:6	28.75 ± 4.5	30.63 ± 3.6	18:7:0	16:6:2
Kalaivani *et al*[14]	47.84 ± 10.49	45 ± 11.73	08:17	10:15	NR	NR	NR	NR
Prasad *et al*[17]	38.5 ± 9.83	35.06 ± 7.5	25:5	17:13	23.5 ± 1.98	22.96 ± 2.98	23:7:0	22:8:0
Ellakany *et al*[12]	44.3 ± 13.2	45.9 ± 13.6	07:13	8:12	30 ± 3.9	29.8 ± 4.1	NR	NR
Tiwari *et al*[20]	46.1 ± 12.9	45.07 ±13.19	16:98	13:96	NR	NR	NR	NR
Bessa *et al*[5]	44 (19-50)	40 (16-50)	8:82	11:79	29.1 (23.4-33.1)	28.7 (22.8-34)	NR	NR
Ross *et al*[18]	39.4 ± 11.7	44.9 ± 12.5	3:7	2:8	25.1 ± 4.6	26.1 ± 5.5	1:6:3	3:5:2
Mehta *et al*[16]	38.3	39.1	10:20	14:16	NR	NR	NR	NR
Imbelloni *et al*[13]	45.2 ± 12.1	41.1 ± 12.4	10:23	9:26	NR	NR	NR	NR
Bessa *et al*[21]	40.9 ± 11	41.4 ± 11.1	6:24	5:25	30.8 ± 6.6	31.3 ± 4.1	NR	NR
Tzovaras *et al*[4]	46 (26-65)	44 (23-65)	18:30	20:29	26 (19-30)	25 (18-30)	37:11:0	40:9:0

GA: General anesthesia; RA: Regional anesthesia; NR: Not reported; ASA: American Society of Anesthesiologists; BMI: Body mass index.

Urinary retention: Seven studies reported postoperative urinary retention as an outcome. The urinary retention rates in the RA and GA groups were 4.1% and 1.1%, respectively. The pooled analysis of 751 patients demonstrated that RA was associated with significantly higher postoperative urinary retention when compared to GA (RR: 2.73, 95%CI: 1.13-6.56), $P = 0.03$). There was low between-study heterogeneity ($I^2 = 0\%$, $P = 0.54$).

Operative time: Six studies reported the operative time as one of their outcomes. The pooled analysis included 681 patients and demonstrated that there was no significant

Table 3 Anesthetic agents used in the regional anesthesia group in each study

Ref.	Anesthetic agent used
Majedi *et al*[15]	18 mL of lidocaine 2% plus epinephrine (1:200000) plus 2 mL of sodium bicarbonate 8.4% and fentanyl 50 μg
Sharaf *et al*[19]	15 mg of hyperbaric bupivicaine and 25 μg fentanyl
Donmez *et al*[11]	hyperbaric bupivicaine 16mg and fentanyl 10 micrograms
Kalaivani *et al*[14]	15 mg of hyperbaric bupivicaine and 20 μg fentanyl
Prasad *et al*[17]	15 mg of heavy bupivicaine and 25 μg fentanyl
Ellakany *et al*[12]	5 mg plain bupivicaine and 25 μg fentanyl
Tiwari *et al*[20]	12.5 mg to 17.5 mg of hyperbaric bupivicaine
Bessa *et al*[5]	15 mg of hyperbaric bupivicaine and 20 mcg fentanyl
Ross *et al*[18]	20-25 mL of lidocaine 2%
Mehta *et al*[16]	0.3 mg/kg of hyperbaric bupivicaine 0.5%
Imbelloni *et al*[13]	15 mg of hyperbaric bupivicaine and 20 μg fentanyl
Bessa *et al*[21]	15 mg of hyperbaric bupivicaine and 20 μg fentanyl
Tzovaras *et al*[4]	15 mg of hyperbaric bupivicaine, 0.25 mg morphine and 20 μg fentanyl

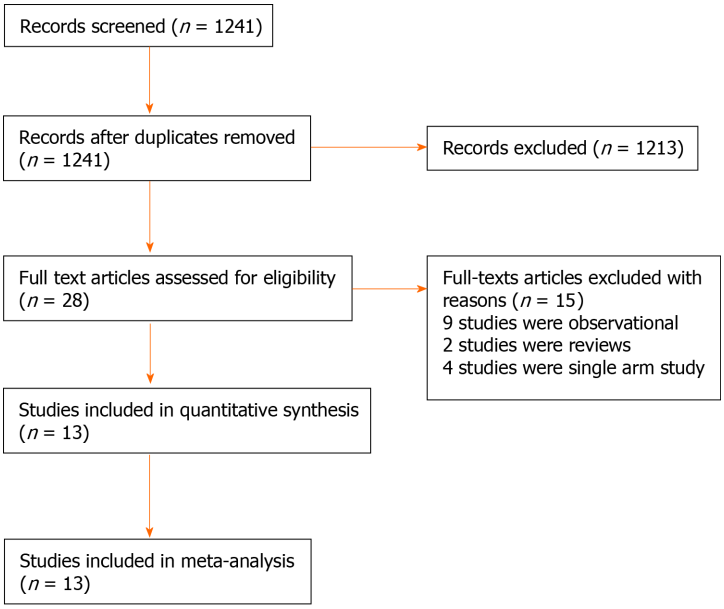


Figure 1 Study flow diagram.

difference in operative time between RA and GA (MD: -2.29, 95%CI: -7.00-2.41, P = 0.34). The heterogeneity among the included studies was significant (I^2 = 90%, P < 0.00001).

Total operative and anesthetic time: Six studies (491 patients) reported the total operative and anesthetic time as one of their outcomes. The meta-analysis demonstrated that there was no significant difference in total operative and anesthetic time between two groups (MD: -1.43, 95%CI: -5.39-2.53, P = 0.48). The heterogeneity between studies was high (I^2 = 77%, P = 0.0005).

Considering the data provided by the included studies, it was not possible to conduct analysis on hypotension which was one of our secondary outcomes.

Sensitivity analysis

Using random-effects fixed-effect models did not affect the pooled effect size in analysis of any of the reported outcomes, except urinary retention where the increased rate of urinary retention in the RA group became insignificant. Nevertheless,

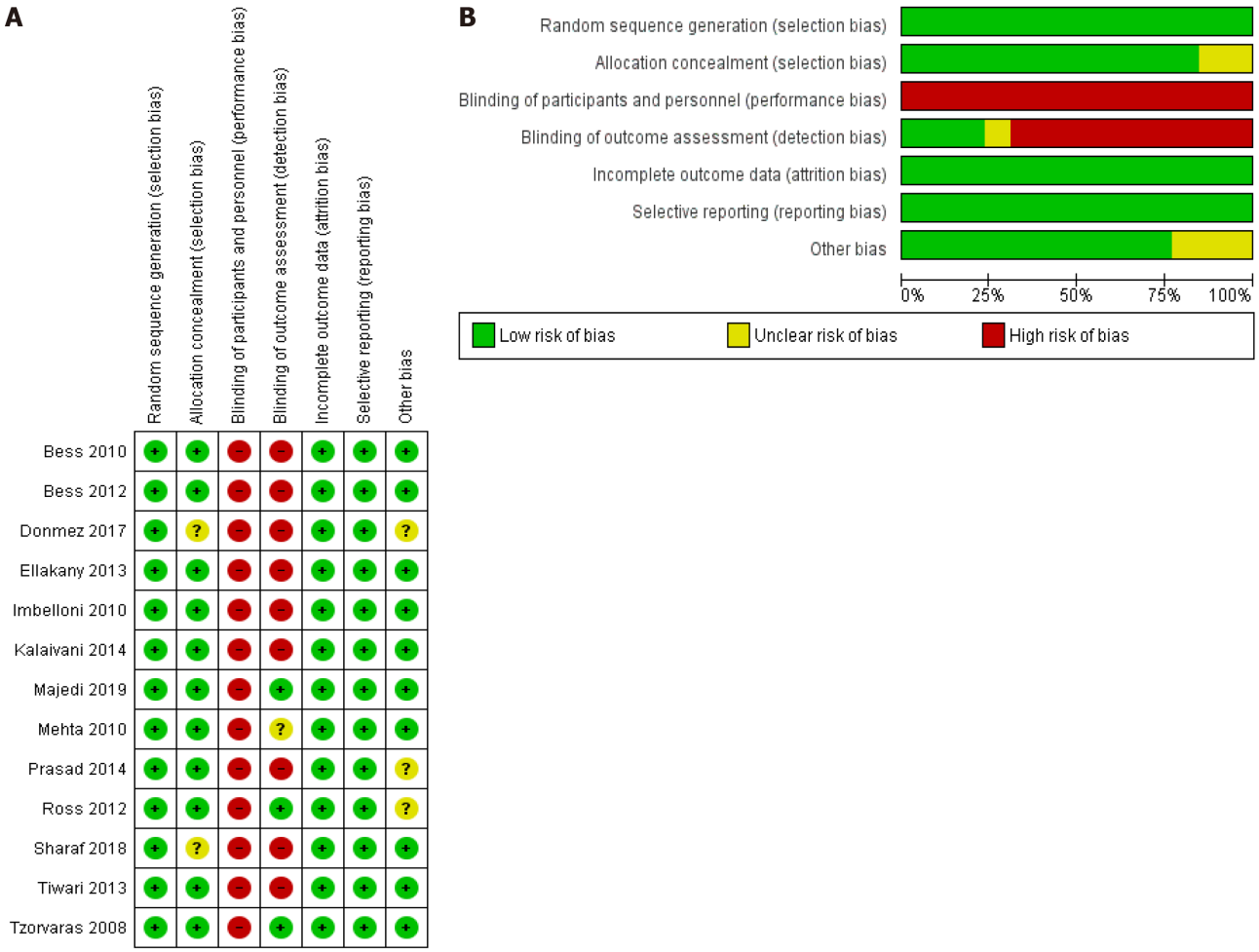


Figure 2 Risk of bias summary and graph showing authors' judgments about each risk of bias item. A: Risk of bias summary; B: Risk of bias graph.

considering heterogeneity of 0%, fixed-effect model was deemed more appropriate. The direction of pooled effect size remained unchanged when odds ratio, RR, or risk difference were calculated for dichotomous variables.

As two of our included studies, Bessa *et al*[21] and Bessa *et al*[5] were conducted by the same group, in order to ensure that potential overlapping patients are not included, we repeated all analyses with exclusion of Bessa *et al*[5] which did not change the direction of pooled effect size in any of our outcomes

Trial sequential analysis

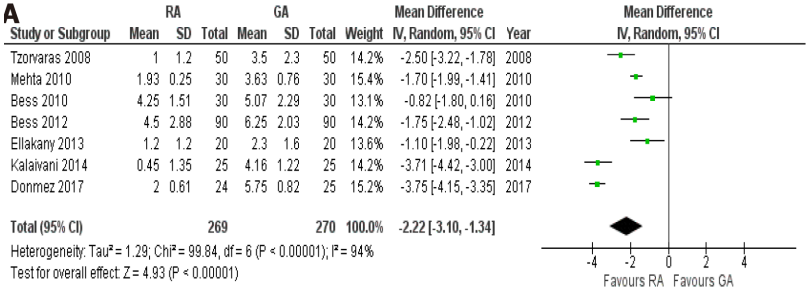
Outcomes are summarised in Figure 4.

VAS score at 4 h: The information size was calculated at 330 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favor of RA before and after the information size was reached and the penalized Z value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.

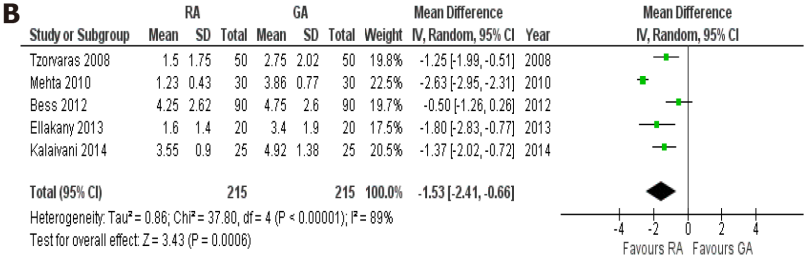
VAS score at 8 h: The information size was calculated at 324 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favor of RA before and after the information size was reached and the penalized Z value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.

VAS score at 12 h: The information size was calculated at 112 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favor of RA before and after the information size was reached and the penalized Z value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.

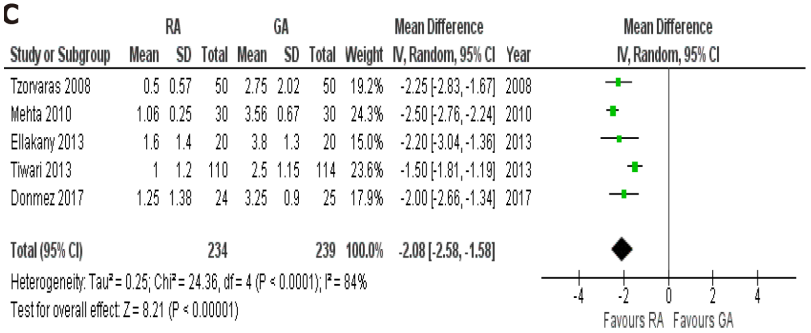
A


RA GA Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year IV, Random, 95% CI
Tzorvaras 2008 1 1.2 50 3.5 2.3 50 14.2% -2.50 [-3.22, -1.78] 2008
Mehta 2010 1.93 0.25 30 3.63 0.76 30 15.4% -1.70 [-1.99, -1.41] 2010
Bess 2010 4.25 1.51 30 5.07 2.29 30 13.1% -0.82 [-1.80, 0.16] 2010
Bess 2012 4.5 2.88 90 6.25 2.03 90 14.2% -1.75 [-2.48, -1.02] 2012
Ellakany 2013 1.2 1.2 20 2.3 1.6 20 13.6% -1.10 [-1.98, -0.22] 2013
Kalaivani 2014 0.45 1.35 25 4.16 1.22 25 14.2% -3.71 [-4.42, -3.00] 2014
Donmez 2017 2 0.61 24 5.75 0.82 25 15.2% -3.75 [-4.15, -3.35] 2017
Total (95% CI) 269 270 100.0% -2.22 [-3.10, -1.34]
Heterogeneity: Tau² = 1.29; Chi² = 99.84, df = 6 (P < 0.00001); I² = 94%
Test for overall effect: Z = 4.93 (P < 0.00001)
-4 -2 0 2 4
Favours RA Favours GA

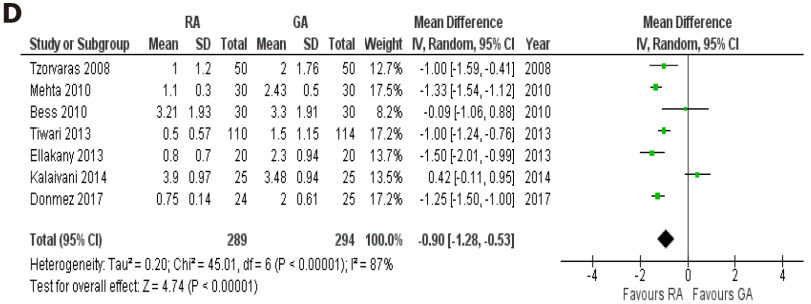
B


RA GA Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year IV, Random, 95% CI
Tzorvaras 2008 1.5 1.75 50 2.75 2.02 50 19.8% -1.25 [-1.99, -0.51] 2008
Mehta 2010 1.23 0.43 30 3.86 0.77 30 22.5% -2.63 [-2.95, -2.31] 2010
Bess 2012 4.25 2.62 90 4.75 2.6 90 19.7% -0.50 [-1.26, 0.26] 2012
Ellakany 2013 1.6 1.4 20 3.4 1.9 20 17.5% -1.80 [-2.83, -0.77] 2013
Kalaivani 2014 3.55 0.9 25 4.92 1.38 25 20.5% -1.37 [-2.02, -0.72] 2014
Total (95% CI) 215 215 100.0% -1.53 [-2.41, -0.66]
Heterogeneity: Tau² = 0.86; Chi² = 37.80, df = 4 (P < 0.00001); I² = 89%
Test for overall effect: Z = 3.43 (P = 0.0006)
-4 -2 0 2 4
Favours RA Favours GA

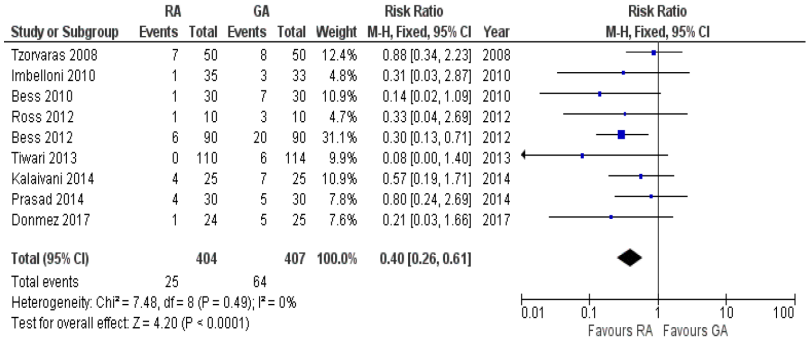
C


RA GA Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year IV, Random, 95% CI
Tzorvaras 2008 0.5 0.57 50 2.75 2.02 50 19.2% -2.25 [-2.83, -1.67] 2008
Mehta 2010 1.06 0.25 30 3.56 0.67 30 24.3% -2.50 [-2.76, -2.24] 2010
Ellakany 2013 1.6 1.4 20 3.8 1.3 20 15.0% -2.20 [-3.04, -1.36] 2013
Tiwari 2013 1 1.2 110 2.5 1.15 114 23.6% -1.50 [-1.81, -1.19] 2013
Donmez 2017 1.25 1.38 24 3.25 0.9 25 17.9% -2.00 [-2.66, -1.34] 2017
Total (95% CI) 234 239 100.0% -2.08 [-2.58, -1.58]
Heterogeneity: Tau² = 0.25; Chi² = 24.36, df = 4 (P < 0.0001); I² = 84%
Test for overall effect: Z = 8.21 (P < 0.00001)
-4 -2 0 2 4
Favours RA Favours GA

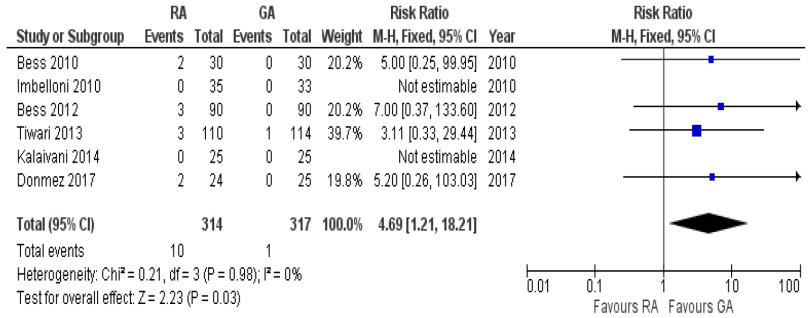
D


RA GA Mean Difference Mean Difference
Study or Subgroup Mean SD Total Mean SD Total Weight IV, Random, 95% CI Year IV, Random, 95% CI
Tzorvaras 2008 1 1.2 50 2 1.76 50 12.7% -1.00 [-1.59, -0.41] 2008
Mehta 2010 1.1 0.3 30 2.43 0.5 30 17.5% -1.33 [-1.54, -1.12] 2010
Bess 2010 3.21 1.93 30 3.3 1.91 30 8.2% -0.09 [-1.06, 0.88] 2010
Tiwari 2013 0.5 0.57 110 1.5 1.15 114 17.2% -1.00 [-1.24, -0.76] 2013
Ellakany 2013 0.8 0.7 20 2.3 0.94 20 13.7% -1.50 [-2.01, -0.99] 2013
Kalaivani 2014 3.9 0.97 25 3.48 0.94 25 13.5% 0.42 [-0.11, 0.95] 2014
Donmez 2017 0.75 0.14 24 2 0.61 25 17.2% -1.25 [-1.50, -1.00] 2017
Total (95% CI) 289 294 100.0% -0.90 [-1.28, -0.53]
Heterogeneity: Tau² = 0.20; Chi² = 45.01, df = 6 (P < 0.00001); I² = 87%
Test for overall effect: Z = 4.74 (P < 0.00001)
-4 -2 0 2 4
Favours RA Favours GA

E


RA GA Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year M-H, Fixed, 95% CI
Tzorvaras 2008 7 50 8 50 12.4% 0.88 [0.34, 2.23] 2008
Imbelloni 2010 1 35 3 33 4.8% 0.31 [0.03, 2.87] 2010
Bess 2010 1 30 7 30 10.9% 0.14 [0.02, 1.09] 2010
Ross 2012 1 10 3 10 4.7% 0.33 [0.04, 2.69] 2012
Bess 2012 6 90 20 90 31.1% 0.30 [0.13, 0.71] 2012
Tiwari 2013 0 110 6 114 9.9% 0.08 [0.00, 1.40] 2013
Kalaivani 2014 4 25 7 25 10.9% 0.57 [0.19, 1.71] 2014
Prasad 2014 4 30 5 30 7.8% 0.80 [0.24, 2.69] 2014
Donmez 2017 1 24 5 25 7.6% 0.21 [0.03, 1.66] 2017
Total (95% CI) 404 407 100.0% 0.40 [0.26, 0.61]
Total events 25 64
Heterogeneity: Chi² = 7.48, df = 8 (P = 0.49); I² = 0%
Test for overall effect: Z = 4.20 (P < 0.0001)
0.01 0.1 1 10 100
Favours RA Favours GA

F


RA GA Risk Ratio Risk Ratio
Study or Subgroup Events Total Events Total Weight M-H, Fixed, 95% CI Year M-H, Fixed, 95% CI
Bess 2010 2 30 0 30 20.2% 5.00 [0.25, 99.95] 2010
Imbelloni 2010 0 35 0 33 Not estimable 2010
Bess 2012 3 90 0 90 20.2% 7.00 [0.37, 133.60] 2012
Tiwari 2013 3 110 1 114 39.7% 3.11 [0.33, 29.44] 2013
Kalaivani 2014 0 25 0 25 Not estimable 2014
Donmez 2017 2 24 0 25 19.8% 5.20 [0.26, 103.03] 2017
Total (95% CI) 314 317 100.0% 4.69 [1.21, 18.21]
Total events 10 1
Heterogeneity: Chi² = 0.21, df = 3 (P = 0.98); I² = 0%
Test for overall effect: Z = 2.23 (P = 0.03)
0.01 0.1 1 10 100
Favours RA Favours GA

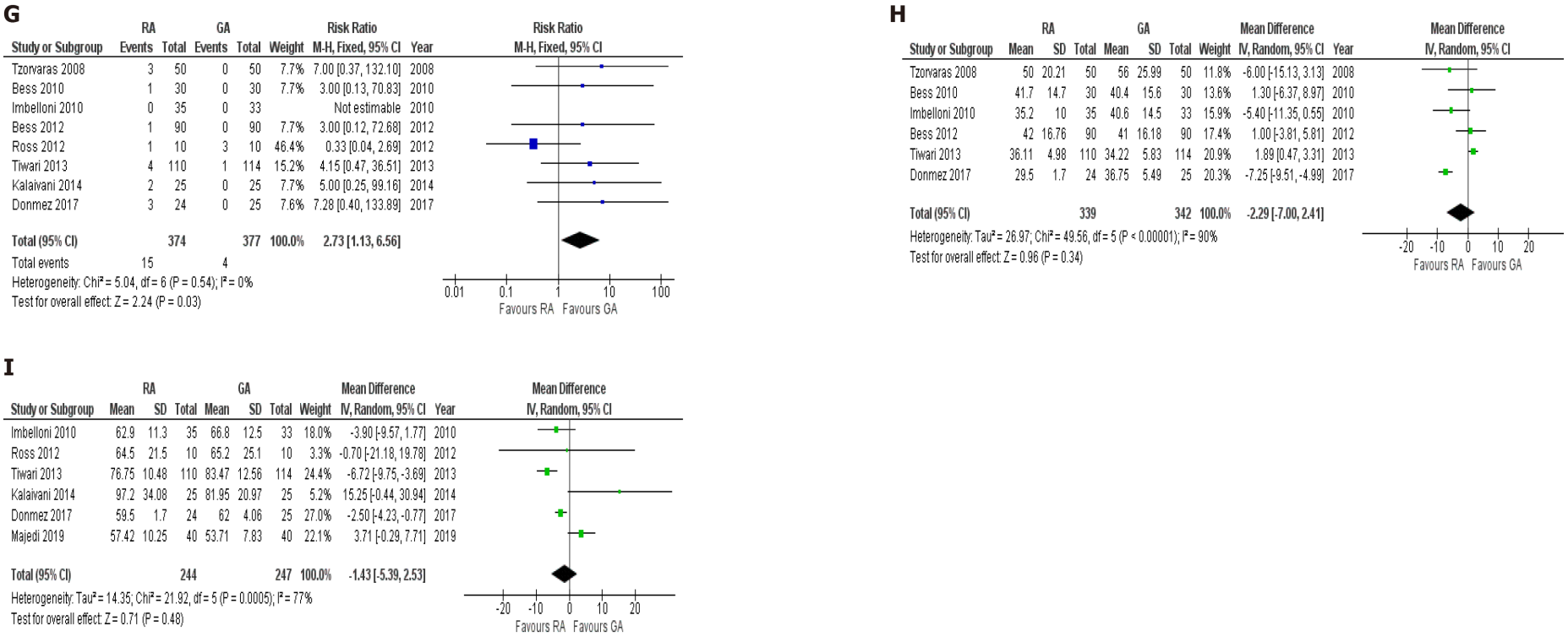
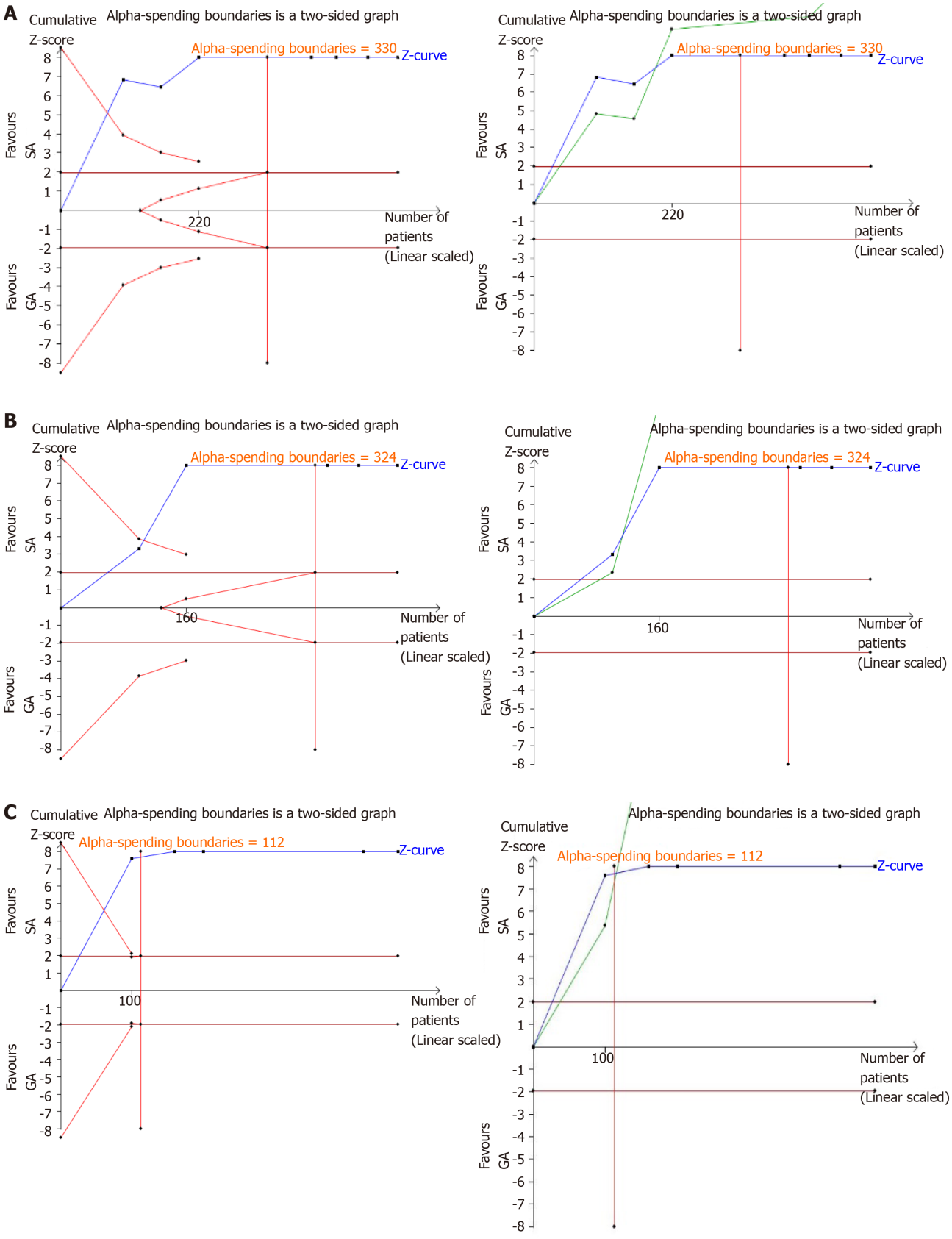
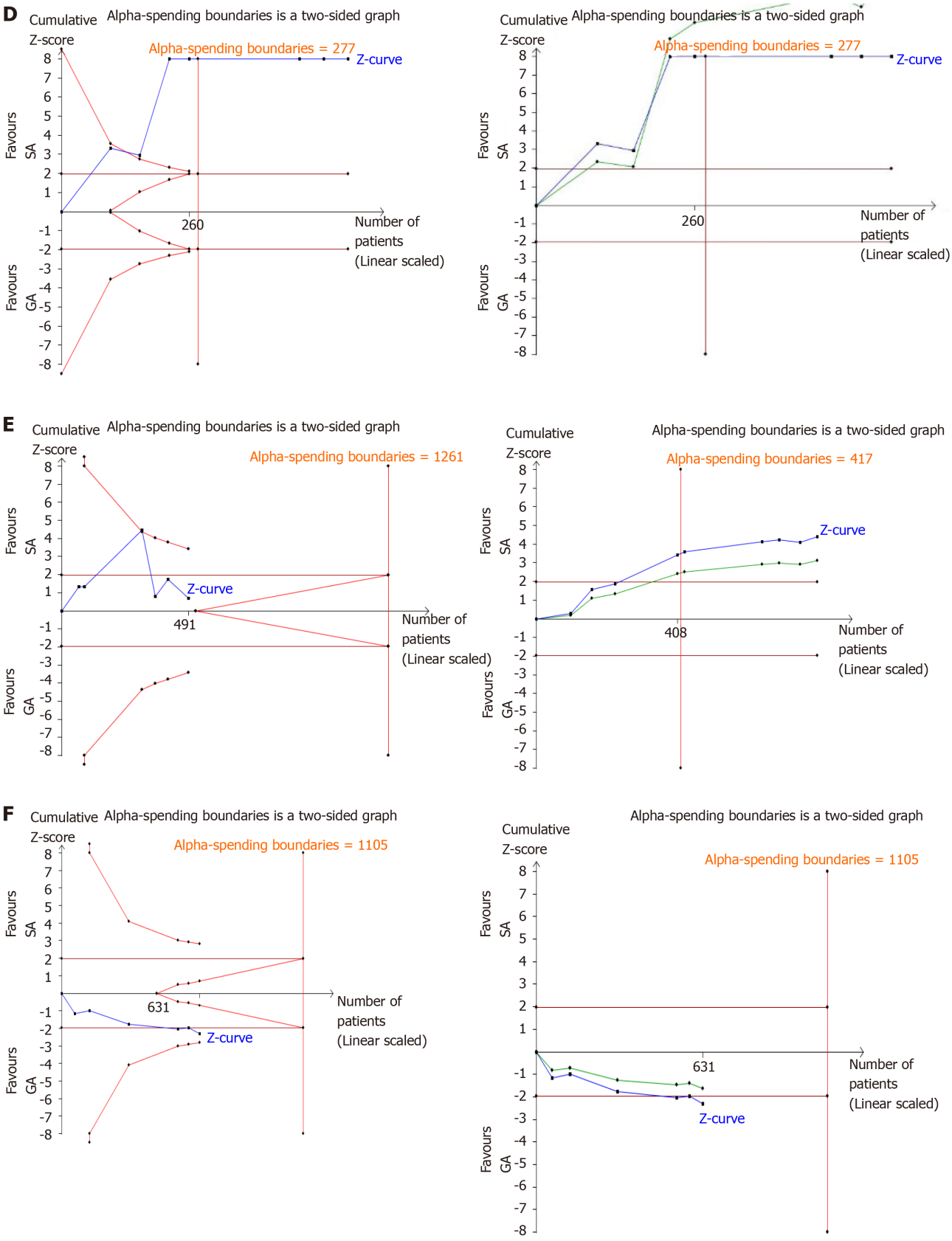


Figure 3 Forest plots of comparison. A: Visual analogue scale (VAS) at 4 h; B: VAS at 8 h; C: VAS at 12 h; D: VAS at 24 h; E: Nausea and vomiting; F: Headache; G: Urinary retention; H: Operative time; I: Total operative and anesthetic. The solid squares denote the risk ratios or mean difference. The horizontal lines represent the 95% confidence intervals, and the diamond denotes the pooled effect size. M-H: Mantel Haenszel test; RA: Regional anesthesia; GA: General anesthesia; CI: Confidence interval; SD: Standard deviation.

VAS score at 24 h: The information size was calculated at 277 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favour of RA before and after the information size was reached and the penalized *Z* value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.

Nausea and vomiting: The information size was calculated at 417 patients. The Z-curve crossed the conventional boundaries and alpha-spending boundaries in favor of RA before and after the information size was reached and the penalized *Z* value remained greater than 1.96; therefore, the meta-analysis was conclusive and the risk of type 1 error was minimal.


A
Cumulative Z-score
Alpha-spending boundaries is a two-sided graph
Alpha-spending boundaries = 330
Z-curve
Favours SA
Favours GA
220
Number of patients (Linear scaled)
B
Alpha-spending boundaries = 324
160
C
Alpha-spending boundaries = 112
100


D
Cumulative Z-score
Alpha-spending boundaries is a two-sided graph
Alpha-spending boundaries = 277
Z-curve
Favours SA
Favours GA
260
Number of patients (Linear scaled)
E
Alpha-spending boundaries = 1261
491
Alpha-spending boundaries = 417
408
F
Alpha-spending boundaries = 1105
631

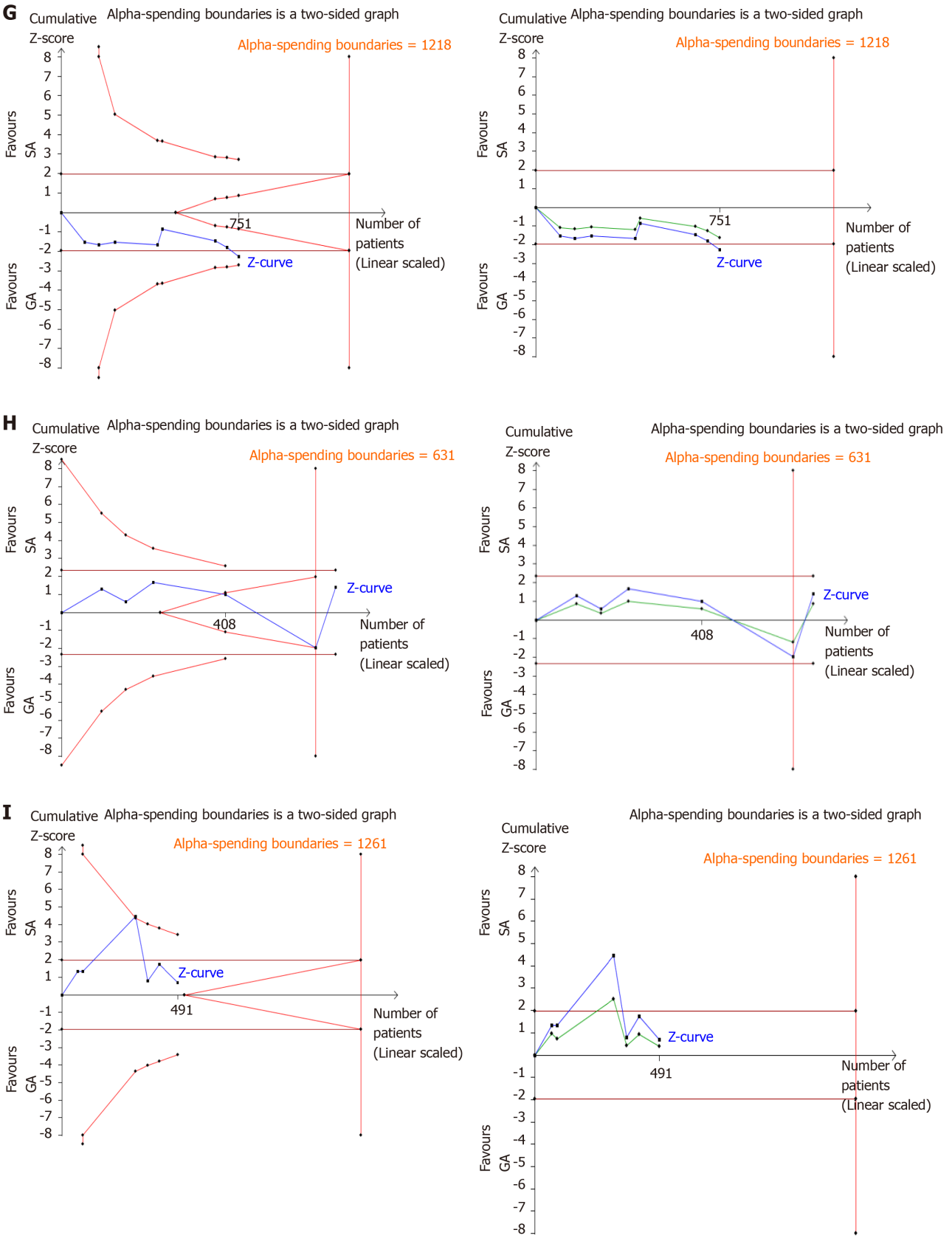


Figure 4 Results of trial sequential analysis. A: Visual analogue scale (VAS) at 4 h; B: VAS at 8 h; C: VAS at 12 h; D: VAS at 24 h; E: Nausea and vomiting; F: Headache; G: Urinary retention; H: Operative time; I: Total operative and anesthetic time. The red inward-sloping dashed lines make up the trial sequential monitoring boundaries. To the right, the outward sloping red dashed lines make up the futility region. The solid blue line is the cumulative *Z* curve. The solid green line presents penalised *Z* value.

Headache: The information size was calculated at 1105 patients. The Z-curve crossed

the conventional boundaries in favor of GA before the information size is reached. However, the Z-curve did not cross the α-spending boundaries and the futility boundaries before the information size is reached and the absolute number for penalized Z value remained smaller than 1.96; therefore, the meta-analysis was not conclusive and the results for this outcome were subject to type 1 error.

Urinary retention: The information size was calculated at 1218 patients. The Z-curve crossed the conventional boundaries in favor of GA before the information size is reached. However, the Z-curve did not cross the α-spending boundaries and the futility boundaries before the information size is reached and the absolute number for penalized Z value remained smaller than 1.96; therefore, the meta-analysis was not conclusive and the results for this outcome were subject to type 1 error.

Operative time: The information size was calculated at 631 patients. The Z-curve did not cross the conventional boundaries and the absolute number for penalized Z value remained smaller than 1.96 in both sides after the information size is reached; therefore, the meta-analysis was conclusive and the risk of type 2 error was minimal.

Total operative and anesthetic time: The information size was calculated at 1261 patients. The Z-curve did not cross the α-spending boundaries and the futility boundaries before the information size is reached and the absolute number for penalized Z value remained smaller than 1.96; therefore, the meta-analysis was not conclusive and the results for this outcome were subject to type 2 error.

DISCUSSION

We have conducted a comprehensive literature review and meta-analysis of the best available evidence to evaluate the comparative outcomes of RA and GA in laparoscopic cholecystectomy. We identified 13 RCTs[4,5,11-21] reporting on a total of 1111 patients who underwent laparoscopic cholecystectomy under RA (n = 557) and GA (n = 554). Our subsequent analysis of outcomes demonstrated that RA was associated with significantly lower postoperative pain within 24 h following the surgery, and lower nausea and vomiting compared to GA. However, it was associated with significantly higher rates of urinary retention and headache. Moreover, there was no significant difference in operative and total procedural (surgical and anesthetic) time between two groups. The heterogeneity between studies for post-operative nausea and vomiting, headaches, and urinary retention were all low, demonstrating the robustness of these results. The between-study heterogeneity in analysis of VAS score was high indicating that our findings on these outcomes may be less robust.

We also conducted a trial sequential analysis to assess for risk of Type 1 and Type 2 errors in our meta-analysis. Overall, we found that the meta-analysis is conclusive for most of the outcomes. The exceptions to this are headache and urinary retention, which have a risk of a type 1 error, and total procedure time, which has a risk of a type 2 error.

There have been two previous systematic reviews and meta-analyses analysing the outcomes between GA and RA for laparoscopic cholecystectomy[7,22]. Yu *et al*[22] in 2015 included 7 RCTs and Wang *et al*[7] in 2016 included 8 RCTs in their meta-analysis, whilst our meta-analysis included 13 RCTs. Yu *et al*[22] found that postoperative pain was significantly lower at 12 h in favor of RA but they did not find any difference in postoperative pain at 24 h between RA and GA. Consistent with our findings, Wang *et al*[7] found significantly lower postoperative pain in favor of RA in the first 24 h of postoperative period. Moreover, Yu *et al*[22] reported that there was no difference in operative time between RA and GA which is in agreement with our findings on operative time. Considering the potential impact of the type of anesthesia on overall procedure time, we analysed total operative and anesthetic time independently and demonstrated that there was no significant difference between two groups. This was not considered by previous meta-analyses. Both studies reported a significant reduction in postoperative nausea and vomiting associated with RA, but an increase in risk of postoperative urinary retention. These results are similar to our findings. Considering that dural puncture is believed to induce distension of intracranial vessels and an increase in brain blood flow playing a primary role in post-dural pain headache formation[23], unlike other meta-analyses, we evaluated the headache as an outcome and found that the use of RA was associated with significantly higher postoperative headache than GA. This has previously been

demonstrated in other laparoscopic procedures carried out under RA[24].

The growing evidence in favour of use of RA in laparoscopic cholecystectomy with regards to postoperative pain convinced us to not only meta-analyse the outcomes but also to evaluate the robustness of the findings of the meta-analysis by a trial sequential analysis. This is the first meta-analysis of the best available evidence complemented by a trial sequential analysis which demonstrated that the findings of our meta-analysis with regard to the postoperative pain are robust.

Postoperative pain is the most common complaint after surgery[22]. It has a unique pathophysiology and is believed to be due to peripheral and central sensitisation, as well as other humoral factors[22]. In day-case surgery, postoperative pain is problematic even when oral analgesia is optimised, as ongoing pain can lead to delayed discharges. In our analysis of the best available evidence, patients undergoing laparoscopic cholecystectomy under RA, have had significantly less postoperative pain when assessed at 4, 8, 12, and 24 h. Only 2.3% of patients had conversions from RA to GA showing that performing laparoscopic cholecystectomy under RA was well-tolerated. Furthermore, the type of anesthetic did not increase the anesthetic time or the surgical time. This further supports the argument that the use of RA for day-case laparoscopic cholecystectomy is feasible.

The second most common complaint after surgery is post-operative nausea and vomiting[25]. It is another cause of delayed discharges following day-case surgery. It has a complex pathophysiological mechanism and is influenced by multiple pre-operative, intraoperative, and postoperative factors, as well as general patient factors. Cholecystectomies in particular are known to have a high incidence of postoperative nausea and vomiting[25]. According to our meta-analysis, there is clear robust evidence that the use of RA for laparoscopic cholecystectomy has led to a significant reduction in postoperative nausea and vomiting. In turn, this should lead to a larger number of patients being successfully discharged on the day of surgery.

Postoperative urinary retention is a common finding after surgery with an incidence up to 70% in some procedures[26]. It is transient in most cases. Catheterisation is the primary treatment for this. Multiple risk factors for this including increasing age, longer surgery, use of postoperative analgesia, as well as the use of RA have been described[27]. The inherent pharmacology of anesthetic drugs can cause changes in the physiology of micturition. Spinal, general and regional nerve blocks can cause postoperative urinary retention by decreasing micturition control at the pontine micturition center and peripherally by blocking neural transmission in the spinal cord[28]. GA relaxes smooth muscle and reduces bladder contractility by interfering with autonomic regulation of the detrusor muscle[29]. This is physiologically apparent given the fact that bladder capacity substantially increases when a patient is subjected to GA[30]. SA and EA affect micturition *via* a different mechanism. They interfere with efferent and afferent nerves of micturition and disrupt the reflex arcs peripherally. The available evidence suggests that SA is associated with highest risk for postoperative urinary retention, followed by EA followed by GA[26]. The results of our meta-analysis are in agreement with this as it showed a significant increase in urinary retention in those patients undergoing laparoscopic cholecystectomy under RA. This finding may discourage some surgeons and patients from using RA.

The use of RA in laparoscopic cholecystectomy should be seen as a “half-full glass”. It is feasible with promising potential to reduce the postoperative pain and nausea or vomiting. Nevertheless, the increased risk of urinary retention and headache associated with RA can potentially cancel-out its effectiveness in pain control in early postoperative period by prolonging the length of hospital stay or need for outpatient assessment. Moreover, the impact of RA compared with GA on surgical outcomes of laparoscopic cholecystectomy is yet to be determined. Unfortunately, the available RCTs have not provided appropriate data about the indication for procedure, procedure related difficulties, and procedure related complications. Performing a laparoscopic cholecystectomy for a gallbladder polyp would be less challenging than doing the procedure for a complex cholecystitis or gallstone pancreatitis. We encourage future randomized studies to evaluate the comparative procedure related outcomes of laparoscopic cholecystectomy under RA and GA.

It is important to consider the limitations of our meta-analysis when interpreting its results. Although we included only RCTs to ensure high quality data, we found that there remained significant between-study heterogeneity when assessing operative time, total procedure time, and post-operative VAS scores. Furthermore, although our trial sequential analysis demonstrated that our meta-analysis was conclusive for most outcomes, it demonstrated a risk of type 1 error for two outcomes: headache and urinary retention. It also demonstrated a risk of type 2 error for total procedure time. Some of the include studies reported their VAS score and procedure time as median

and interquartile range. We have calculated their mean and standard deviation using the method described by Hozo *et al*[30]. This might have subjected our findings to some degree of bias. Moreover, some the included studies excluded patients who had failure of RA which is not consistent with intention to treat concept. This might have significantly affected the results in favor of RA and subsequently introduced bias to our findings. Finally, all the risk of performance and detection bias was high among the included studies due to lack of blinding. With regards to the performance bias, the blinding of participants and surgeons would have been impossible; however, blinding of outcome assessor would have been possible to reduce the risk of detection bias.

CONCLUSION

Our meta-analysis of the best available evidence (Level 1 evidence) demonstrated that RA may be a safe and feasible anesthetic modality for laparoscopic cholecystectomy considering its associated lower postoperative pain and nausea and vomiting compared to GA. This makes it a potentially attractive option to expedite discharge planning in day-case surgery. However, its associated risk of urinary retention and headache may not help facilitating such aim. Moreover, lack of knowledge on the impact of RA on specific procedure related outcomes may discourage surgeons from selecting RA as the first choice of anesthesia for laparoscopic cholecystectomy. Most importantly, intention-to-treat principle has been breached in some of the included studies by excluding failed RA attempts. Considering our findings and the limitations of the available evidence, we do not hesitate to highlight that available evidence does not justify using RA as the first line anesthetic choice for laparoscopic cholecystectomy although it may be an option in patients who are not fit for GA. Future research should focus on procedure related outcomes of RA and GA in laparoscopic cholecystectomy with respect to intention-to-treat concept.

ARTICLE HIGHLIGHTS

Research background

In an effort to further reduce the morbidity and mortality profile of laparoscopic cholecystectomy, the outcomes of such procedure under regional anesthesia (RA) have been evaluated.

Research motivation

In the context of cholecystectomy, combining a minimally invasive surgical procedure with a minimally invasive anesthetic technique can potentially be associated with less postoperative pain and earlier ambulation.

Research objectives

The main objective of this meta-analysis was to evaluate comparative outcomes of RA and general anesthesia (GA) in patients undergoing laparoscopic cholecystectomy.

Research methods

A comprehensive systematic review of randomized controlled trials (RCTs) with subsequent meta-analysis and trial sequential analysis of outcomes were conducted in line with Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement standards.

Research results

Thirteen RCTs enrolling 1111 patients were included. The study populations in the RA and GA groups were of comparable age (P = 0.41), gender (P = 0.98) and body mass index (P = 0.24). The conversion rate from RA to GA was 2.3%. RA was associated with significantly less postoperative pain at 4 h [mean difference (MD): -2.22, P < 0.00001], 8 h (MD: -1.53, P = 0.0006), 12 h (MD: -2.08, P < 0.00001), and 24 h (MD: -0.90, P < 0.00001) compared to GA. Moreover, it was associated with significantly lower rate of nausea and vomiting [risk ratio (RR): 0.40, P < 0.0001]. However, RA significantly increased postoperative headaches (RR: 4.69, P = 0.03), and urinary retention (RR: 2.73, P = 0.03). The trial sequential analysis demonstrated that the meta-analysis was conclusive for most outcomes, with the exception of a risk of type 1 error for headache

and urinary retention and a risk of type 2 error for total procedure time.

Research conclusions

Our findings indicate that RA may be an attractive anesthetic modality for day-case laparoscopic cholecystectomy considering its associated lower postoperative pain and nausea and vomiting compared to GA. However, it associated risk of urinary retention and headache and lack of knowledge on its impact on procedure-related outcomes do not justify using RA as the first line anaesthetic choice for laparoscopic cholecystectomy.

Research perspectives

The available RCTs have not provided appropriate data about the indication for procedure, procedure related difficulties, and procedure related complications. We encourage future randomised studies to evaluate the comparative procedure related outcomes of laparoscopic cholecystectomy under LA and GA.

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CASE REPORT

Peroral endoscopic myotomy in a pregnant woman diagnosed with mitochondrial disease: A case report

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Abstract

BACKGROUND

Achalasia is a primary esophageal motility disease characterized by impairment of normal esophageal peristalsis and absence of relaxation of the lower esophageal sphincter. Sometimes is can be a part of some genetic disorders. One of the causes of gastrointestinal motility disorders, including achalasia, is mitochondrial defects.

CASE SUMMARY

We report about a pregnant woman with a history of symptoms associated with inherited mitochondrial disease, which was confirmed by genetic tests, and who was treated *via* peroral endoscopic myotomy.

CONCLUSION

Peroral endoscopic myotomy is possible treatment option for a pregnant woman with achalasia caused by mitochondrial disease.

Key Words: Mitochondrial disease; Pregnancy; Esophagus; Peroral endoscopic myotomy; Achalasia; Biopsy; Case report

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Core Tip: Achalasia is a primary esophageal motility disease. Sometimes is can be a part of some genetic disorders. One of the causes of gastrointestinal motility disorders, including achalasia, is mitochondrial defects. We report about a pregnant woman with a history of symptoms associated with inherited mitochondrial disease, which was confirmed by genetic tests, and who was successfully treated *via* peroral endoscopic myotomy.

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INTRODUCTION

Achalasia is a primary esophageal motility disease characterized by impairment of normal esophageal peristalsis and absence of relaxation of the lower esophageal sphincter[1]. It can exist as an independent disease or part of some genetic disorders. One of the causes of gastrointestinal (GI) motility disorders, including achalasia, is mitochondrial defects[2,3]. Peroral endoscopic myotomy (POEM) is the safest and most effective method for achalasia treatment[4-7].

CASE PRESENTATION

Chief complaints

A 30-year-old woman presented to our hospital complaining of swallowing difficulty.

History of present illness

A patient had a violation of physical development and constipation from an early age. At the age of 7 years, she was diagnosed with partial bilateral symmetric ptosis. At the age of 8 years, she was referred to the hospital with diagnoses of generalized viral infection of unspecified etiology, postinfectious encephalopathy, cerebro-asthenic syndrome, neurosis, urinary bladder and gut atony, chronic pyelonephritis, mydriasis, semiptosis, and dystrophy. At the age of 9 years, she had suspected high intestinal obstruction which was followed by surgery. The obstruction was not revealed during the surgery. In the postoperative period, signs of intestinal obstruction persisted, and they were managed conservatively. After the surgery, she developed meningeal signs, gaze paresis, double vision, and reduced vision. Electrocardiogram showed an incomplete type of blockade of the right branch of the bundle of His. Esophago-gastroduodenoscopy (EGD) showed gastric hypotony. Computed tomography scans of the head revealed moderate diffuse cortex atrophy. Cerebrospinal fluid was clear with 0.066. The patient was seen by a neurologist, ophthalmologist, infectious diseases specialist, and neurosurgeon. However, the diagnosis remained unclear. The following pathologies were excluded: neuro infections, intestinal infections, oncohematology, and endocrine pathologies. Further generalized pathology persisted. At the age of 10 years, a second laparotomy was performed followed by a temporary ileostomy because of signs of acute intestinal obstruction. From the ages of 11 years to 14 years, the patient was annually referred to the surgery department with signs of acute intestinal obstruction, which were managed conservatively. At the age of 11 years, she was diagnosed with intestinal pseudo-obstruction. From the age of 11 years, paradontosis began. From the age of 14 years, the patient had daily dysphagia while eating solid and liquid food. She lost 5 kg and began feeling weak and fatigued. At the age of 15 years, resection of the jejunum was performed two times with an overall resection length of 90 cm because of acute intestinal obstruction which was not managed conservatively. The patient was dystrophic, which was thought to be because of malabsorption as a consequence of the resection of the jejunum. At the age of 25 years, the patient lost all her teeth because of progressive paradontosis. From the age of 26 years, she developed amenorrhea. At the age of 29 years, esophagography

showed signs of achalasia, gastroptosis, and delayed gastric and duodenum emptying time. At the age of 30 years, the patient was referred to the endoscopy department of Pavlov Medical University for achalasia treatment.

History of past illness

History of present illness includes the patient's entire life. That is why we suppose that this part is irrelevant in this case.

Personal and family history

The mother, father, and sister are healthy. There was no family history of GI or autoimmune pathologies or allergic disorders. The niece (4 years of age) had sensorineural hearing loss.

Physical examination

Eckardt score was 4. Her weight was 38 kg. Her body mass index was 16.9, and she had protein energy malnutrition. During preoperative preparation, the patient was revealed to be 16 wk pregnant. She was not aware of the pregnancy. In addition, intraventricular blockage was diagnosed. High-resolution esophageal manometry showed achalasia type I (Figure 1). Hemoglobin and total blood protein levels were 106 g/L and 64 g/L, respectively. Creatine phosphokinase and lactate levels were normal. Neurologic and ophthalmologic disorders were not observed. Considering all data, we suspected mitochondrial disease: incomplete Kearns-Sayre syndrome (KSS) or mitochondrial neurogastrointestinal encephalopathy (MNGIE) disease.

Laboratory examinations

Histology of the esophageal muscular layer specimens: There were myocytes of different thicknesses with sites of wave-like deformation and dystrophic changes. There were also single myocytes with necrobiotic changes and small vessels with "edge standing" leukocytes (Figure 2 and 3).

Genetic testing of mitochondrial DNA (lymphocytic): It showed segment deletion in mitochondrial DNA (mDNA) which affected the genes *RNR1* (MTRNR1) and *RNR2* (MTRNR2). This aberration is considered to be pathogenic and most frequently observed in patients with KSS[8]. Unfortunately, after discharge, the patient refused further genetic testing.

FINAL DIAGNOSIS

Achalasia. Mitochondrial disease. KSS? MNGIE?

TREATMENT

Considering the severe dysphagia and cachexia, a multidisciplinary team decided to perform POEM. After performing a submucosal tunnel myotomy of 8 cm in the esophageal muscular layer, a myotomy of 3 cm in the gastric muscular layer was also performed. From the region of the lower esophageal sphincter, 5 mm × 5 mm specimens of the lower and middle parts of the esophageal muscle (circular and longitudinal muscles) were obtained for further histological investigation. After the procedure, the endoscope was able to freely pass the lower esophageal sphincter.

OUTCOME AND FOLLOW-UP

The postoperative period was unremarkable. On postoperative day (POD) 2, liquid intake was initiated. It was later followed by eating liquid food. On POD 6, she was discharged in a satisfactory condition with a continuing pregnancy. The first follow-up was performed 3 mo after POEM: Eckardt score was 2, weight was 39 kg (+ 1 kg), EGD was normal, and pregnancy was 29 wk without any ultrasound findings of fetal pathology.

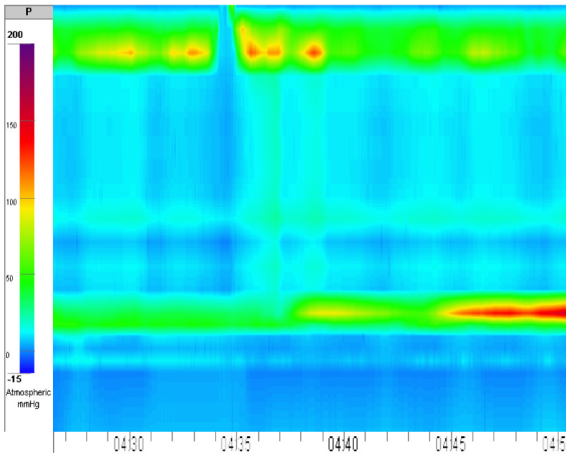

Figure 1 High-resolution esophageal manometry, manometric signs of achalasia type I.

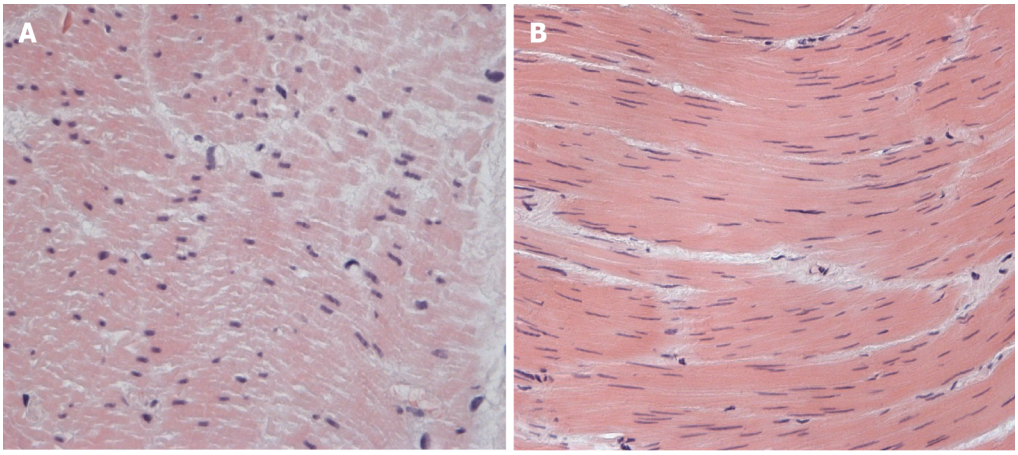

Figure 2 Muscle specimen of the upper part of the esophagus. A: Wave-like deformation of the myocytes, hematoxylin-eosin, magnification × 200; B: Myocytes of different thicknesses, hematoxylin-eosin, magnification × 100.

DISCUSSION

There are no guidelines on achalasia management in pregnant women. In the literature, achalasia cases in pregnant women were treated in different ways based on the duration of gestation, severity of the disease, and maternal and fetal risk. The most common are botulotoxin injections[9], balloon dilatation[10], Heller myotomy, or in some cases, treatment was delayed until childbirth, and patients received parenteral or enteral nutrition. Concerning nasojejunal feeding tube, the patient was in the beginning of second trimestr of pregnancy. Thus we decided that enteral nutrition is impractical for that long period because it can cause erosions and ulcers in stomach and esophagus. In addition to, long-term usage of nasojejunal feeding tube can also be a source of psychological stress to the patient. As far as dilatation concerned, the first course of dilatation with the use of 30 mm balloon has an efficacy of no more than 80% over the next 6 mo after surgery, resulting in an esophageal perforation rate of 1.1%[11,12]. The patient had not undergone Balloon Dilatation before, and we know from the literature that initiating dilatation is 10 times more likely to result in perforation, with a rate of up to 9.7%[13]. At the same time, the immediate clinical efficacy of POEM in some studies is more than 1.5 times higher than the efficacy of Balloon Dilatation (94% and 52%, respectively), and POEM is less likely to cause significant complications[14].

To the best of our knowledge, there are no cases of POEM in pregnant women published in the literature. A study by Vogel *et al*[15] showed a significant deterioration of the disease when achalasia developed and was not treated before pregnancy.

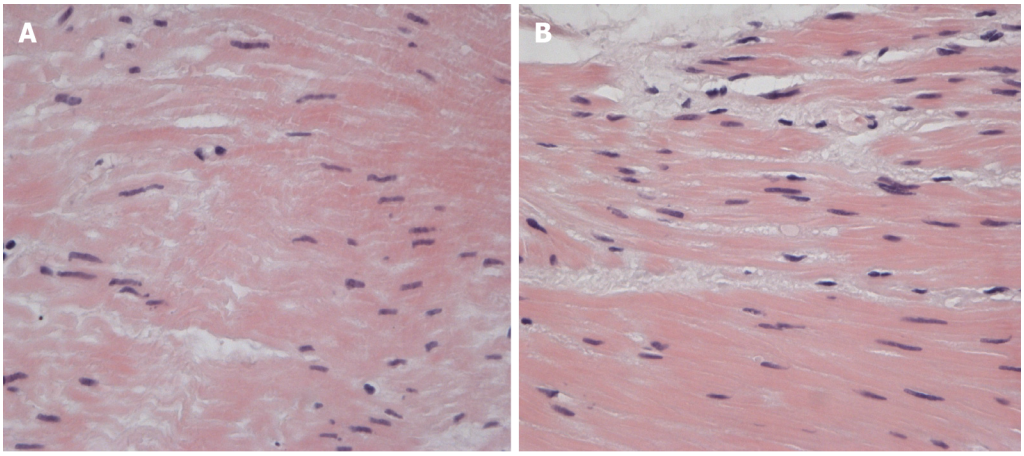

Figure 3 Muscle specimen of the esophagus. A: Muscle specimen of the upper part of the esophagus. Dystrophic and necrobiotic changes with focal myocytolysis of muscle fibers, hematoxylin-eosin, magnification × 400; B: Muscle specimen of the lower part of the esophagus. Intracellular edema, myocytes of different thicknesses, hematoxylin-eosin, magnification × 400.

In our case, we chose POEM as the treatment method because we have extensive experience in such endoscopic procedures (more than 150 POEMs). In addition, we have a multidisciplinary team taking care of patients with achalasia.

We revealed a deletion in mDNA; however, this phenotype can as well be observed when mDNA damage is caused by a primary mutation in nuclear DNA (nDNA). These genetic disorders, unlike sporadic isolated mDNA mutations, usually have autosomal recessive inheritance, are less frequently autosomal dominant, and steadily progress[16]. Mutations in *TYMP* (MNGIE syndrome) and gene *POLG* (MNGIE–like syndrome) are the most common mutations of nDNA, which cause impairment of mDNA replication, resulting in severe GI motility disorders, cachexia, polyneuropathy, leukoencephalopathy, ptosis, ophthalmoplegia, and sensorineural hearing loss. In addition, mutations in the *RRM2B* gene[17-20]. In all aberrations listed above according to the literature, the most common symptom is severe GI motility disorders.

CONCLUSION

To the best of our knowledge, this is the first case of a pregnant woman with a mitochondrial disorder treated successfully with POEM and the first histology of the esophageal muscle layer of a patient with achalasia caused by mitochondrial disease.

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MINIREVIEWS

Best practices for prevention of post-endoscopic retrograde cholangiopancreatography pancreatitis

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Abstract

Acute pancreatitis is of one the most common gastroenterology-related indications for hospital admissions worldwide. With the widespread reliance on endoscopic retrograde cholangiopancreatography (ERCP) for the management of pancreaticobiliary conditions, post-ERCP pancreatitis (PEP) has come to represent an important etiology of acute pancreatitis. Despite many studies aiming to better understand the pathogenesis and prevention of this iatrogenic disorder, findings have been heterogeneous, and considerable variation in clinical practice exists. Herein, we review the literature regarding PEP with the goal to raise awareness of this entity, discuss recent data, and present evidence-based best practices. We believe this manuscript will be useful for gastrointestinal endoscopists as well as other specialists involved in the management of patients with PEP.

Key Words: Post-endoscopic retrograde cholangiopancreatography pancreatitis; Endoscopic retrograde cholangiopancreatography; Pancreatitis; Practice guidelines; Pharmacology; Prevention

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Core Tip: Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis (PEP) represents an important etiology of acute pancreatitis and is the most common

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major adverse event post-ERCP. Nevertheless, gaps in knowledge remain, as do large variations in clinical practice. Best practices with respect to the prevention of PEP continue to evolve as new evidence becomes available. Herein, we review the literature regarding PEP to increase awareness of this entity, facilitate best practices in PEP prevention and subsequent management, and ultimately improve clinical outcomes.

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INTRODUCTION

Acute pancreatitis is an acute, inflammatory disease of the pancreas, responsible for over 100000 hospital admissions annually in the United States[1,2]. It represents a major cause of morbidity and healthcare consumption in the United States and indeed worldwide[1-3]. There are numerous established etiologies of acute pancreatitis, among which gallstones and alcohol are generally the most common[4]. A number of other etiologies have been elucidated and better appreciated over the last several decades, including acute pancreatitis which arises as an adverse event (AE) following endoscopic retrograde cholangiopancreatography (ERCP), *i.e.* post-ERCP pancreatitis (PEP)[5]. PEP is the most common major AE of ERCP and has garnered significant interest from the biomedical community. However, its pathogenesis has yet to be fully understood, and its clinical management remains heterogeneous[1,6] Identifying those at high-risk for PEP is critical to formulating an individualized prophylactic and therapeutic approach[6,7]. A multitude of pharmacological and endoscopic measures have been studied to mitigate the risk of PEP[7], include the use of rectal non-steroidal anti-inflammatory drugs (NSAIDs), aggressive intravenous (IV) hydration, and pancreatic duct stenting[8]; which of these is most effective or appropriate, however, remains a subject of ongoing study and debate. Herein, we review the current prophylactic and therapeutic measures for the prevention and management of PEP in attempt to provide evidence-based clinical guidance for best practices.

PATHOGENESIS OF ACUTE PANCREATITIS

The pathogenesis of acute pancreatitis is centered around direct acinar cell injury with subsequent activation of proteolytic pancreatic enzymes. Inciting injuries include obstruction (*e.g.*, from stone or tumor), alcohol and other toxins, and trauma, among others[9]. In PEP, activation of inflammatory pathways can occur for multiple reasons, which similarly include mechanical obstruction, direct trauma, or toxic injury[9,10]. When bile duct cannulation is difficult, prolonged papillary manipulation and repeat instrumentation can lead to mechanical injury and edema, impairing flow of pancreatic enzymes from the exocrine pancreas into the small intestine[8]. Electrocautery can also cause edema and similarly impair flow of pancreatic enzymes. Hydrostatic injury can occur secondary to intraductal water or contrast injection[8]. Contrast agents themselves can potentially cause chemical injury (even without significant changes in hydrostatic pressure); however, their role in this regard in the pathogenesis of PEP remains controversial and may depend on the chemical properties of the specific contrast agent[11]. The ensuing sequence of inflammation and recruitment of cytokines can manifest locally or go on to activate a systemic inflammatory response syndrome, resulting in higher severity of acute pancreatitis.

APPROACH TO DIAGNOSING PEP

The diagnosis of acute pancreatitis (of any etiology) can be made with at least two of the following three criteria: (1) Typical epigastric abdominal pain (often radiating to

the back); (2) Serum pancreatic enzyme levels > 3 × the upper limit of normal; and (3) Imaging findings consistent with acute pancreatitis (Table 1), as indicated by the revised Atlanta classification[8]. Although this criteria will accurately lead to the diagnosis of acute pancreatitis from other etiologies, these criteria are not always accurate in patients following ERCP. As a result of the biliary trauma caused by ERCP, many times these patients will meet two of these criteria but in reality lack acute pancreatitis. Nevertheless, the revised Atlanta criteria has been shown to more accurately predict PEP severity as compared to the consensus criteria[9]. The Cotton criteria used to diagnose PEP was developed in 1991 and has since been modified to specify whether the post-procedural abdominal pain is "new or worsened" (Table 1)[8]. Additional criteria to be classified as *mild* PEP includes an amylase level > 3 × the upper limit of normal within 24 h post-procedure and any hospitalization of at least 2 d, while moderate disease requires 4-10 d. Severe PEP is characterized by: (1) Hospitalization for > 10 d; (2) The development of a complication (*e.g.*, necrosis/abscess); or (3) The need for intervention (surgery)[8].

Of note, the diagnosis of PEP in the post-ERCP patient can sometimes be challenging, potentially leading to over- or under-diagnosis. In acute pancreatitis, epigastric pain is typically constant and radiates to the back; conversely, bowel distention and painful spasms occurring after ERCP are episodic and fleeting in nature, though the two may be difficult to distinguish. Elevations in serum pancreatic enzyme levels can occur post-ERCP in the absence of abdominal pain or imaging features of acute pancreatitis, rendering routine post-ERCP ordering of these tests of unclear (or no) clinical significance; however, marked elevations of serum amylase and/or lipase > 1000 units/L at two hours after ERCP are highly predictive of PEP[8,10-12]. The adoption of a uniform definition for the diagnosis of PEP will not only aid in its early diagnosis but also impact its subsequent treatment, though an individualized management approach would likely still be needed given the potential nuances of such procedures.

PREDICTORS OF PEP

Predicting which patients are at high risk for PEP is crucial. Several factors have been regarded as important predictors of a patient's risk of developing PEP. These risk factors are additive and can be categorized as: (1) Patient-; (2) Procedure-; or (3) Operator-related[8]. Patient-related risk factors include age (younger and older), female sex, normal serum bilirubin, recurrent pancreatitis, prior PEP, or those with sphincter of Oddi dysfunction[13]. While controversy surrounds age as risk factor for PEP, data have illustrated that pancreatitis in the elderly population could present differently and even be asociated with different outcomes[14,15]. Of note, patients with pancreas divisum may be at higher risk of acute pancreatitis which might influence clinical decision making with regard to the prophylactic measures taken to prevent PEP in this population[16]. Procedure-rated factors include difficult cannulations, pancreatic duct injection, sphincter of Oddi manometry, or precut sphincterotomy. Hospital and endoscopist procedure volume also seems to correlate with outcomes[17]. In fact, a database study involving nearly 200000 ERCPs performed in the inpatient setting found a significantly lower procedural failure rate and shorter length of stay in hospitals performing ≥ 200 ERCPs per year[4]. Additional factors such as pancreatotoxic drugs, biliary stents, or bile duct stones may influence the risk of PEP but their roles are not yet fully established (Table 2)[13].

ENDOSCOPIC TECHNIQUE AS A PREVENTATIVE STRATEGY

Prophylactic measures that may help curtail PEP[18]. Several well-designed meta-analyses have found an association between early needle-knife precutting and lower rates of PEP, as compared to persistent attempts at cannulation[19,20]. A recent study showed that prophylactic pancreatic stenting following a double-guide wire technique reduces the rate of PEP, as double-guidewire technique alone was associated with higher PEP[21]. As such, international endoscopic societies recommend early needle-knife precut sphincterotomy (or papillotomy) and double-guide wire technique with prophylactic pancreatic duct stenting, especially in difficult biliary cannulation, to prevent ERCP-related AEs[2,18,22-29].

Table 1 Mild, moderate, and severe acute pancreatitis as delineated by the revised Atlanta classification and the post-endoscopic retrograde cholangiopancreatography pancreatitis-specific Cotton criteria

Revised Atlanta classification		Cotton criteria
Mild	Requires 2 out of 3: Epigastric abdominal pain; amylase/lipase > 3 × normal limit; abdominal image findings; no organ failure; no local or systemic complications	New or worsened abdominal pain and amylase > 3 × upper limit of normal within 24 h after the procedure and requiring hospital stay/extension by 2-3 d
Moderate	Transient organ failure (resolves within 48 h). Local or systemic complications without persistent organ failure	All the above with requiring 4-10 d hospitalization
Severe	Persistent organ failure (> 48 h). Single/multiple organ failure	> 10 d hospitalization or requiring intervention. Development of a complication (pseudocyst, necrosis) or Need for surgical intervention

Table 2 Reported patient-, procedure-, and operator-related risk factors for post- endoscopic retrograde cholangiopancreatography pancreatitis

Risk factors for post-ERCP pancreatitis by category		
Patient-related	Procedure-related	Operator-related
Sphincter of Oddi dysfunction	Pancreatic sphincterotomy	Endoscopist inexperience
Age (young or old)	Recent sphincter of Oddi manometry	Lower ERCP case volume
Normal bilirubin	Difficult biliary cannulation	Poor fluoroscopic imaging
Female sex	Papillary balloon dilation	Aggressive attempts at cannulation
History of PEP	Numerous pancreatic duct cannulations	Poor ancillary services
History of pancreatitis	Inadvertent/high-pressure pancreatography	Unfamilarity with preventative methods

PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography.

INTRAVENOUS FLUIDS AS A PREVENTATIVE STRATEGY

The use of IV fluids, in particular aggressive periprocedural IV hydration, has been recommended for the prevention of PEP[18,22]. Two meta-analyses found that the use of aggressive hydration with lactated Ringer's Solution, 35-45 mL/kg administered over 8-10 h, decreased the incidence of PEP[30,31]. Another more recent study found similar results when comparing aggressive to standard IV hydration[32]. There is evidence that suggests lactated Ringer's solution may be preferable as compared to normal saline[33,34]. Of note, aggressive hydration should be tempered in patients that are at risk of fluid overload (those with heart failure, anisarca, poor renal function, ascites *etc.*) and may be less impactful in those that have a prophylactic pancreatic duct stent placed[18].

PHARMACOLOGICAL PREVENTION

Numerous pharmacological approaches have been studied as a means to preventing (or decreasing the severity of) PEP. These include: NSAIDs, somatostatin, protease inhibitors, antibiotics, nitrates, heparin, and others. Prophylactic NSAIDs are perhaps the most studied pharmacological tool found to help prevent PEP[35-42]. Indeed, numerous meta-analyses have examined the effect of NSAIDs, and while the overwhelming majority found a significantly lower incidence of PEP — a few found a nonsignificant difference[35-42]. As such, it has been recommended to use 100 mg of diclofenac or indomethacin (per rectum) before ERCP in all patients who do not have a contraindication[18]. Of note, the use of NSAIDs in combination with other pharmacologic measures to prevent PEP is not recommended by the European of society of gastrointestinal endoscopy[18]. However, recommendations from other societies do not support or deny the use of NSAIDs with other pharmacological measures[2,43]. Studies to better understand the role and optimal timing, route, and dose of NSAIDs in this regard are ongoing[44].

Somatostatin is a cyclic peptide that has an inhibitory effect on multiple systems of the body[45]. There are a few studies that have shown that its use is associated with an overall reduction in the incidence of PEP; however, these studies may be biased by a small sample size and have had conflicting results with other studies[18]. Additionally, octreotide, a somatostatin analogue, was shown to have no significant difference in PEP incidence when compared to a placebo, unless used at a dose higher that 0.5 mg[46]. Thus, this somatostatin is not recommended for PEP prophylaxis.

Protease inhibitors can be used to inhibit the activation of proteolytic enzymes that are released from the pancreas and play a role on the pathogenesis of PEP[47]. However, at this time the results of its usefulness in PEP prevention are inconclusive [18]. Notably, a study from 2010 found that the main protease inhibitors, gabexate mesylate and ulinastatin, had no effect on PEP[48]. As such, it is not recommended to administer protease inhibitors for PEP prophylaxis[2,18,43].

Nitrates can also be used as a form of prophylaxis, with sublingual administration being the best studied route[49]. This most recent meta-analysis showed that the use of glyceryl trinitrate reduces the overall incidence of PEP, which was consistent with four previously published meta-analyses[49-53]. It is currently recommended that sublingual glyceryl trinitrate be considered in patients with a contraindication to NSAIDs or to aggressive hydration for prevention of PEP[18].

Epinephrine has also been proposed as a method for PEP prevention. It is administered by spraying the papilla to reduce the edema and prevent PEP. However, there are conflicting results in two randomised controlled trials which compared epinephrine and saline[54,55]. Topical administration of epinephrine onto the papilla for PEP prophylaxis is not recommended[18].

BEST PRACTICE

Best practice with respect to the prevention of PEP continues to progress as the literature evolves and new evidence becomes available. First, we suggest that prior to ERCP, clinicians should conduct a thorough assessment for possible risk factors for PEP. Second, rectal indomethacin (or diclofenac) should be considered for all patients undergoing ERCP. Third, IV fluids (lactated Ringer's solution or alternatively normal saline) should be given pre-, intra-, and post-procedure to those who do not have a contraindication to high-volume hydration, particularly in those with a contraindication to NSAIDs. Fourth, pancreatic duct stenting should be performed prophylactically in cases of difficult cannulation and when pancreatic duct access is readily achieved. Fifth, in patients without a prior sphincterotomy who are at high-risk for PEP, cannulation with needle-knife precut techniques (*e.g.*, suprapapillary fistulotomy) should be progressed to early or considered as a primary approach so as to avoid trauma to the pancreatic duct orifice. Finally, pancreatic duct injections should be minimized (Figure 1).

CONCLUSION

Despite advances in collective knowledge of the mechanisms of and risk factors for PEP, it remains the most common major AE of ERCP and incompletely understood. Best practice with regards to prevention is through careful patient selection, sound endoscopic technique, and evidence-based prophylactic measures. Thoughtful attention to risk factors for PEP is vital in order to guide specific procedural and other preventative techniques and to optimize outcomes. Preventive measures include administration of (rectal) NSAIDs, aggressive IV hydration, various procedural techniques aimed at avoiding trauma to the papillary region, pancreatic duct stenting, and avoiding contrast injection into the pancreatic duct. The optimal choice and/or combination of these measures often requires individualized decision-making. Future high-quality studies are needed to better evaluate these and other approaches and thereby decrease the incidence and severity of PEP.

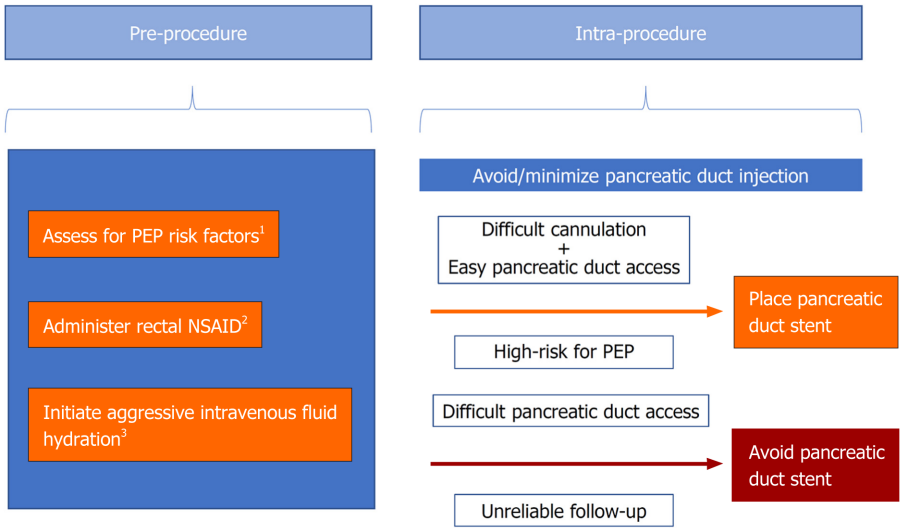

Figure 1 Flow chart illustrating the best-practice approach to post-endoscopic retrograde cholangiopancreatography pancreatitis prevention and management. Notably, in patients with complications of underlying advanced liver disease and/or comorbidities such as portal hypertension, coagulopathy, renal dysfunction, and volume overload, the selection of these prophylactic options should be made on a case-by-case basis and, when available, based on clinical evidence. [1]Younger age, female sex, normal bilirubin, recurrent pancreatitis, prior post endoscopic retrograde cholangiopancreatography pancreatitis, sphincter of Oddi dysfunction; [2]Rectal indomethacin or diclofenac; [3]Lactated Ringers preferred, 35-45 mL/kg administered over 8-10 h. PEP: Post endoscopic retrograde cholangiopancreatography pancreatitis; NSAID: Non-steroidal anti-inflammatory drug.

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SYSTEMATIC REVIEWS

Anatomic variations of the intra-hepatic biliary tree in the Caribbean: A systematic review

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Abstract

BACKGROUND

In the classic descriptions of the human liver, the common hepatic duct forms at the confluence of left and right hepatic ducts. Many authors have documented variations in the intra-hepatic ductal system, but to the best of our knowledge there has been no report on bile duct variations in Caribbean populations.

AIM

To evaluate the variations in bile duct anatomy using magnetic resonance cholangiography (MRC) in unselected patients at a major hepatobiliary referral centre in the Eastern Caribbean. Knowledge of the intra-hepatic biliary anatomy is important to optimize service delivery for any physician treating liver and biliary disorders.

METHODS

This study was carried out at a tertiary referral hospital for hepatobiliary diseases in the Eastern Caribbean. We retrospectively evaluated magnetic resonance cholangiograms in 152 consecutive patients at this facility over a two-year period from April 1, 2017 to March 31, 2019. Two consultant radiologists experienced in MRC interpretation reviewed all scans and described biliary anatomy according to the Huang's classification. A systematic review of published studies was performed and relevant data were extracted in order to calculate the global

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prevalence of each biliary variant. The variants in our population were compared to the global population.

RESULTS

There were 152 MRCs evaluated in this study in 86 males and 66 females. There were 109 (71.7%) persons with "classic" biliary anatomy (type A1) and variants were present in 43 (28.3%) persons. There was no statistical relationship between the presence of anatomic variants and gender or ethnicity. We encountered the following variants: 29 (19.1%) type A2, 7 (4.6%) type A3, 6 (3.95%) type A4, 0 type A5 and a single variant (quadrification) that did not fit the classification system. Compared to the global prevalence, our population had a significantly greater occurrence of A1 anatomy (71.7% *vs* 62.6%; $P = 0.0227$) and A2 trifurcations (19.1% *vs* 11.5%; $P = 0.0069$), but a significantly lower incidence of A3 variants (4.61% *vs* 11.5%; $P = 0.0047$).

CONCLUSION

There are significant differences in intra-hepatic biliary anatomy in this unselected Eastern Caribbean population compared to global statistics. Specifically, persons of Caribbean descent have a greater incidence of Huang A2 trifurcations and a lower incidence of Huang A3 variants.

Key Words: Liver; Variant; Biliary; Duct; Intra-hepatic; Aberrant; Trifurcation, Bifurcation

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Core Tip: Many authors have documented variations in the intra-hepatic ductal system, but to the best of our knowledge there has been no report on bile duct variations in Caribbean populations. In the unselected Eastern Caribbean population, 71.7% of persons have normal intra-hepatic biliary anatomy. Variant anatomy in this population occurs with the following frequencies: A2 (19.1%), A3 (4.6%) and A4 (3.95%).

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INTRODUCTION

There have been prior reports of variant surface anatomy[1] and vascular supply[2] of the hepatobiliary tree in Caribbean populations. However, to the best of our knowledge there has been no report on bile duct variations in Caribbean populations. This study sought to evaluate the variations in bile duct anatomy using magnetic resonance cholangiography (MRC) at a hepatobiliary referral centre in the Eastern Caribbean.

MATERIALS AND METHODS

This study was carried out at the Port-of-Spain General Hospital in Trinidad and Tobago. This 750-bed hospital was a major tertiary referral centre for hepatobiliary diseases serving patients in the Eastern Caribbean. At this centre, a dedicated multidisciplinary team met on a weekly basis to plan the management of patients with hepatobiliary diseases. Permission was granted to examine consecutive MRCs in all patients evaluated at multidisciplinary team meetings between April 1, 2017 to March 31, 2019.

All MRCs were performed using a 1.5 T Magnet with a phased array body coil. Our MRC protocols did not include the use of gadolinium compounds or morphine augmentation. The biliary anatomy on each scan was reported from these studies. The

following scans were excluded: duplicate scans, scans with incomplete demographic data and scans with inadequate coverage of the biliary tree.

We described the biliary anatomy on MRC according to the classification proposed in 1996 by Huang *et al*[3]. This classification system was the one most commonly used in the medical literature. In this system, the "classic arrangement" of the intra-hepatic biliary tree is for the left hepatic duct (LHD) and right hepatic duct (RHD) to join, forming the common hepatic duct (CHD). The RHD has two tributaries: the right posterior sectoral duct (RPSD) that drains hepatic segments VI and VII coursing in a horizontal plane and the right anterior sectoral duct (RASD) that drains hepatic segments V and VIII, coursing in a vertical plane. In the left hemi-liver, the left superior sectional duct that drains segment IVa joins the left inferior sectional duct that drains segment II, III and IVb. Both tributaries form the LHD that drains the left hemi-liver. Biliary drainage from the caudate lobe is variable and may join either the LHD or RHD at its origin. The normal anatomy and described variants are illustrated in Table 1 and Supplementary Figure 1.

In this study, two consultant radiologists experienced in MRC interpretation reviewed all scans and independently interpreted the images. In cases where there was disagreement in interpretation, the images were re-examined to achieve consensus. Data from the MRC scans were recorded in a Microsoft Excel® table and descriptive analyses were performed using SPSS version 20 statistical software.

We then conducted a systematic literature search using medical archiving platforms, including PubMed, Medline, Google Scholar and the Cochrane database of Systematic Reviews. We used the following search terms: "intra-hepatic duct", "bile duct variant", "biliary variant", "ductal anatomy", "hepatic duct variant" and "aberrant bile duct". All relevant studies were retrieved and the data and images reviewed in detail. Inclusion criteria were: case series reporting > 15 cases, reports with detailed descriptions of variants, studies in adults > 18 years of age and those using magnetic resonance cholangiopancreatography imaging to detect ductal anatomy. We excluded data from duplicated publications, individual case reports and small series with less than 15 cases. In instances where other classifications were used, we studied the written descriptions and published images within the articles of the variants in order to re-classify them in keeping with Huang's classification[3]. When the variant was not reported or the data could not be reliably extrapolated from published descriptions, data and/or images, the study data were excluded from the global prevalence statistics.

Statistical analysis

Raw data extracted from the published studies were used to calculate the global prevalence of anatomic variants[4]. The global prevalence was defined as the total number of individuals with a defined anatomic variant divided by the sum of the total number of individuals in each study. The global prevalence was then compared with the prevalence of each variant in our population using Chi square tests to compare contingency tables in SPSS version 20 (IBM Corp, Armonk, NY, United States). Fisher exact tests were used for values < 5. A P value < 0.05 was considered significant.

RESULTS

There were 159 MRCs performed during the study period. Seven scans on six patients were excluded from the final analysis because: one patient was scanned twice, three images were of insufficient quality for analysis and three were not retrievable from the digital archiving system. Therefore, a total of 152 MRCs were evaluated in this study.

There were 86 males and 66 females included in the final analysis with a mean age of 62.6 years (SD ± 10.8; median 65; range 34-80 years). These patients were of Indio-Caribbean (74), Afro-Caribbean (55), Asian (10), Caucasian (9) and Latin (4) descent.

Classic type 1 anatomy

Of 152 examinations analyzed, 109 (71.7%) had the "classic" type 1 biliary anatomy (Figure 1). There were 63 men and 46 women with "classic" anatomy. These persons were of Afro-Caribbean (41), Indio-Caribbean (57), Asian (7), Caucasian (3) and Latin (1) descent. In one patient with classic intra-hepatic biliary anatomy, a solitary Type 1c choledochal cyst was noted at the common bile duct in the extra-hepatic biliary tree.

Table 1 Intra-hepatic bile duct variants according to Huang's classification[3]

Description	Taiwan[3], *n* = 958 (%)	Caribbean, *n* = 152 (%)
Type A1: The RHD and LHD join to form the CHD. The intra-hepatic RHD is formed by the union of RASD and RPSD. The LHD is formed by the union of LSSD and LISD	600 (62.6)	109 (71.7)
Type A2: A trifurcation is formed by the union of RASD, RPSD and LHD	182 (19)	29 (19.1)
Type A3: The RPSD or RASD drains directly into the LHD	105 (11)	7 (4.61)
Type A4: The RPSD drains directly into the CHD	56 (5.8)	6 (3.95)
Type A5: The RPSD drains into the cystic duct	15 (1.6)	0

RASD: Right anterior sectional duct; RPSD: Right posterior sectional duct; RHD: Right hepatic duct; LHD: Left hepatic duct; CHD: Common hepatic duct; LSSD: Left superior sectional duct; LISD: Left inferior sectional duct.

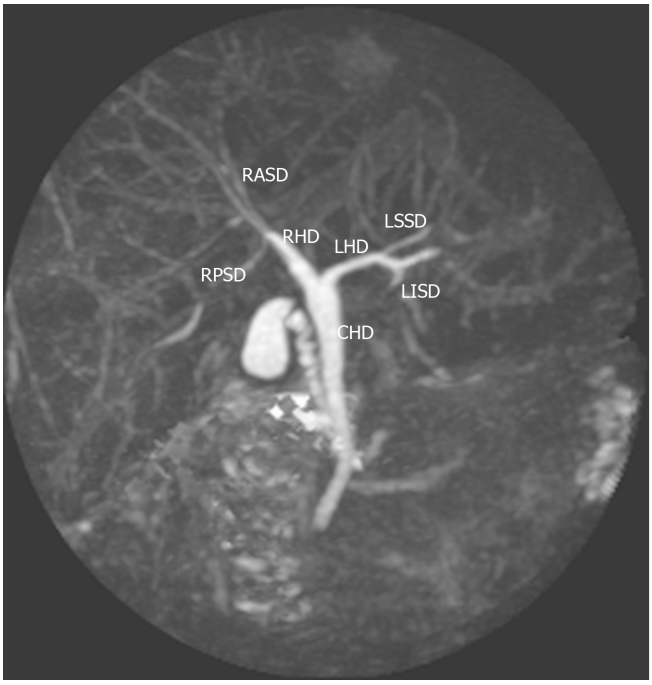

Figure 1 Type 1 (classic) variant. In this system, the right hepatic duct (RHD) is formed by two tributaries: the right posterior sectional duct that drains segments VI and VII coursing in a horizontal plane and the right anterior sectional duct draining segments V and VIII and coursing in a vertical plane. The left hepatic duct (LHD) is formed by two tributaries: the left superior sectional duct that drains segment IVa joins the left inferior sectional duct that drains segment II, III and Ivb. The RHD and LHD then join to form the common hepatic duct (CHD). RASD: Right anterior sectional duct; RPSD: Right posterior sectional duct; RHD: Right hepatic duct; LHD: Left hepatic duct; CHD: Common hepatic duct; LSSD: Left superior sectional duct; LISD: Left inferior sectional duct.

Variant anatomy

There were variations from the "classic" biliary anatomy in 23 (15.1%) men and 20 (13.2%) women. There was no statistical relationship between the presence of anatomic variants and gender (26.7% *vs* 30.3%; $P = 0.717$), Afro-Caribbean (25.5% *vs* 29.9%; $P = 0.581$), Indio-Caribbean (22.97% *vs* 33.3%; $P = 0.207$), Asian (30% *vs* 28.2%; $P = 1.000$) or Latin ethnicity (75% *vs* 27%; $P = 0.0687$). Bile duct variants were commoner in persons of Caucasian ethnicity (66.7% *vs* 25.9%; $P = 0.0158$), although the statistical power of this association was reduced since there were only 9 (5.9%) Caucasians in the study population.

Type A2 anatomy was present in 29 (19.1%) individuals (Figure 2), type A3 variants in 7 (4.6%) individuals (Figure 3) and type A4 variants in 6 (3.95%) individuals (Figure 4). In this study population, we did not encounter any type A5 variants. One person had a variant that did not fit into the Huang classification. This individual had a quadrification where RASD, RPSD, LHD and segment IVa ducts met at the hilum to form the CHD (Figure 5).

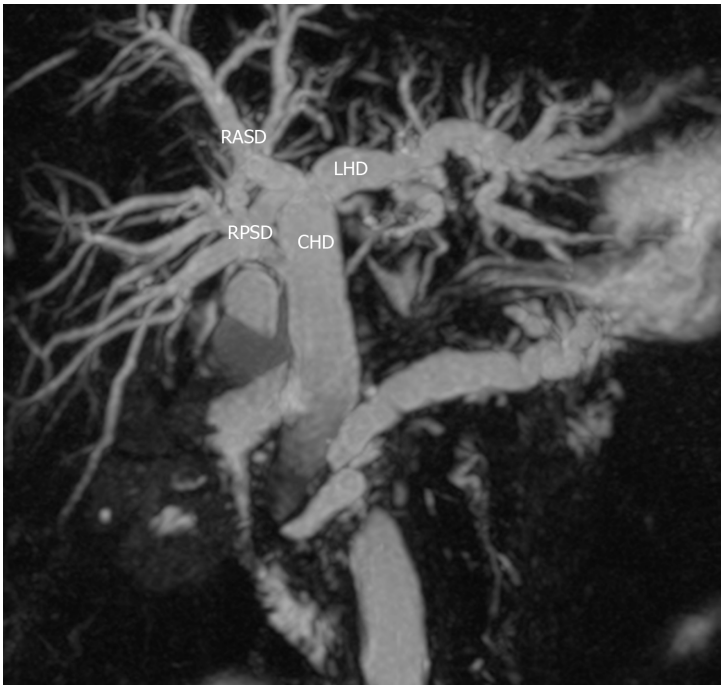

Figure 2 Type 2 variant. A trifurcation that is formed by the union of the right anterior sectoral duct, right posterior sectoral duct and the left hepatic duct. RASD: Right anterior sectional duct; RPSD: Right posterior sectional duct; LHD: Left hepatic duct; CHD: Common hepatic duct.

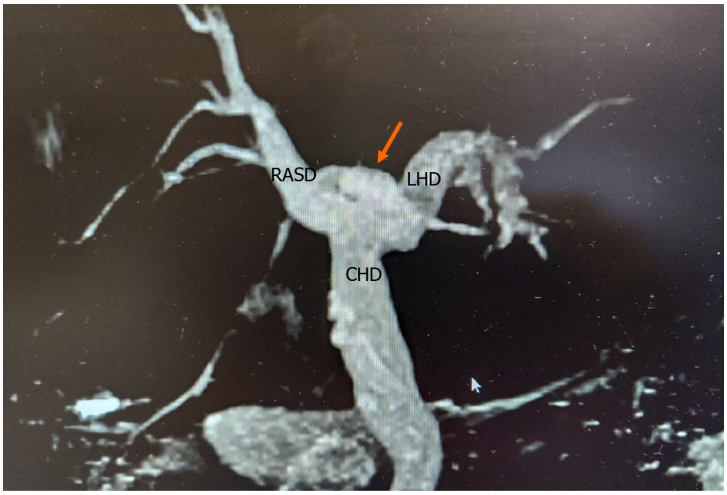

Figure 3 Type 3 variant. The right posterior sectoral duct (arrow) drains directly into left hepatic duct. RASD: Right anterior sectional duct; LHD: Left hepatic duct; CHD: Common hepatic duct.

Systematic review

In order to calculate the global prevalence of each variation, we conducted a systematic literature search using medical archiving platforms. We retrieved 47 articles that reported on variations in intra-hepatic biliary ductal anatomy in a total of 17045 persons[3,5-50]. Table 2 summarizes the data extracted from published reports of intra-hepatic bile duct variations across the globe. There were 10668 type A1 variants reported in 17045 persons. The global prevalence of type A1 variants (62.6%) was significantly lower than seen in our population (71.7%; $P = 0.0227$).

One published study did not report the number of A2 variants[8]. Therefore, data from this study were not included in the calculation of global prevalence of type A2 variants. In the remaining studies there were 1853 A2 variants in 16087 persons. There was a significantly greater prevalence of Huang A2 variants in our population (19.1% *vs* 11.5%; $P = 0.0069$).

After excluding one published study that did not specify the number of A3 variants [14], there were 1903 type A3 variants in 16570 persons. There were significantly less

Table 2 Global prevalence of intra-hepatic bile duct variants

Ref.	Country	Classification	Study population	Huang classification of biliary variants					
				A1 (%)	A2 (%)	A3 (%)	A4 (%)	A5 (%)	Other
Couinaud[5], 1957	France	Couinaud[1]	298	173[2] (58)	33[2] (11.1)	53[2] (30.6)	17[2] (5.7)	0	22
Puente and Bannura[6], 1983	Chile	Descriptive[1]	3845	2217 (57.6)	426 (11.1)	498 (13.0)	249 (6.5)	NS	455
Huang *et al*[3], 1996	Taiwan	Huang	958	600 (62.6)	182 (19)	105 (11)	56 (5.8)	15 (1.6)	0
Yoshida *et al*[7], 1996	Japan	Yoshida[1]	1094	741 (67.7)	193 (17.7)	66 (6.0)	88 (8.0)	0	0
Cheng *et al*[8], 1997	Taiwan	Huang	958	624 (65.1)	NS	105 (11)	NS	0	200 (21)
Nakamura *et al*[9], 2002	Japan	Couinaud[1]	120	78 (65)	11 (9.2)	10 (8.3)	19 (15.8)	2 (1.7)	0
Kitagawa *et al*[10], 2003	Taiwan	Huang	180	113 (62.7)	36 (20.0)	26 (14.4)	5 (2.8)	0	0
Choi *et al*[11], 2003	South Korea[2]	Choi[1]	300	188 (63)	29[2] (10)	34[2] (11)	19[2] (6)	6[2] (2)	28[2]
Ayuso *et al*[12], 2004	Spain	Couinaud[1]	25	10[2] (40)	1[2] (4)	2[2] (8)	10[2] (40)	2[2] (8)	0
Ohkubo *et al*[13], 2004	Japan	Ohkubo[1]	110	72[2] (65)	6[2] (5)	13[2] (12)	5[2] (4.6)	1[2] (0.9)	13
Düşünceli *et al*[14], 2004	Turkey	Descriptive[1]	475	360[2] (75.8)	4[2] (0.8)	NS	27[2] (5.7)	0	84
Lee *et al*[15], 2004	United States	Couinaud[1]	108	78[2] (72.2)	6[2] (5.6)	4[2] (3.7)	3[2] (2.8)	1[2] (9.3)	16
Limanond *et al*[16], 2004	United States	Huang	27	19 (70.4)	5 (18.5)	2 (7.4)	1 (3.7)	0	0
Wang *et al*[17], 2005	United States	Yoshida[1]	62	35[2] (56.0)	7[2] (11)	11[2] (18)	8[2] (13)	0	1
Chen *et al*[18], 2005	United States	Couinaud[1]	56	33[2] (58.9)	7[2] (12.5)	10[2] (17.9)	5[2] (1.8)	0	1
MacDonald *et al*[19], 2005	United States	Choi[1]	39	24[2] (61.5)	3[2] (7.7)	7[2] (17.9)	1[2] (2.6)	0	4
Kim *et al*[20], 2005	Canada	Champetier[1]	30	17[2] (56.7)	1[2] (3.3)	9[2] (30)	2[2] (6.7)	1[2] (3.3)	0
Wietzke-Braun *et al*[21], 2006	Germany	Ohkubo[1]	18	2[2] (11)	2[2] (11)	4[2] (22)	1[2] (6)	0	9
Kitami *et al*[22], 2006	Japan	Ohkubo[1]	158	116 (73)	8 (5.1)	19 (12)	5 (3)	NS	10
Vidal *et al*[23], 2007	France	Descriptive[1]	45	36 (80)	2 (4.4)	1 (2.25)	3 (6.6)	0	3
Cho *et al*[24], 2007	Japan	Cho[1]	60	38[2] (63.3)	14[2] (23.3)	7[2] (12)	1[2] (2)	0[2]	0
Sirvanci *et al*[25], 2007	Turkey	Modified Huang[1]	62	43 (69.3)	6 (9.7)	9	3	0	1
Song *et al*[26], 2007	South Korea	Modified Huang[1]	111	67 (60.4)	9 (8.1)	22 (19.8)	8 (7.2)	2 (1.8)	3
Karakas *et al*[27], 2008	Turkey	Karakas[1]	112	61[2] (55)	16[2] (14)	24[2] (21)	11[2] (10)	0	0
De Filippo *et al*[28], 2008	Italy	Descriptive[1]	350	202[2] (57.7)	28[2] (7.9)	11[2] (3.1)	NS	NS	109
Kim *et al*[29], 2008	South Korea	Modified Yoshida[1]	33	25 (75.8)	1 (3)	3 (9.1)	0	1 (3)	
Sharma *et al*[30], 2008	India	Couinaud[1]	253	134 (52.9)	29 (11.5)	46 (18.2)	18 (7.1)	1 (0.4)	25
Kashyap *et al*[31], 2008	United States	Couinaud[1]	36	22 (61.1)	4 (11.1)	4 (11.1)	3 (8.3)	1 (2.8)	2
Cucchetti *et al*[32], 2011	Italy	Choi[1]	200	129 (64.5)	28 (14)	24 (12)	16 (8)	NS	3
Lyu *et al*[33], 2012	Taiwan	Yoshida[1]	462	307 (65.8)	42 (9.1)	60 (13)	41 (8.9)	15 (3.2)	0
Tawab *et al*[34], 2012	Egypt	Huang[1]	106	67[2] (63.2)	11[2] (10.4)	18[2] (17)	8[2] (7.5)	2 (1.9)	0
Thungsuppawattanakit and Arjhansiri[35], 2012	Thailand	Couinaud[1]	163	106 (65)	28 (17.2)	15 (9.2)	9 (5.5)	0	5 (3.1)

Barsoum *et al*[36], 2013	Egypt	Hakki[1]	50	28[2] (56)	3[2] (6)	15[2] (30)	2[2] (4)	0[2]	0
Mariolis-Sapsakos *et al*[37], 2012	Greece	Couinaud[1]	73	48[2] (65.7)	7[2] (9.59)	11[2] (15.1)	2[2] (2.74)	1[2] (1.37)	4[E]
Uysal *et al*[38], 2014	Turkey	Choi[1]	1011	803 (79.4)	81 (8.01)	42 (4.15)	73 (7.23)	NS	12
Deka *et al*[39], 2014	North India	Choi[1]	299	173 (57.8)	24[2] (8)	52[2] (17.4)	20[2] (6.6)	7[2] (2.3)	23
Al-Jiffry[40], 2015	Saudi Arabia	Couinaud[1]	177	104[2] (58.8)	19[2] (10.7)	7[2] (3.9)	12[2] (6.8)	2[2] (1.1)	33[2]
Khanduja *et al*[41], 2016	North India	Huang	100	63 (63)	18 (18)	9 (9)	8 (8)	0	2[3]
Nayman *et al*[42], 2016	Turkey	Yoshida[1]	2143	1329 (62)	202 (95)	245 (11)	149 (7)	1 (0.05)	9
Sarawagi *et al*[43], 2016	North India	Karakas[1]	224	124 (55.3)	26 (9.3)	62 (27.6)	9 (4)	2 (0.8)	0
Adwan *et al*[44], 2016	Jordan	Yoshida[1]	120	82[2] (68.4)	10[2] (8.3)	15[2] (12)	NS	NS	
Taghavi *et al*[45], 2017	Iran	Huang	362	163 (45)	78 (21.5)	48 (13.3)	13 (3.6)	0	60 (16.6)
Mazroa *et al*[46], 2017	Egypt	Hakki[1]	50	24[2](48)	4[2](8)	15[2](30)	7[2](14)	0[2]	0
Adatepe *et al*[47], 2016	Turkey	Choi[1]	1041	616[2] (40.7)	133[2] (12.8)	126[2] (12.1)	52[2] (4.99)	0[2]	114
Abdelkareem *et al*[48], 2019	Palestine	Modified Huang[1]	342	266 (77.8)	29 (8.5)	2 (0.6)	1 (0.3)	1 (0.3)	43
El Hariri *et al*[49], 2019	Egypt	Modified Huang[1]	120	79 (65.8)	14 (11.7)	16 (13.3)	9 (7.5)	2 (1.67)	0
Medişoğlu *et al*[50], 2020	Turkey	Huang	79	29 (36.7)	27 (34.2)	16 (20.3)	7 (8.9)	0[2]	0
Global prevalence	Global	-	17045	10668/17045 (62.6)	1853/16087 (11.5)	1903/16570 (11.5)	1006/15617 (6.4)	66/11361 (0.58)	
Present study	Caribbean	Huang	152	109 (71.7)	29 (19.1)	7 (4.61)	6 (3.95)	0	1
P value				0.0227	0.0069	0.0047	0.2466	1.0	-

[1]Different classification used.
[2]Extrapolated from raw data and/or published images.
[3]Removed by authors from analysis due to poor visualization. NS: Not specified.

type A3 variants in our population (4.61% *vs* 11.5%; $P = 0.0047$).

The number of A4 variants were not reported and could not be reliably extrapolated from published descriptions and/or images in three publications[8,28,44]. Therefore, these studies were not included in the calculation of A3 global prevalence. The remaining studies documented 1006 type A4 variants in a total of 15617 persons. There was no statistical difference between the prevalence of type A4 variants in our population and the global prevalence (3.95% *vs* 6.4%; $P = 0.2466$).

The number of A4 variants were not reported and could not be reliably extrapolated from published descriptions and/or images in six publications[6,22,28,32,38,44]. In the remaining publications, there were 66 (0.58%) type A5 variants in a total of 11,361 persons. We did not encounter A5 variants in our population.

DISCUSSION

Although there are many techniques used to evaluate biliary anatomy, we agree that MRC is ideal[39,51,52] because it is non-invasive, does not require the administration of iodine-based contrast media and is associated with minimal patient-associated risk. Conventional T2-weighted MRC works on the concept that T2-weighted images demonstrate high signal intensity from fluid-containing structures, but it is limited in its ability to demonstrate small ducts and those not distended with bile[33,52].

Unfortunately, there is no standardized classification system to describe biliary anomalies. Numerous classification systems have been proposed and all are used in medical literature. These include classification systems described by Yoshida *et al*[7], Couinaud[5], Huang *et al*[3], Choi *et al*[11], Ohkubo *et al*[13], Karakas *et al*[27], Barsoum

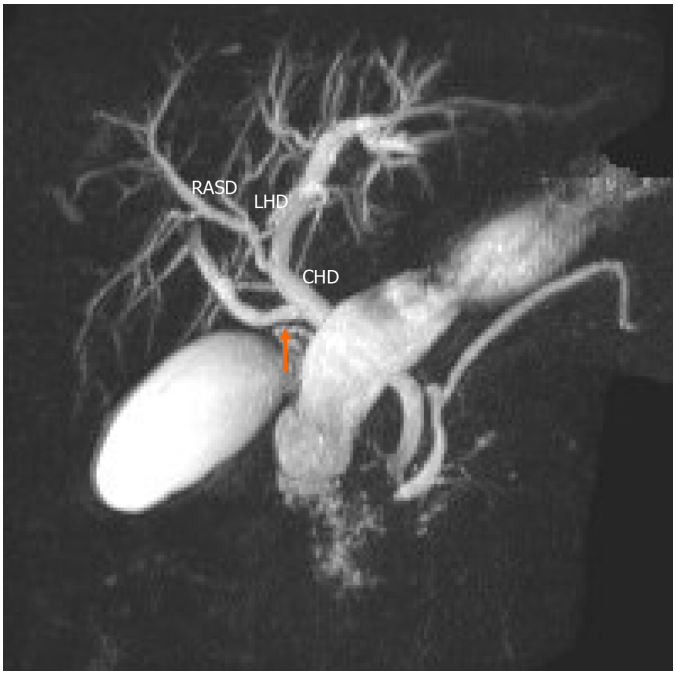

Figure 4 Type 4 variant. An aberrant right posterior sectoral duct (arrow) can be seen emptying directly into the common hepatic duct. RASD: Right anterior sectional duct; LHD: Left hepatic duct; CHD: Common hepatic duct.

et al[36] and Champetier[53]. Each system has its individual merits. For example, some classifications[11] document the presence of accessory ducts, reportedly found in 2% [11,52] to 14%[39] of persons, while other systems do not include these data. As another example, many systems focus on biliary anatomy in the right-hemi liver[5,11, 39,53] while others[3,7,13] also include detailed information on left-sided biliary anatomy.

Each system also has individual drawbacks. For example, the detailed classification proposed by Ohkubo *et al*[13]does not describe separate drainage from multiple segment IV ducts into LHD. Evaluating this from another perspective, most authors who proposed a classification system found anomalies that did not fit into their classifications: 1% by Choi *et al*[11], 2% by Khanduja *et al*[41], 3.3% by Couinaud[5], 11.1% by Karakas *et al*[27], 34% by Champetier[53]and 9.4% by Ohkubo *et al*[13]. In the general medical literature, the classification proposed by Huang *et al*[3] was the most commonly utilized system[3,8,10,16,25,26,34,41,45,48-50]. Therefore, we used the Huang classification to characterize variations encountered in our population.

All classification systems in use describe the "classic" anatomic pattern. This information is important when performing any operative or interventional radiologic procedures on the liver. This pattern is considered ideal for harvesting liver where a right or left lobe is required for living donor liver transplant[11]. This "classic" anatomic pattern was present in 71.7% of unselected persons in our population. In the general medical literature, the prevalence of the "classic" anatomic pattern ranged from 36.7%[50] to 80%[23]. Wietzke-Braun *et al*[21] reported type A1 variants in only 11% of their population. However, this was a small series of only 18 highly-selected individuals undergoing transplant evaluation. Therefore, we did not consider this outlier to be representative of A1 variants in the general population. The global prevalence of A1 anatomy was lower than encountered in our population (62.6% *vs* 71.7%; $P = 0.0227$).

In our population, 28.3% of unselected persons had variant intra-hepatic biliary anatomy. This compared well with published global data in which the prevalence of bile duct variants ranges from 20% in France[23] up to 60% in Spain[12]. Cucchetti *et al* [32] suggested that there was a relationship between gender and biliary anatomy, with significantly more women having biliary anomalies (45% *vs* 26%; $P = 0.005$), but we found no statistically significant relationship between the presence of anatomic variants and gender (27.6% *vs* 29.2%; $P = 1.000$) in our study. This was consistent with most other reports in the literature[3,5,26,33,39,52].

In our population, there are equal proportions of persons from the West African (40%) and North Indian (40%) diaspora as a result of the trans-Atlantic slave trade and indentured labour systems. Therefore, we sought to compare the prevalence of

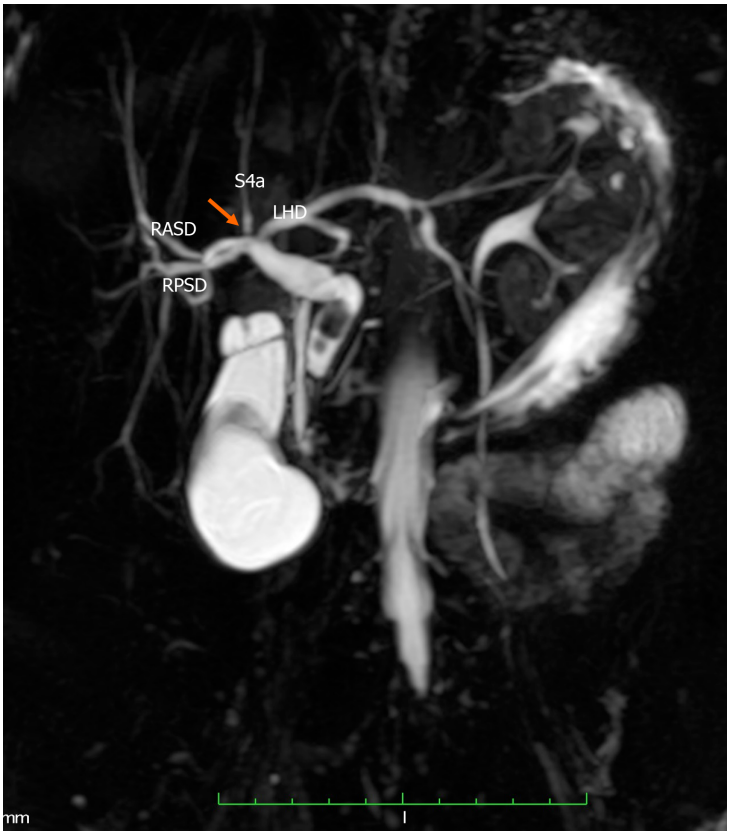

Figure 5 Undefined variant. The image shows a quadrification (arrow) that is formed by the union of the right anterior sectoral duct, right posterior sectoral duct, segment IVa duct (S4a) and the left hepatic duct (LHD). RASD: Right anterior sectional duct; RPSD: Right posterior sectional duct; LHD: Left hepatic duct; S4a: Segment Iva.

variants to studies from these geographic locations. There were no published studies reporting biliary variants in West African populations but there were four studies reporting 494 variants in 876 individuals from North Indian populations[30,39,41,43]. In our population there was a significantly lower incidence of all bile duct variants than that seen in Indian populations (28.3% *vs* 56.4%, $P < 0.001$), probably due to decades of population mixing in our setting.

The most common variant we encountered was a triple confluence (A2), occurring in 19.5% of unselected individuals. In the general medical literature, the prevalence of a trifurcation ranges from 0.8%[14] to 34.2%[50] and the calculated global prevalence was 11.5%. Therefore, in our population there was a significantly greater prevalence of A2 trifurcations (19.1% *vs* 11.5%; $P = 0.0069$). Interestingly, it was closest to the 18% prevalence reported by Khanduja *et al*[41] in a North Indian population and we previously noted that 40% of our population is from the North Indian diaspora. It is important for transplant surgeons to be aware that trifurcations are more common in persons of Caribbean extract. This has important implications for partial liver transplantation. For both, a formal right-left lobe split and a right lobe living donation, it would need a bi-ductal anastomosis in a recipient with higher chances of post-operative biliary complications. It is sometimes considered to be a relative contraindication for right lobe living donation[52].

The second most prevalent anomaly was a type-A3 variant that was present in 4.6% of our population. In the medical literature the prevalence of type 3 variations ranges from 0.6%[48] to 30%[5,36,46] and the global prevalence was calculated to be 11.5%. Type A3 variants are clinically significant for many reasons. The presence of this variant predisposes patients to inadvertent biliary tract injury in the donor[13]. However, this anomaly can be identified either during a pre-operative donor or intra-operative cholangiography during donor right hepatectomy. Patients with an unrecognized type-A3 variant who undergo a left hepatectomy may be at risk for significant post-operative bile leak from the transected RPSD if not properly secured in the liver remnant. This type of bile leak would remain unresolved despite an ERCP. Alternatively, the RPSD is at risk for ligation leading to biliary stasis, repeated infections and finally cirrhosis in the right posterior section.

In patients with type-3 anomaly, a Bismuth 3b hilar choangiocarcinoma is often misinterpreted as a type 4 Lesion since the right anterior and posterior sectoral ducts are deemed not to join. Such patients can then be incorrectly labelled as inoperable.

Finally, there may also be a theoretic relationship between a type-3 variant and hepatolithiasis[11]. Consider the prevailing theory that biliary stasis and secondary cholangitis may contribute to intra-hepatic lithiasis[11,54]. This is supported by the fact that intra-hepatic lithiasis is more common in the left liver because the LHD joins at a more acute angle than the RHD[54]. But the most acute angulation would be present in a person with a type-3 variation, where the RPSD joins the LHD[11]. Therefore, these patients are theoretically more likely to experience stasis and a greater incidence of intra-hepatic lithiasis[11].

The type A4 variant was present in 3.95% of our population. The prevalence of this variant in the general medical literature ranges from 0.3%[48] to 15.8%[9] and the calculated global prevalence was 6.4%. General surgeons should make an effort to identify A4 variants before performing laparoscopic cholecystectomy because the abnormal RPSD might be mistaken as the cystic duct[33], putting it at risk for inadvertent bile duct injury. Interventional radiologists should also attempt to identify A4 variants before percutaneous drainage procedures, because drain placement in the left duct system would not effectively drain the right posterior segment when this anatomy is present[11]. The issues with the right-left split and right lobe living donation are somewhat similar to the ones discussed for the type A3 variant. However, a type A4 is probably more favourable since the RASD is essentially inserted low into the CHD and can often be dissected out extra-hepatically and for a longer length, thereby making a bi-ductal recipient anastomosis comparatively easier.

We did not encounter any persons with type A5 variants in our population. This was not surprising as many authors published series without identifying A5 variants [3,5,8,10,14,16-19,21,23-25,27,35,36,41,45,46,50]. In the general medical literature, the frequency of A5 variants ranged from 0.05[42] to 9.3%[15] and we calculated the global prevalence of A5 variants to be 0.58%.

There was one person in our study with a quadrification that did not fit the Huang classification. Although uncommon, this variation has been reported before. Adatepe *et al*[47] reported a quadrification in 0.38% of 1,041 persons, which was similar to the prevalence in our population (0.65%). The clinical significance of this variation is probably similar to that of a Huang A2 variant. Most of the existing classification systems downplay the significance of the segment IV ducts due to the vagrant nature of its insertion, and in fact many of the classification systems do not mention the variable segment IV duct. Additionally, we believe that in many instances the segment IV duct is too small to be meaningfully represented on MRCs. Moreover, it has little bearing on resectability of a hilar cholangiocarcinoma, right lobe or a left lateral section living donor.

There were no accessory ducts in our study. The term accessory duct refers to extra bile ducts draining a single liver segment in addition to its normal drainage[33,55]. Accessory bile ducts are reported to occur in 2%[55] to 6%[11] of persons in the medical literature. Accessory ducts are important to transplant surgeons who would tailor harvesting techniques in the donor. They may also be inadvertently ligated at operation leading to the formation of biliary fistulae, biliary sepsis and biliary cirrhosis.

A limitation of this study was that the MRCs were done on a scanner with a 1.5 T magnet without the administration of gadolinium compounds. Although we did not identify aberrant or accessory ducts, we do appreciate that small accessory ducts and aberrant ducts may not have been detected because they were below the resolution of the protocol scan/equipment.

CONCLUSION

In this Eastern Caribbean population, MRC identified variant anatomy in 28.3% of unselected persons. There are significant differences in intra-hepatic biliary anatomy in this unselected Eastern Caribbean population compared to global statistics. Specifically, Caribbean persons have a greater incidence of Huang A2 trifurcations and a lower incidence of Huang A3 variants.

ARTICLE HIGHLIGHTS

Research background

There have been many documented variations of the anatomy of the intra-hepatic bile ducts, but to the best of our knowledge there has been no report on bile duct variations in Caribbean populations. This information is important to optimize healthcare services for providers with interests in treating liver disorders.

Research motivation

This research sought to determine the bile duct variations in a Caribbean population. This will help to optimize hepatobiliary services in the region. We have also defined the global prevalence which will serve as a basis for further research in this field.

Research objectives

We sought to document the variations in bile duct anatomy using magnetic resonance cholangiography (MRC) at a major hepatobiliary referral centre in the Eastern Caribbean.

Research methods

We evaluated MRC images from 152 consecutive patients over a two-year period and described biliary anatomy according to the Huang's classification. A systematic review of all available published studies was performed. Raw data were extracted and used to calculate the global prevalence of each variant for comparisons to the variants in our population.

Research results

Classic anatomy was present in 71.7% of persons and 28.3% of persons had variant anatomy. The most common variant was Huang type 2 (19%), followed by type 3 (4.6%), type 4 (3.95%) and type 5 (0). One variant did not fit the Huang classification system. This Caribbean population had a significantly greater number of type 2 variants (19.1% *vs* 11.5%; $P = 0.0069$), but a significantly lower incidence of type 3 variants (4.61% *vs* 11.5%; $P = 0.0047$).

Research conclusions

There are significant differences in biliary anatomy in this Caribbean population compared to global statistics. The new method this study proposes is to use the definition of global prevalence to compare anatomic variations.

Research perspectives

Future research can focus on variations of extra-hepatic biliary anomalies using the global prevalence template.

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CASE REPORT

First splenic rupture following an endoscopic esophageal myotomy: A case report

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Abstract

BACKGROUND

The occurrence of splenic rupture is extremely rare during an upper gastro-intestinal endoscopy. Although infrequent, splenic rupture is a known complication secondary to colonoscopy. However, occurrence of splenic rupture after peroral endoscopic myotomy (POEM) has never been reported to date.

CASE SUMMARY

We describe a case of a splenic rupture following a POEM for recurrent achalasia in a patient who previously had a Heller myotomy. Splenic rupture remains very uncommon after an upper gastro-intestinal endoscopic procedure. The most plausible cause for this rare splenic injury appears to be the stretching of the gastro-splenic ligament during the endoscopy. A previous surgery may be a risk factor contributing to this complication.

CONCLUSION

The possibility for the occurrence of specific complications, such as splenic rupture, does exist even with the development of advanced endoscopic procedures, as presented in the present case after POEM.

Key Words: Achalasia; Myotomy; POEM; Splenic rupture; Complication; Case report

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Core Tip: Splenic rupture is extremely rare but may occur during an upper gastro-intestinal endoscopy. Occurrence of splenic rupture after peroral endoscopic myotomy

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(POEM) has never been reported to date. The first reported case of splenic rupture following a POEM is presented. This very unusual but severe complication will probably occur again as this procedure will continue to be developed and implemented. Physicians must be aware that splenic rupture can happen after POEM.

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INTRODUCTION

Peroral endoscopic myotomy (POEM) is now considered as an effective therapy for achalasia, at least as efficient as laparoscopic Heller myotomy[1]. Only in about 7.5% of the cases with POEM, adverse events were reported, which were minor in the majority of the cases[2]. To our knowledge, there have been no reports of splenic rupture during or after POEM.

The occurrence of splenic rupture is quite rare during an upper gastro-intestinal endoscopy. Majority of the cases occurred after endoscopic retrograde cholangio-pancreatography[3]. Splenic rupture is however a known complication after colonoscopy, with approximately 1 case out of 100000 procedures[4].

Only two cases of splenic rupture after gastroscopy[5,6], and three cases following esophageal endoscopic procedures[7-9] have been reported in the literature since the advent of flexible endoscopes. However, there has been no report of splenic rupture after endoscopic myotomy for achalasia of the esophagus.

We present here for the first time, a patient with recurrent achalasia, who underwent an endoscopic myotomy and developed a splenic rupture, secondary to this procedure.

CASE PRESENTATION

Chief complaints

Three days after POEM, a patient suddenly developed severe diffuse abdominal pain and nausea.

History of present illness

The patient was admitted electively to undergo POEM for recurrent achalasia.

History of past illness

The patient was diagnosed with achalasia and underwent a laparoscopic Heller myotomy with posterior Toupet fundoplication in 2004. He had no history of hepatic or hematologic disease. After one year of improvement, the patient complained of a relapse of achalasia symptoms with significant worsening in the late 2019. He complained about recurrent dysphagia, significant weight loss of 8 kg in 1 year, and repeated food impaction, which needed endoscopic clearance. Food stasis was found with dilated esophagus and resistance at the gastro-esophageal junction (GEJ) without any stricture. A barium meal demonstrated barium stasis and dilated esophagus caused by a large concentric narrowing at the GEJ. Manometry confirmed a recurrence of type 2 achalasia, with ineffective swallowing, incomplete relaxation of the lower esophageal sphincter and pan-pressurization. Computed tomography and magnetic resonance imaging in 2020 for staging workup of prostatic cancer revealed normal size spleen without vascular abnormality or signs of portal hypertension.

Based on the clinical presentation and manometry results we decided to perform a POEM. The procedure was performed under general anesthesia, using carbon dioxide insufflator, in November 2020. A 14 cm long submucosal tunnel that ended 3 cm below the GEJ was made with a triangle type knife using spray coagulation. A selective posterior myotomy was performed involving the circular inner layer using electric

endocut. However, a significant bleeding at the GEJ was noted, requiring hemostasis with a hemostatic forceps. The hemostasis maneuvers were efficient but caused a deeper muscle dehiscence. At the end of the procedure, the incision was closed with 6 endoscopic clips, and the iatrogenic pneumoperitoneum was decompressed. The procedure lasted 40 min. The patient was hospitalized for 24 h. Soft diet was resumed the next day, and the patient was discharged. His hemoglobin level was 129 g/L (Normal: 134-170 g/L).

Personal and family history

The patient is a 66-year-old man with a history of hypertension, and alcoholism with the consumption of 3 drinks *per* day. He had a prostatic adenocarcinoma that was treated with curie therapy in 2020. Family history was irrelevant.

Physical examination

Upon admission, the patient had left upper abdominal pain without defense or rebound tenderness. His vital signs were stable with blood pressure of 100/64 mmHg, HR of 76, and temperature of 37.0 °C.

Laboratory examinations

The blood tests revealed low hemoglobin level at 69 g/L (Normal: 134-170 g/L). Liver function tests and coagulation parameters were within the normal limits.

Imaging examinations

The enhanced abdominal computed tomography demonstrated a subcapsular hematoma in the spleen, measuring a maximum diameter of 12 cm and perpendicular diameter of 6 cm, with no active bleeding, and moderate hemoperitoneum but no pneumoperitoneum (Figure 1). There was still no sign of cirrhosis or portal hypertension.

FINAL DIAGNOSIS

Splenic rupture after POEM for recurrent achalasia.

TREATMENT

Considering the hemodynamic stability of the patient, supportive treatment was initiated with volume repletion and transfusion of two units of red blood cells. Close observation for 48 h confirmed his hematoma to be stable.

OUTCOME AND FOLLOW-UP

After a 48-h observation period, the patient was discharged from the hospital and his hemoglobin was 109 g/L (Normal: 134-170 g/L). The patient was contacted two, four and eight weeks after discharge. His evolution was uneventful. He was also eating normally.

DISCUSSION

Since its development, POEM is considered as an efficient procedure in the treatment of achalasia[1]. It has also evolved as a therapeutic modality in cases of achalasia recurrence after a surgical approach[10].

POEM appears to have a lower morbidity than the surgical approach[1]. Various complications have been reported with POEM including mucosal injuries, esophageal leak, bleeding or submucosal hematoma, chest pain or empyema. The most frequently reported complications are related to insufflation (capnoperitoneum, capnothorax and capnomediastinum), but these are usually minor[2]. A recent multicentric study reported the global and severe adverse events to be 7.5% and 0.5%, respectively[2]. Reported cases of hemorrhage were limited to esophagus or stomach[2]. To our knowledge, no cases of splenic injury have been reported to date in the literature.

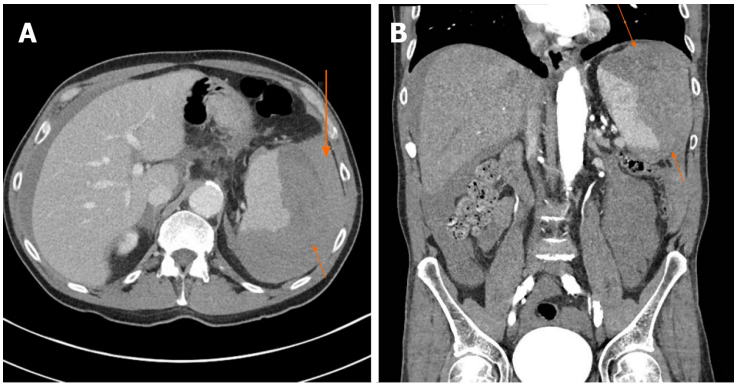

Figure 1 Transversal and coronal enhanced computed tomography with contrast showing a large splenic hematoma (short arrows) with perisplenic fluid (long arrow). A: Transversal; B: Coronal.

Although splenic rupture is very rare, it is a known complication after colonoscopy [4]. It occurs secondary to the traction that is exerted on the splenocolic ligament either upon advancing or retrieving the colonoscope, leading to capsular lacerations and avulsions.

Cases of splenic rupture have been reported secondary to endoscopic retrograde cholangiography[3]. Splenic injury occurring during this procedure is most likely due to looping of the endoscope and scope-related direct traction or shear forces on the greater curvature of the stomach, short gastric vessels, and splenic capsule[3].

However, this phenomenon of splenic injury is rare during flexible gastroscopy. Such a case was previously described in a patient with a gastric ulcer[6] and also in another patient with a tumor at the esophagogastric junction[5]. In both these cases, endoscopic exams were reported to be easy and no technical factor could evidently explain the splenic injury[5,6].

The precise underlying causes for splenic injury after gastroscopy remain unknown. Bowing of the endoscope along the greater curvature of the stomach can cause avulsion of the gastrosplenic ligament and/or short gastric vessels[3,6]. Some propose that the splenic injury can be caused by insufflation as well as the excessive retching experienced during the procedure, which could result in stretching of the peri-gastric ligaments[5]. In the present case, the procedure was carried out under general anesthesia, and the patient did not have significant nausea or vomiting after surgery. Moreover, no gastric pushing with the endoscope during the intervention was necessary and, despite the relatively long-time procedure, carbon dioxide insufflation significantly prevented distension. While all the other reported cases of splenic rupture following an upper endoscopy splenic rupture occurred immediately after the procedure[3,5-9], the latency for the onset of symptoms may share some similarity to the delayed splenic rupture that occurs after colonoscopy[4,11] or trauma[12].

Three cases of splenic laceration have previously been described after esophageal procedures and manipulation. A case of splenic injury was reported after placing a feeding tube through an extrinsic, probably neoplastic, stenosis of the middle esophagus using a 5.2 mm-gastroscope[9]. A second case of a splenic rupture was described after bougienage through a neoplastic stenosis at the GEJ[8]. Finally, a third case of splenic rupture occurred in a patient with a tortuous esophagus, narrowing of the esophageal sphincter, and enormous, almost completely intrathoracic stomach[7]. When performing a POEM, some force exerted at the GEJ, while forming submucosal tunnel at the tight distal esophagus, due to the hypertonicity of the inferior esophageal sphincter, could possibly contribute to splenic injury. However, this could not have been the cause in our case as we did not experience any unusual or specific difficulty during the procedure. Nevertheless, manipulation at the GEJ seems to be a constant adjunct to the mechanism of splenic injury[7-9].

A previous Heller myotomy along with a posterior partial anti-reflux procedure (Toupet) was carried out more than fifteen years ago in our patient. Earlier scarring around the GEJ and fundus might have inadvertently contributed to the splenic injury in this case. Not all the short gastric vessels could be divided during the previous fundoplication, and thus could be overstretched and became susceptible to bleeding. The exact mechanism that contributed to the splenic rupture is yet to be elucidated. Previous surgery is identified as a known risk factor of splenic rupture after colonoscopy[4]. However, these cases of splenic rupture after upper gastro-intestinal

procedures in patients with previous surgery[3] are anecdotal, similar to the present case, and no conclusion can be drawn about antecedent surgery as a significant contributing factor.

In the last ten years, POEM stands-out as the eventual treatment of choice of esophageal achalasia[1]. Thousands of cases have been reported and audited[2]. Cases of repeated POEM, after either endoscopic or surgical procedures, have been reported and evaluated[10]. Not even a single case of splenic rupture has been reported, reflecting the safety of POEM but this adverse event deserves consideration when more procedures will be done in the future by this approach.

CONCLUSION

This is the first reported case of splenic rupture after POEM. This very unusual but severe complication will probably occur again as this procedure will continue to be developed and implemented. Physicians must be aware that splenic rupture can happen after POEM and pay specific attention in patients with previous Heller myotomy.

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CASE REPORT

Endoscopic treatment of primary aorto-enteric fistulas: A case report and review of literature

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Author contributions: Berner-Hansen V drafted and registered the protocol, retrieved the data, analysed the data, drafted the manuscript, and approved and submitted the final manuscript; Olsen AA retrieved the data, reviewed the drafted manuscript, and approved the final manuscript; Brandstrup B conceived and designed the study, reviewed the protocol, supervised the study, reviewed the drafted manuscript, and approved the final manuscript.

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Abstract

BACKGROUND

Primary aorto-enteric fistula (PAEF) is a rare condition, traditionally treated in the acute, bleeding phase with open surgery or endovascular repair. However, these approaches have high morbidity and mortality, indicating a need for new methods. With advances in endoscopic techniques and equipment, haemoclipping of fistulas has now become feasible. Therefore, we present a systematic review of the English literature and a rare case of a PAEF successfully treated by endoscopic haemoclipping.

CASE SUMMARY

A 74-year-old man with an abdominal aortic aneurysm presented with symptoms of haemorrhagic shock and bloody stools. An oesophago-gastro-duodenoscopy was performed with haemoclipping of a suspected PAEF in the third part of the duodenum. Afterward, a computed tomography-angiography showed a contrast filled protrusion from the abdominal aortic aneurysm. Based on the clinical presentation and the combined endoscopic and radiographic findings, we argue that this is a case of a PAEF.

CONCLUSION

Endoscopic therapy appears capable of achieving haemodynamic stabilisation in patients with bleeding PAEF, serving as a bridge to final therapy.

Key Words: Endoscopy; Gastrointestinal haemorrhage; Surgical clip; Intestinal fistula, Vascular fistula; Systematic review; Case report

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Core Tip: Primary aorto-enteric fistula is a rare condition with high mortality. The current acute phase treatment is surgical or endovascular and is followed by high morbidity and mortality. The aim of this systematic review and case report was to put forward endoscopic haemoclipping as a new treatment option in the acute bleeding phase of an aorto-enteric fistula and, in a systematic manner, to search the literature for any evidence behind this therapy, including other reported cases.

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INTRODUCTION

A primary aorto-enteric fistula (PAEF) is a communication between the native aorta and the enteric system without prior surgery on the aorta[1]. Traditionally, treatment of a PAEF with acute bleeding includes open emergency surgical repair with *in situ* reconstruction or an extra-anatomic bypass of the aorta combined with repair of the bowel lesion. Over the last decades, endovascular aortic stenting has been introduced as a minimally invasive treatment option for abdominal aneurysms[2-4]. Closure of enterovascular fistulas from the vascular side is associated with better early survival than open surgery. A review of literature by Saers *et al*[5] reported an overall 30-d mortality rate for patients with PAEF of 44% and a mortality of 34% for patients who have had surgical treatment. By comparison, they found a 30-d mortality of 14% in a small group of patients who had endovascular repair. However, most of the benefit of lower mortality rates for patients treated with endovascular aortic stent was lost during long-term follow-up due to recurrent infection or recurrent AEF[6,7].

An aorto-duodenal fistula often presents itself with upper gastrointestinal bleeding and circulatory shock, which are symptoms identical to those of the much more common bleeding duodenal or gastric ulcers. Oesophago-gastro-duodenoscopy (OGD) is recommended as the first diagnostic choice in patients with signs of upper gastrointestinal haemorrhage[8,9]. OGD is, in most cases, successful in achieving haemostasis in patients with bleeding ulcers, and dual therapy with injection of epinephrine, electrocoagulation, or haemoclipping of the bleeding site or vessel is the state of art technique[10]. Sometimes, however, the bleeding is not caused by an ulcer but by a Dieulafoy lesion, a Cameron lesion, or bleeding from varicose veins among other reasons. Endoscopic treatment is also effective in achieving haemostasis and preventing rebleeding in these cases[11]. With advances in endoscopic techniques and equipment, large clips for the closure of vascular-enteric fistulas have come forward [12]. Per the literature and in our institution, such clips are successfully used for endoscopic closure of full-thickness gastrointestinal wall defects as well as interenteric or enterocutaneous fistulas[13,14]. Thus, clipping of fistulas has now become feasible, and the clipping of aorta-duodenal fistulas might be the next step forward.

The aim of this systematic review and case report was to put forward endoscopic haemoclipping as a new treatment option in the acute bleeding phase of an AEF and in a systematic manner to search the literature for any evidence behind this therapy, including other reported cases.

Literature search

This case report adheres to the SCARE criteria[15]. The systematic review follows the PRISMA guidelines[16]. The protocol was registered in Prospero (number CRD42019142202) before the literature search was commenced. Included were all original studies, including case reports describing symptomatic PAEFs treated with therapeutic endoscopy. A PAEF was defined as a fistula from the thoracic or abdominal aorta to the intestines, including the duodenum, ileum, jejunum, and all segments of the colon. Endoscopic treatment was defined as all therapeutic endoscopic procedures. Excluded were papers describing treatment of secondary fistulas, fistulas

from other branches of the aorta and other segments of the gastrointestinal tract, and papers not using endoscopy for treatment. The language was limited to English.

We performed an electronic literature search in PubMed, Embase, and The Cochrane Library for articles published between January 1999 and April 2020. The search was built as a "text word" search combining synonyms for "aortoenteric fistula" and "primary" and limited to English literature. The first author screened all titles and abstracts of the retrieved studies and performed full-text assessments to determine the inclusion. In any case of doubt, the second author assessed the study. Disagreements were resolved through discussion and consultation of the supervisor (BB).

Additional articles were found by screening reference lists of studies included after full-text assessment. To assess the risk of bias, the included studies were analysed according to the assessment tool provided by Murad *et al*[17]. Figure 1 shows the PRISMA search strategy and the inclusion of studies. The data extracted were patient age, gender, anatomic location of the fistula, endoscopic finding, endoscopic treatment modality, subsequent treatment, follow-up length, and outcome. Because we did not expect to find any randomized clinical trials or high-quality cohort studies, we did not plan for any statistical analysis.

CASE PRESENTATION

Chief complaints

A 74-year-old man was admitted to our department with fresh bloody stools and melena during the evening.

History of present illness

Earlier on the same day, the patient was discharged after 4 d of admission due to gastrointestinal bleeding. During the earlier admission, an OGD to the second part of the duodenum revealed two small (8.0 mm) fibrin-covered ulcers in the duodenum with no sign of bleeding. Because this was the only pathological finding and considering the patient's history, they were treated with dual therapy (injection of diluted epinephrine and electrocoagulation). Also, the patient received blood transfusions, intravenous fluid, and pantoprazole. During the following 4 d, the patient had minor episodes of dark stools but no fresh bleeding, and the haemoglobin levels increased.

History of past illness

The patient had several comorbidities including oropharynx cancer, chronic obstructive pulmonary disease, paroxysmal atrial fibrillation, and essential arterial hypertension. Also, the patient had an infrarenal abdominal aortic aneurysm with a diameter of 6.3 cm and a long neck of 2.2 cm in diameter, and an aneurysm on the right common iliac artery measuring 5.0 cm. The patient had regular check-ups for his aorta aneurysm at a vascular surgical department in another hospital.

Physical examination

At admission, the patient was pale but alert with a blood pressure of 95/70 mmHg and a heart rate of 68 beats per minute. On physical examination, auscultation of heart and lungs was normal, the abdomen was soft and without tenderness, but a pulsating filling could be felt to the left of the umbilicus. The rectal examination showed melena with fresh blood.

Laboratory examination

The plasma haemoglobin was 4.0 mmol/L.

FINAL DIAGNOSIS

The final diagnosis of the presented case is, in our opinion, PAEF, based on the combined endoscopic and CT-angiographic findings.

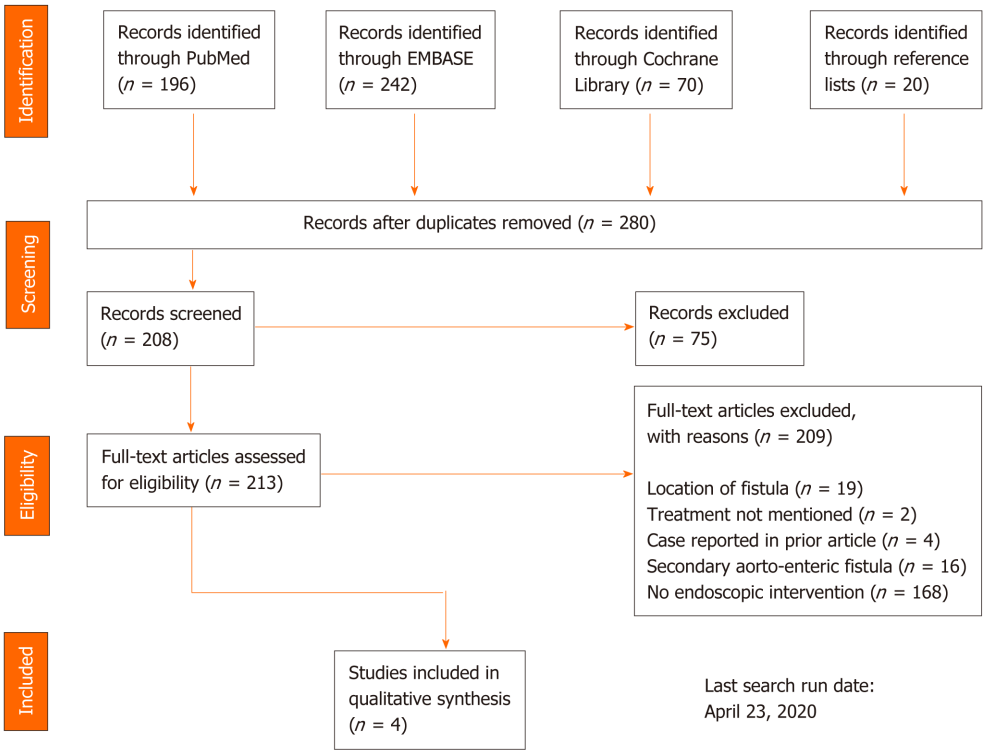

Figure 1 The PRISMA search strategy.

TREATMENT

The patient was readmitted with the abovementioned symptoms. An emergency OGD was performed, and the nonbleeding small ulcers in the duodenum were visualized without signs of bleeding. However, this time the endoscope was advanced further, and an erosion of the mucosa in the third part of the duodenum (measuring 5.0 mm) with a blood clot and a visible pulsating aorta underneath was found (Figure 2A). A PAEF was suspected, and haemostasis was achieved with three haemoclips placed deep in the wall of the gut, covering the fistula (Figure 2B). Following this procedure, no subsequent haemorrhage was identified. To support the hypothesis of an aorto-duodenal fistula, contrast-enhanced computed tomography (CT) with arterial and venous phase was performed the following day. The CT showed a contrast-filled protrusion from the abdominal aortic aneurysm towards the haemoclips adjacent to the aneurysm sack, separated by a mural thrombus (Figure 3). For possible vascular intervention, we contacted two vascular surgical departments. However, based on the patient's cancer disease and the CT-angiography, they did not find vascular therapy indicated and did not find it proven that a PAEF caused the bleeding. To our knowledge, the endoscopic pictures were not included in the decision-making.

OUTCOME AND FOLLOW-UP

The patient was discharged in his habitual condition after 10 d, without any signs of infection or rebleeding. Fourteen months later, the patient succumbed due to respiratory problems and terminal cancer without any incidences of gastrointestinal bleeding. The death was expected, and an autopsy was not sought.

DISCUSSION

The English literature identified only four case reports[18-21] fulfilling the inclusion criteria (Table 1). The anatomical location of the PAEF varied, and the endoscopic findings included pigmented protuberances, lesions/erosions, and oozing bleeding[22, 23]. In two of the cases, the treatment was dual, as recommended for bleeding ulcers

Table 1 Cases of primary aorto-enteric fistula

	Tsai *et al*[18]	Lee *et al*[19]	Kim *et al*[20]	Mok *et al*[21]	Present case
Age in year, Sex	69, male	86, female	63, male	67, male	74, male
Anatomic location	Third part of duodenum	Sigmoid colon	Second part of duodenum	Oesophago-jejunal anastomosis	Third part of duodenum
Cause of PAEF	Aortic aneurysm	Aortic aneurysm	Aortic aneurysm	Infectious thoracic pseudo-aneurysm; oesophago-jejunal anastomotic leak	Aortic aneurysm
Endoscopic finding	Vessel-like bleeding with blood clot adhesion	Nodular lesion with central dimpling (small, depressed area)	Active bleeding	Oozing blood and blood clot	Mucosal erosion/nodular lesion with central depression and blood clot; Pulsating aorta underneath
Endoscopic treatment	Epinephrine and haemoclips	Electro-coagulation and haemoclips	Haemoclips alone	Fibrin sealant	Haemoclips alone
Endoscopic outcome	Successful haemostasis	Initial haemostasis, rebleeding	Successful haemostasis	Successful closure of fistula	Successful haemostasis
Following treatment	Open surgical repair of the aneurysm and bowel	Angiographic embolization	Endovascular stent repair with angiographic embolization and open surgical repair of the bowel	Endovascular stent repair with drainage of aneurysm sac (performed before endoscopic treatment)	None
Outcome	Alive at 24 mo follow-up	Died during the angiographic procedure	Alive at 12 mo follow-up	Alive at 14 mo follow-up	Died 14 mo after endoscopy

PAEF: Primary aorto-enteric fistula.

[8]: Diluted epinephrine injection and haemoclipping[18]; and respective electrocoagulation and haemoclipping[19]. In the third case, haemoclipping alone was used as a bridge to surgery[20]. A fourth case described fibrin sealant placed through the endoscope combined with percutaneous endovascular aneurysm repair[21]. In all four cases initial endoscopic haemostasis was achieved. In one case, endoscopic haemostasis was only achieved for a couple of hours whereafter massive rebleeding occurred[19]. Two cases described successful endoscopic haemostasis until final surgery was performed[18,20]. In the fourth case, the combined treatment successfully closed the fistula[20].

More than 50% of PAEF are situated in the duodenum because of its close anatomical relation to the aorta. Other locations include the oesophagus, stomach, ileum, jejunum, and colon[5,24]. One review found an incidence of PAEF as the cause of gastrointestinal haemorrhage in 0.18% of cases[25]. Another study, asking 180 surgeons if they have ever treated a patient with a PAEF during their career, suggested the incidence to be greater[26]. The classic clinical presentation includes abdominal pain, signs of upper gastrointestinal bleeding, and an abdominal pulsating mass.

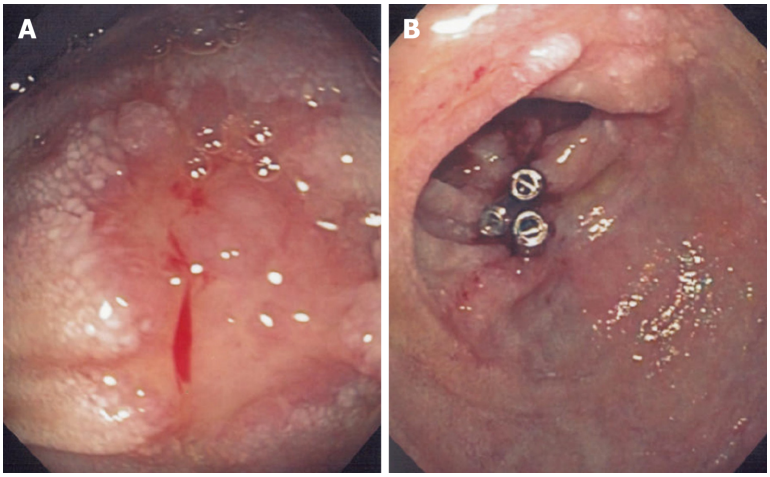

Figure 2 Endoscopic findings. A: The mucosal erosion with a blood clot; B: The erosion closed with three haemoclips.

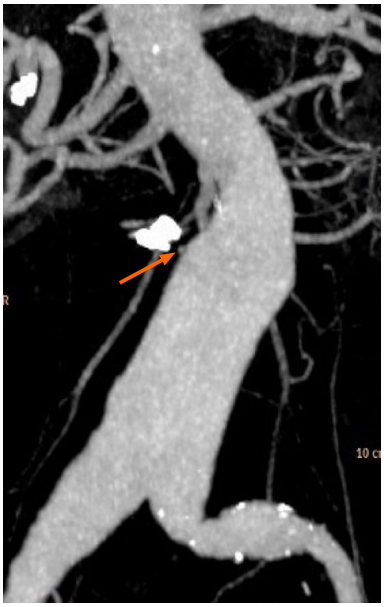

Figure 3 Computed tomography-angiography reconstruction showing the protrusion from the aortic aneurysm towards the haemoclips in the duodenum (arrow).

Before the diagnosis, patients often have a "herald bleeding" that may cause exsanguination and death. However, only 6%-28% of the cases present all three symptoms. Thus, the majority of the patients present as "atypical"[5,24,27,28]. An AEF is therefore important to consider in patients with gastrointestinal haemorrhages and an aortic aneurysm.

A contrast-enhanced CT scan is regarded as the best diagnostic tool for the detection of AEF[28-31]. However, in a patient without a history of vascular surgery presenting with upper gastrointestinal bleeding, an AEF is not the first diagnosis that comes to mind. Hughes *et al*[31] investigated the signs found on CT scans. They showed that CT scans have an overall specificity of 100%, but the sensitivity was only 50%. The presence of ectopic bowel gas or extravasation of contrast into the bowel lumen increased the sensitivity to 100%. The finding of a branch from the aortic wall had a sensitivity of 80% and specificity of 75%. These numbers are in agreement with the findings of others[5,24,31,32]. Thus, in the diagnosis of an AEF, a positive CT result is useful but a negative CT finding does not yield reliable information. Because ulcers are common, OGD is the gold standard for the diagnosis and treatment of upper gastrointestinal bleeding. An OGD identified the AEF or showed other abnormalities in only 25%-50% of confirmed AEF cases, likely due to a typical OGD often omitting the examination of the third part of the duodenum[5,33]. In four of the cases described in this study, active bleeding was seen at the sight of the fistula during OGD[18,20,21].

In other cases, where OGD was the diagnostic tool, the AEF was described as a submucosal tumour-like lesion and being "pulsating"[23,34]. Sometimes oozing bleeding, the presence of a blood clot or the sense of pulsation may be the only thing that differentiate the descriptions given of the AEF from a description of other enteric fistulas[35].

No study on the diagnostic specificity and sensitivity for the endoscopic detection of PAEF exists. In our opinion, the negative CT finding in the case presented here does not necessarily rule out an AEF, especially following endoscopic haemostasis. On the contrary, the CT-angiography with three-dimensional reconstruction showed a contrast-filled branch from the abdominal aorta aneurysm in close relation to the duodenum, a finding with a specificity of 75% according to the literature[31]. In our opinion, the endoscopic and the CT findings together strengthen the diagnosis.

In all the cases described in the literature, final surgery (endovascular or open) followed the endoscopic treatment, and the endoscopically achieved haemostasis successfully formed a bridge to surgery. The patient presented herein was the only patient who did not have surgery after endoscopic haemostasis was achieved. The reason for this was due to the patient's multiple comorbidities, including incurable cancer, a limited life expectancy, and a high risk of postoperative adverse outcomes. However, the haemoclipping was immediately lifesaving and was an effective long-term treatment.

Haemoclips can remain *in situ* for a long period, but we found no literature describing the life span or the mean *in situ* time for a haemoclip. Olmez *et al*[36] described a haemoclip *in situ* for more than 2 years. In our experience, a well-placed haemoclip for haemostasis after polypectomy is often found *in situ* at the adenoma control endoscopy after 6-12 mo, but no studies were found to support this. However, the clip functions as a ligation, and the nature of the fistula determines whether a ligation is sufficient to close it. Open vessels are closed by ligation, as are fistulas following anastomotic leakage of the gut. It is unknown whether a PAEF can be closed by simple ligation (clipping).

When a PAEF is clipped, the clip may function as a marker for the fistula site before final therapy. A clip can mark a lesion in the gastrointestinal tract[37] and increases the success rate of angiographic embolization of bleeding arteries in ulcers[38]. Based on our knowledge of the more common secondary AEFs, we know that infection is a common problem when the fistula is closed from the vascular side only. In a trial comparing closure of secondary AEFs using a vascular stent to open surgical repair, Kakkos *et al*[6] found that vascular stent repair can achieve immediate haemostasis and has a better short-term outcome. However, an infection of the stent and sepsis often follow the procedure, losing most of the benefit during long-term follow-up. The open communication to the bacteria-filled enteric side likely causes the infection. Therefore, closure of the enteric lesion by open surgery is recommended to follow vascular stenting[6,39].

The option of two minimally invasive procedures combined have not been investigated. It may be possible to clip (or stent in the oesophagus) the fistula from the enteric side followed by stenting from the vascular side. A successful case of secondary AEF initially closed from the vascular side immediately followed by endoscopic closure from the enteric side has been reported[40].

The small number of endoscopically treated PAEFs described in the literature limits this study. This small number increases the difficulty of creating clinical recommendations. However, bleeding from an AEF is a life-threatening condition, and every effort to stop the loss of blood as soon as possible is desirable. By creating a bridge to surgery and achieving haemostasis, critical time is bought for the patient. This time may mean that the experienced surgeon is present or that the patient can be transferred to another facility for optimal care. Thus, any modality creating immediate haemostasis for these patients represents a therapeutic improvement. It is unknown whether endoscopic treatment such as haemoclipping or epinephrine injection can aggravate ongoing bleeding from an AEF.

CONCLUSION

Endoscopy is the first-choice modality for the diagnosis and treatment of upper gastrointestinal bleeding including a PAEF, which is a rare finding. Endoscopic therapy including haemoclipping can establish lifesaving, immediate haemostasis from a bleeding PAEF, thus stabilizing the patient without hampering subsequent endovascular therapy or surgery. Endoscopic therapy might be useful as a bridge to

surgery.

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MINIREVIEWS

Innovation of endoscopic management in difficult common bile duct stone in the era of laparoscopic surgery

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Abstract

Common bile duct (CBD) stone is a common biliary problem, which often requires endoscopic approach as the initial treatment option. Roughly, 7%-12% of the subjects who experience cholecystectomy were subsequently referred to biliary endoscopist for further management. In general, there are three classifications of difficult CBD stone, which are based on the characteristics of the stone (larger than 15 mm, barrel or square-shaped stones, and hard consistency), accessibility to papilla related to anatomical variations, and other clinical conditions or comorbidities of the patients. Currently, endoscopic papillary large balloon dilation (EPLBD) of a previous sphincterotomy and EPLBD combined with limited sphincterotomy performed on the same session is still recommended by the European Society of Gastrointestinal Endoscopy as the main approach in difficult CBD stones with history of failed sphincterotomy and balloon and/or basket attempts. If failed extraction is still encountered, mechanical lithotripsy or cholangioscopy-assisted lithotripsy or extracorporeal shockwave lithotripsy can be considered. Surgical approach can be considered when stone extraction is still failed or the facilities to perform lithotripsy are not available. To our knowledge, conflicting evidence are still found from previous studies related to the comparison between endoscopic and surgical approaches. The availability of experienced operator and resources needs to be considered in creating individualized treatment strategies for managing difficult biliary stones.

Key Words: Difficult common bile duct stones; Endoscopic sphincterotomy; Endoscopic papillary large balloon dilatation; Mechanical lithotripsy; Cholangioscopy; Laparoscopic surgery

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Core Tip: Difficult common bile duct stone is defined based on the characteristics of the stone, accessibility to papilla related to anatomical variations, and other clinical conditions or comorbidities of the patients. Currently, endoscopic papillary large balloon dilation (EPLBD) of a previous sphincterotomy or EPLBD combined with limited sphincterotomy performed on the same session is still recommended as the main approach in difficult common bile duct stone with history of failed sphincterotomy and balloon and/or basket attempts. No significant difference has been observed in mortality and morbidity rates, as well as conversion to open surgery between groups treated with a single-stage laparoscopic procedure and two-stage endoscopic and laparoscopic procedures.

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INTRODUCTION

Common bile duct (CBD) stone is a common biliary problem which often need endoscopic approach as the initial treatment option. Roughly, 7%-12% of the subjects who experience cholecystectomy were subsequently referred to biliary endoscopist for further management[1,2]. Approximately, 85%-95% of all CBD stone cases can be managed with standard conventional endoscopic approaches, such as endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (EST) accompanied with basket or balloon extraction[1]. ERCP itself has been known as a standard therapeutic option for bile duct stone removal since 1974[3]. In around 15% of the patients, however, the clearance of biliary system cannot be successfully achieved with standard approaches; making these cases referred as "difficult CBD stone". A study performed in a single tertiary center showed that 13.6% from 1529 patients had been diagnosed with difficult CBD stone[4]. One of pioneered study by Lesmana[5] in Indonesia also showed approximately 16.9% patients with difficult CBD stones (defined as large, impacted, or stones located in the distal narrowing). Until now, there is no general agreement or consensus on the definition of difficult CBD stone yet. In general, there are three classifications of difficult CBD stone, which are based on the characteristics of the stone (> 15 mm, barrel or square-shaped stones, and hard consistency); accessibility to papilla related to anatomical variations; and other clinical conditions or comorbidities of the patients (coagulation problems the use of anti-platelets or anti-thrombotic agents, age > 65 years old)[3,6].

ENDOSCOPIC MANAGEMENT FOR DIFFICULT CBD STONE

Endoscopic mechanical lithotripsy

First introduced in 1982, mechanical lithotripsy has been commonly used for fragmentation of the stone. High success rate (79%-96%) of mechanical lithotripsy for CBD stone larger than 2 cm has been demonstrated due to high breaking strength of contemporary lithotripter baskets[1,7]. Moreover, the procedure is widely available, cost-effective, and simple. In general, there are two types of mechanical lithotripters, depending on elective or salvage therapeutic goal. The basket for elective model ('through-the-scope' model) consists of the basket, inner plastic sheath, and outer metal sheath. Fragmentation of the stones can also be performed after removing the duodenoscope from the patient and removing the handle from the basket. Additionally, basket impaction can also happen with this type of scope (less frequent compared to extraction baskets with thinner wires and weaker handles). The basket intended for salvage therapy is a type in which a traditional basket is used to crush a stone impacted in the bile duct[1,3].

However, higher failure rate has been observed in patients with stones larger than 2 cm in diameter[3,8]. A retrospective cohort study in 162 subjects showed significantly lower cumulative probability of bile duct clearance ($P < 0.02$) in clearance of stones larger than 2.8 cm in diameter[7,8]. A study in 102 subjects demonstrated stones larger than 30 mm [odds ratio (OR) = 4.32], impacted (OR = 17.8), and ratio of bile duct diameter larger than 1 (OR = 5.47) as the predictors for failure in doing mechanical lithotripsy[9]. Another study added another predictive factor for mechanical lithotripsy, which was the impacted stone in the bile duct due to inability of the basket to grasp the stone properly or to pass the basket proximally towards the stone[10]. Stones with harder consistency have also been associated with higher failure rates and may not be easily managed by the lithotripter basket[11]. However, there was a contradictory evidence from a single center study in 592 subjects, which showed high clearance rates for impacted stones (96%) and stones larger than 2 cm in diameter (96%)[12].

Lack of preferences in using mechanical lithotripsy is also due to its potential complications. Common technical and medical complications issue which might occur, such as basket impaction, fracture of the basket wire, broken handle, bleeding, pancreatitis, perforation or injury to the bile duct, and cholangitis, particularly in patients with larger stones[1,12]. However, a multi-center study indicated lower rate of complications associated with mechanical lithotripsy (3.6%)[13]. When complications occur, non-surgical interventions are sometimes necessary, for instance, extended sphincterotomy, use another lithotripter, shift towards other procedures (*e.g.*, electrohydraulic lithotripsy, EHL), or spontaneous passage of impacted stones or basket[1].

EHL

As an option in managing difficult bile duct stones, EHL was initially used as an industrial tool for disintegrating stones in mines. The first attempt of using this technique in biliary stone was performed by Koch *et al*[14]. The device contains a bipolar lithotripsy probe and a charge generator with an aqueous medium. The principal mechanism of EHL is a production of high-frequency hydraulic pressure waves, which is subsequently absorbed by bile duct stones. The procedure can be done by inserting a cholangioscope through the instrument channel of another scope with continuous water irrigation under the guidance of fluoroscopy. The water acts as a propagator of shock waves and as a fluid medium which can flush away the debris, and therefore providing clearer visualization of the stones and ductal wall[15]. This mechanism, however, can lead to several adverse events, such as unintended perforation of the bile duct wall (related to the inappropriate probe positioning) or poor direct visualization by fluoroscopic guidance since it only utilizes two-dimensional imaging[16].

EHL has been proposed as one of the best methods for disintegration of biliary stones due to its compact and relatively cost-effective equipment. In addition, the procedure does not require supplementary protective gear or specialized trainings[1]. Recently, a study by Kamiyama *et al*[17] established a clinical evidence of technical feasibility and clinical effectiveness from utilizing EHL with a digital single-operator cholangioscope (SPY-DS). In this pilot study, complete stone clearance rate achieved was 97% in 42 subjects who underwent EHL with SPY-DS[17]. Another study by Binmoeller *et al*[18] also showed successful results of EHL in 63 of 64 subjects with history of failed mechanical lithotripsy. High rates of stone disintegration (96%) and stone clearance (90%) were also demonstrated by Arya *et al*[19].

It has also been demonstrated that it is possible using EHL technique under ERCP or per-oral transluminal cholangioscopy (PTLC) guidance. Several indications for performing EHL under ERCP guidance are large or multiple bile duct stones, intrahepatic bile duct stones, assemblage of multiple stones, and bile duct stricture. The technique involves insertion of a duodenoscope into the ampulla of Vater and inserting an ERCP catheter into the CBD simultaneously. The high frequency shockwaves are applied as a continuous discharge, generated using an electrohydraulic shock wave generator. Removal of bile duct stones is conducted with basket or balloon catheter. On the other hand, EHL under PTLC guidance is usually performed in the case of surgically altered anatomy or duodenal obstruction, where the papilla becomes inaccessible for ERCP to be performed. EHL under PTLC guidance can also be performed on a large stone, which cannot be removed by basket or balloon catheter. The mechanism consists of creating a fistula between biliary tract and stomach, through which EHL will be performed. Before performing PTLC, the operator needs to perform an endoscopic ultrasound-guided hepaticogastrostomy (EUS-HGS) first for placing the stent from the intrahepatic bile duct to the stomach. Detection of intrahepatic bile duct is done by inserting an echoendoscope into the

stomach. For small CBD stones, a balloon catheter can be used to perform antegrade stone extraction, while in larger CBD stones, stone fragmentation is necessary by performing antegrade stone extraction through EHL with SPY-DS. EUS-HGS stent is particularly beneficial for performing stone extraction in extremely small stones after EHL[17].

Overall, the rate of complications in EHL is relatively low (approximately 7%-9%). The most common complications are cholangitis, ductal perforation or injury, and hemobilia[1]. A retrospective study showed higher success rate (80%) with lower rate of complications (7.7%) in subjects with history of failed conventional attempts who underwent EHL and further ERCPs, compared to stenting as a single procedure. These data also included elderly and frail population[20]. In a study by Kamiyama *et al*[17], adverse events (cholangitis and acute pancreatitis) were observed in approximately 14% of the subjects. Nevertheless, the complications were able to be treated conservatively in the study.

Extracorporeal shockwave lithotripsy

The basic principle of extracorporeal shockwave lithotripsy (ESWL) is the generation of high-pressure electrohydraulic shockwaves outside the body. The waves are produced by piezoelectric crystals of electromagnetic membrane technology and directed by elliptical transducers through a liquid medium. This procedure is conducted under the guidance of ultrasound machine or fluoroscopy. Sometimes, a nasobiliary tube (NBT) can also be inserted for better visualization. The success of single session of ESWL procedure is critically determined by the size and structure of the stones, as well as the presence of bile duct stenosis. Moreover, ESWL allows fragmentation of multiple stones simultaneously[1].

High success rate of ESWL procedure has been established from previous studies. A study by Sauerbruch and Stern[21] demonstrated high efficacy of CBD stones fragmentation (approximately 90%) with minimal adverse events. A single-center study in 214 subjects who underwent ESWL throughout 15 years of observation also showed high complete stone clearance (89.7%). Around 57% of the subjects with clearance had biliary stones smaller than 2 cm (0.8-5 cm) in diameter, while 51% of the subjects without clearance had biliary stones larger than 2 cm (1-3.5 cm) in diameter [22]. Similar finding was also found by Tandan and Reddy[23], showing complete clearance of the large CBD stones (84.4%) with over 75% of the subjects only needed three or fewer ESWL sessions (delivering 5000 shocks per session). Generally, ESWL also showed minimal and mild adverse events, although more serious adverse events, such as transient biliary colic, subcutaneous ecchymosis, cardiac arrhythmia, haemobilia (often self-limiting), cholangitis, ileus, pancreatitis, perirenal hematoma, bowel perforation, splenic rupture, lung trauma, and necrotizing pancreatitis also need to be anticipated[1,23]. In addition, considerably low recurrence rate of CBD stones after CBD clearance has also been indicated from previous studies (roughly, 14% of recurrence rate)[24,25].

ESWL can also be particularly beneficial for patients with anatomically abnormal structures. For instance, in patients with inaccessible papilla due to history of Billroth-II or Roux-en-Y surgeries. Also, in cases with surgically altered anatomy, not only the size of bile duct stones, but also the size of CBD itself is often large. In these cases, endoscopic nasobiliary drainage tube placement is often required to guide ESWL. If optimal result cannot be achieved with ESWL, then percutaneous transhepatic biliary drainage (PTBD) or endoscopic ultrasound (EUS)-guided intraductal lithotripsy can be performed[1,26].

Laser lithotripsy

First introduced in 1986, the general concept of laser lithotripsy (LL) includes laser light at a certain wavelength, directed towards the surface of the stone. This process induces a generation of wave-mediated disintegration of stone[1]. The first type of laser utilized for bile duct stones is pulsed laser, followed by neodymium-doped yttrium aluminium garnet (Nd:YAG), coumarin, rhodamine, and the new Frequency Doubled Double Pulse Nd:YAG (FREDDY) system[1,27]. LL can be conducted by transhepatic approach or under direct visualization using cholangioscopic or fluoroscopic guidance[1]. The use of cholangioscopic guidance has been widely accepted as more superior compared to fluoroscopic guidance, especially with the emerging single-operator cholangioscopy-guided system. In a prospective multicenter clinical study, 94.1% of the patients successfully underwent complete stone clearance after one session with cholangioscopy-guided LL and/or EHL procedures[28]. The main concern of using this approach is lower quality of fiber optic image compared to the quality of videocholangioscopes[1].

Although the range of success rate is quite wide compared to other modalities (64%-97%), previous evidence have pointed out the superiority of LL in stone clearance rate and faster duration of treatment and stone fragmentation, therefore, also contributing to its cost-effectiveness[1]. A randomized study by Neuhaus *et al*[29] showed significantly higher success rate ($P < 0.05$) of bile duct clearance achieved by LL (97%) compared to ESWL (73%). This study involved 60 subjects with history of previous failed standard stone extraction. The study also indicated significantly shorter duration of treatment (0.9 ± 2.3 d in LL *vs* 3.9 ± 3.5 d in ESWL, $P < 0.001$) and a smaller number of sessions (1.2 ± 0.4 in LL *vs* 3.0 ± 1.3 in ESWL, $P < 0.001$)[29]. Another prospective randomized study by Jakobs *et al*[30] also reinstated the superiority of LL compared to ESWL, in terms of complete stone fragmentation percentages (82.4% *vs* 52.4%). Groups treated with LL also demonstrated significantly lower number of fragmentation sessions ($P = 0.0001$) and additional endoscopic sessions ($P = 0.002$)[30].

Recent evidence related to LL mentioned an innovation in the procedural aspect, as well as the possibility of this method to reduce the necessity for post-procedure surgery. A randomized trial by Buxbaum *et al*[31] was comparing the use of cholangioscopy-guided LL and conventional therapy in 60 subjects with bile duct stones larger than 1 cm in diameter. In this study, conventional therapies, such as mechanical lithotripsy and papillary dilation were included in the laser group. Successful endoscopic stone clearance was shown in 93% of the subjects who underwent cholangioscopy, compared to only 67% in patients who underwent only conventional approaches ($P = 0.009$). However, the mean duration of procedure was significantly longer in cholangioscopy-guided LL group (120.7 ± 40.2 min) compared to conventional therapy group (82.1 ± 49.3 min, $P = 0.0008$)[31]. The use of double-lumen basket has also been introduced from a case series for providing LL with higher effectiveness by allowing a passage of a laser probe after the stone is caught by the basket[32].

Direct peroral cholangioscopy

A direct observation with direct peroral cholangioscopy (DPOC) utilizes a high-definition ultra-slim upper endoscope with narrow band imaging capability through the biliary sphincter into the bile duct. Gradually, with this technique, DPOC becomes a preferable method for managing bile duct stones due to its therapeutic potentials, digital image quality, and the capability to be performed with a single operator. Aside from high-resolution optics, DOPC also has 2.00 mm working channel which can be helpful in the intervention for malignant strictures of impacted bile duct stones with additional accessories which cannot pass through other cholangioscopes[1,3].

The role of additional accessories or techniques has been regarded as important in DPOC, especially for increasing the success rate of DPOC. A major challenge of using an ultra-slim endoscope is the looping of endoscope in the stomach or duodenum due to the difficulty of directing its flexible shaft from the duodenum into the biliary tract. A study by Moon *et al*[33] demonstrated a utilization of intraductal balloon in ropeway technique. This balloon is attached in an intrahepatic bile duct to facilitate the ultra-slim upper endoscope into the biliary tree. The authors, however, mentioned the presence of technical problems for maintaining the position of the endoscope when the balloon was withdrawn[33]. Aside from intra-ductal balloon, the use of an over tube balloon has also been proposed to assist the advancement of ultra-slim upper endoscope. However, this method is not very recommended due to discomfort for patient and possibility of looping as a result of larger inner diameter of the over tube (10.8 mm), compared to the outer diameter of the upper endoscope (5.2-6 mm)[34,35]. Another approach is by inserting upper endoscope assisted with a guidewire, which is placed during ERCP. However, there is also a possibility of dislodged guidewire and looping with this method. In some cases, applying manual pressure on the abdomen of the patient has been shown to allow wider passage of the upper endoscope into the hilar area[35,36]. A small study conducted in 18 patients with prior failed attempt of conventional therapy demonstrated a favorable result of DPOC-guided EHL and LL, showing almost 90% of success rate with average of 1.6 endoscopic sessions for every patient[37].

Despite its effectiveness, DPOC has been associated with a handful of adverse events. One of the most serious complications is air embolism, which manifests from asymptomatic to hypoxia, cardiac arrest, or even severe cerebral ischemia[3]. One case report presented an occurrence of left-sided hemiparesis after the application of direct cholangioscopy with intraductal balloon anchoring system[38]. Several ways have been advised to anticipate this problem, such as using saline irrigation or copious water, and using CO_2 for insufflation[3,39].

Endoscopic papillary large balloon dilation

Endoscopic papillary large balloon dilation (EPLBD), or also known as dilatation-assisted stone extraction (DASE), was first reported by Ersoz *et al*[40], who utilized an esophageal dilatation balloon with 12-20 mm in diameter. The stone extraction in this procedure is performed after partial biliary sphincterotomy and dilation of papillary orifice. Initial studies demonstrated promising success rates (88%-100%) with acceptable and self-limited complication rates (0%-16%) from this procedure[1]. A study consisting of two prospective trials from 2014 to 2019 also exhibited similarly high success rates (91.3%) in 299 subjects with difficult bile duct stones (defined as larger than 1 cm in diameter, impacted, or multiple stones) with low rate of complications (10.8%). No hospital mortality was observed among 46 subjects who underwent EPLBD after prior failed attempt of conventional approaches[41].

Divided opinions still arise pertaining to the relationship between EPLBD and EST, especially related to whether EPLBD should be first preceded by EST or not. One meta-analysis comparing EPLBD and EST showed similar rates of complete stone removal between both techniques (95% *vs* 96%, $P = 0.36$). However, the use of EPLBD was associated with lower number of hemorrhages, compared to EST (0.1% *vs* 4.2%, $P < 0.00001$). Higher utilization of endoscopic mechanical lithotripsy was also found in EPLBD group (35% in EPLBD *vs* 26.2% in EST, $P = 0.0004$)[42]. Another problem is the high incidence of pancreatitis in cases of EPLBD without a prior EST, which possibly due to the injury of pancreatic sphincter caused by the balloon. Meanwhile, the risk of bleeding or retroduodenal perforation is also higher in large EST. There is insufficient evidence regarding the efficacy of EPLBD without EST, particularly in managing large bile duct stones. Nevertheless, theoretically, a large balloon dilatation can be implemented safely by making a small EST to detach the pancreatic orifice from biliary opening, while minimizing the risk of pancreatitis, bleeding, or perforation[3]. A study in 60 subjects with full length EST performed before EPLBD for large CBD stones (average size of 16 mm) showed high success rate of complete stone clearance in a single session procedure[43]. In the meantime, there were also studies showing high stone removal rates using balloon dilatation without EST (95%-98%) with around 1-1.2 mean endoscopic session per patient[44,45].

As implied above, despite being a promising therapeutic option, EPLBD is also associated with serious complications. Higher risk of post-ERCP pancreatitis is associated with compressed pancreatic duct, which can be caused by intra-mucosal bleeding, inflammation of the papilla, and abnormally loose sphincter of Oddi[46]. A large multi-center study showed approximately 6% of 946 subjects experienced bleeding after EPLBD procedure. From the multivariate analysis, there are three factors which may influence the hemorrhage risk, *i.e.*, the presence of cirrhosis (OR = 8, $P = 0.003$), full-length EST (OR = 6.22, $P < 0.001$), and stones ≥ 16 mm (OR = 4, $P < 0.001$)[47]. However, another study pointed out only a small number of self-limited bleeding complications (around 8%) in EPLBD procedure preceded with full-length EST[43]. One randomized controlled trial proposed longer duration of dilatation (5 min *vs* 1 min) to increase the adequacy of the loose sphincter of Oddi, thus, also reducing the risk of post-ERCP pancreatitis[48].

EPLBD has also become an alluring option for patients with surgically altered anatomy, where sphincterotomy cannot be performed adequately. A retrospective study with EPLBD or combination between EPLBD and EST performed in 30 subjects with previous history of Billroth-II gastrectomy, demonstrated 96.7% successful stone removal rate and successful stone retrieval during the first session in 90% of the subjects. One subject underwent further surgery after the procedure due to severe CBD stricture, while two subjects underwent mechanical lithotripsy afterwards[49]. One systematic review also supported the positive findings of EPLBD in surgically altered anatomy cases, exhibiting technical success rate ranging between 89%-100% and rate of complete clearance in one session ranging between 96.7%-100%[26].

Endoscopic biliary stenting

Endoscopic biliary stenting has been proposed as a useful alternative approach for patients with difficult bile duct stones and high risk of complications (*i.e.*, elderly, patients with serious comorbidities, patients on anti-thrombotic, or patients who are frail). This method can also be a definitive therapy for those who cannot undergo surgical approach[1,3]. A study in 201 subjects who underwent plastic biliary stenting and could not undergo repeated ERCP for stone extraction demonstrated exceptional median stent patency of almost five years with low number of complications (7.4% of the subjects suffered from cholangitis)[50]. The application of fully covered self-expandable metal stents (FCSEMs) has also become more popular these days. In a

large retrospective study involving 44 subjects with difficult bile duct stones and history of incomplete stone clearance, 82% of the subjects had complete stone clearance using FCSEMs[51].

In general, there is no detailed mechanism yet on how biliary stents can contribute towards stone removal. It has been indicated that stone fragmentation may be caused by mechanical friction against the stones. A study has supported this theory by showing 60% of decrease in the size of bile duct stones within 1-2 years after biliary stenting was performed[1,52]. A study in 28 geriatric subjects who were unresponsive towards endoscopic approaches displayed a significant decrease in the size of bile duct stones within six months after endoscopic biliary stenting. This procedure, however, was also combined by oral consumption of ursodeoxycholic acid and terpene therapy [53]. A single study performed in a tertiary center also highlighted the benefit of performing endoscopic biliary stenting. In approximately 208 subjects with difficult stones, the diameter of the largest stone appeared to be reduced significantly after periodic endoscopic biliary stenting was performed (17.41 ± 7.44 mm *vs* 15.85 ± 7.73 mm, $P < 0.001$). In further multivariate analysis, CBD diameter (OR = 0.78, $P = 0.001$) and the diameter of the largest stone (OR = 0.808, $P = 0.001$) were considered as significant independent risk factors to success rate[4].

EUS-guided stone extraction

In recent years, the application of EUS in therapeutic interventions of hepatopancreatobiliary problems has been emerging steadily. Previously, removal of CBD stones under solely EUS guidance has been proposed to minimize the use of fluoroscopy and contrast medium injection. Artifon *et al*[54] demonstrated the feasibility of adapting this strategy by showing a comparable EUS-guided successful cannulation of the bile duct with ERCP cannulation. This strategy, though, was performed by an endosonographer with high expertise in both EUS and ERCP. Altogether, EUS-guided technique is preferable in conditions of previous failed biliary cannulation attempts or difficulty in accessing the papilla (*e.g.*, malignant duodenal obstruction, altered surgical anatomy, large duodenal diverticulum)[3].

EUS-guided stone extraction consists of several steps. Initially, the biliary system needs to be punctured under EUS guidance from the stomach or from any location where dilated left intrahepatic duct can be accessed easier from the duodenal bulb. A wire will then be passed through the FNA needle into the duodenum (can be performed under fluoroscopy guidance). This procedure can be performed with a balloon-pushed antegrade (EUS-AG) (when the papilla cannot be accessed) or with rendezvous technique (EUS-RV) (when the papilla is accessible). Consequently, the stone will be pushed with a retrieval balloon[3,55].

Previous studies have evaluated the outcome of performing EUS-guided stone extraction. A multicenter retrospective study demonstrated 72% of technical success rate and 17% of complication rate. In this study, technical issue occurred due to failure in making a puncture on the intra-hepatic bile duct[56]. Other possible technical problems, which may need to be considered, are guidewire passage and stone extraction through the ampulla. Application of EPLBD can also overcome the problem of large distal CBD to increase the possibility of complete stone removal. However, this technique is also associated with higher risk of bile leak due to utilization of multiple modalities and prolonged duration of the procedure. To minimize the risk of bile leak, EUS-HGS or EUS-hepaticojejunostomy can be performed since the first session[55].

EUS-guided approach is also propitious, especially in cases with surgically altered anatomy. A study by Weilert *et al*[57] in six subjects with history of Roux-en-Y gastric bypass showed 67% technical success rate with only one subject suffered from adverse event (*i.e.*, subcapsular hematoma). Additionally, a finding by Hosmer *et al*[58] from a single-center study, although with smaller sample size, showed 100% success rate of EUS-HGS followed by stone extraction in nine subjects with Roux-en-Y anatomy. In 89% of the subjects, ≥ 10 mm balloon dilation of papilla was conducted[58]. Nevertheless, the technical success rate of EUS-guided management of bile duct stones in patients with surgically altered anatomy is varied widely between 60% to 100%[55]. Possible disadvantages of EUS-guided stone management in cases with surgically altered anatomy include limited approach to the left intrahepatic bile duct and risk of bile leak. Overall, in surgically altered anatomy patients, EUS-guided approach yields better results when the procedure is not performed as a single procedure, but with various therapeutic options (*i.e.*, EUS-AG, EUS-RV, peroral cholangioscopy with intraductal lithotripsy, and EUS-guided enterobiliary fistula)[26,55].

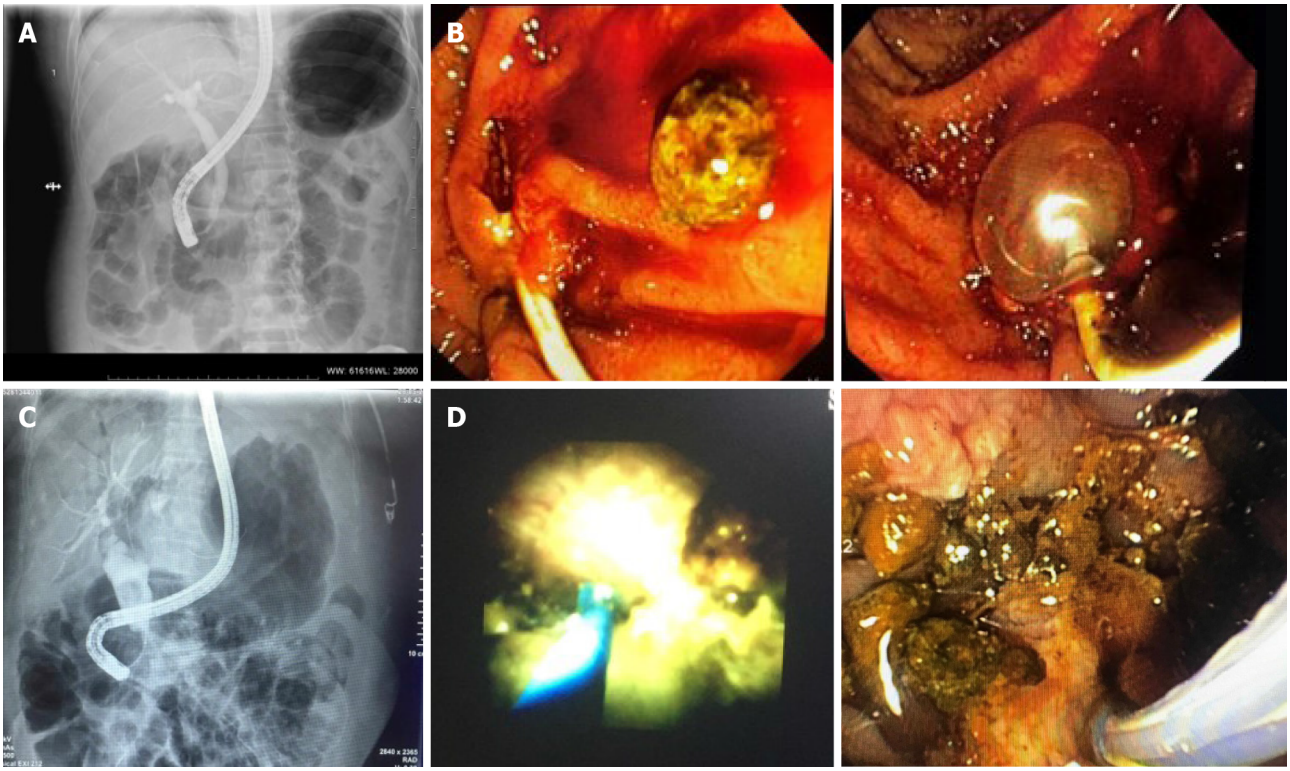

Figure 1 Multiple procedures or additional interventional techniques are often necessary to achieve complete stone clearance. A: A cholangiography image showing dilated biliary tract with distal narrowing and impacted stone. Endoscopy unit database Medistra Hospital, Jakarta; B: Endoscopy images of impacted distal common bile duct (CBD) stone removal with balloon. Endoscopy unit database, Medistra Hospital, Jakarta; C: The cholangiography image of a patient with CBD dilatation on the proximal and large CBD stone with distal narrowing. Endoscopy unit database, Medistra Hospital, Jakarta; D: Patient underwent laser lithotripsy with Spy Glass Cholangioscopy and multiple fragmentation of stones removal. Endoscopy unit database, Medistra Hospital, Jakarta.

ENDOSCOPIC APPROACH *VS* SURGICAL APPROACH IN MANAGING DIFFICULT BILIARY STONES

As mentioned before, management of difficult biliary stones can be considered as a complex matter. Multiple procedures or additional interventional techniques are often necessary to achieve complete stone clearance (Figure 1). Aside from endoscopic approach, surgical approach has also been proposed as one of the procedures involved in the management. The European Society of Gastrointestinal Endoscopy (ESGE) defines difficult biliary stones according to the number of stones, diameter of stones (larger than 1.5 cm), unusual shapes, location, or anatomical factors. Currently, EPLBD of a previous sphincterotomy and EPLBD combined with limited sphincterotomy performed on the same session is still recommended by ESGE as the main approach in difficult CBD stones with history of failed sphincterotomy and balloon and/or basket attempts. If failed extraction is still encountered, mechanical lithotripsy, cholangioscopy-assisted lithotripsy, or ESWL can be considered. Surgical approach can be considered when the stone extraction is still failed or no available facilities to perform lithotripsy[59] (Figure 2).

Conflicting evidence are still found from previous studies related to the comparison between endoscopic and surgical approaches. Although ESGE has suggested laparoscopic cholecystectomy, trancystic or transductal exploration of the CBD as safe and effective approaches, it has also been stated that the recommendation highly depends on the availability of facilities and local expertise[59]. A systematic review by Dasari *et al*[60] showed no significant difference in the mortality rates between groups treated with open surgery and groups treated with ERCP clearance. This review also favored the surgical approach by showing that groups treated with open surgery had significantly less retained stones (P = 0.0002). In addition, the authors also compared a single-stage laparoscopic procedure and two-stage endoscopic procedures. There was no significant difference in mortality and morbidity rates, as well as conversion to open surgery between both groups[60]. One meta-analysis has also shown higher success rate and significantly shorter hospital stay in one-stage laparoscopic procedure (laparoscopic CBD exploration and cholecystectomy) compared to sequential endo-

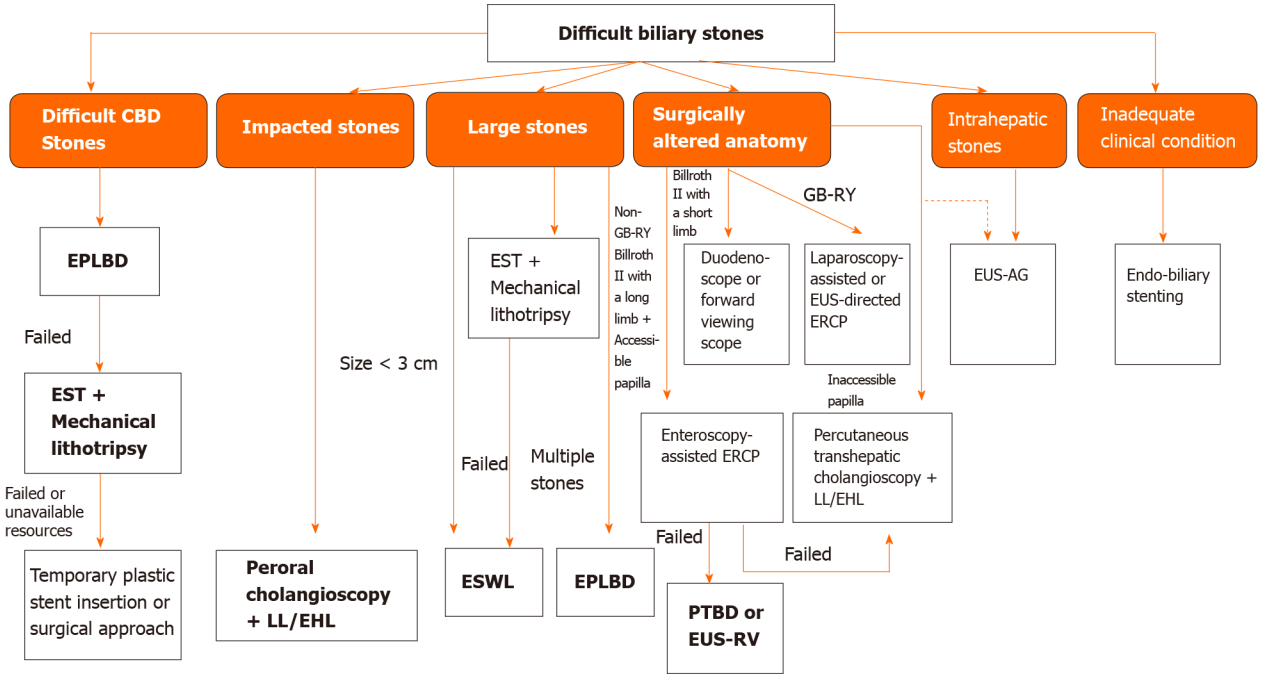

Figure 2 Proposed algorithm for management of difficult biliary stones[6,59,62]. CBD: Common bile duct; EPLBD: Endoscopic papillary large balloon dilation; EST: Endoscopic sphincterotomy; LL: Laser lithotripsy; EHL: Electrohydraulic lithotripsy; ESWL: Extracorporeal shockwave lithotripsy; ERCP: Endoscopic retrograde cholangiopancreatography; PTBD: Percutaneous transhepatic biliary drainage; EUS-RV: Endoscopic ultrasound-rendezvous technique; EUS: Endoscopic ultrasound; EUS-AG: Endoscopic ultrasound-antegrade.

laparoscopic procedures (two-stage endoscopic stone extraction followed by laparoscopic cholecystectomy). No significant differences were observed in morbidity and mortality rates, cost, as well as retained or recurrent stones. The authors, however, addressed the significant heterogeneity between studies which may reduce the validity of the analysis and the need for further studies due to the underpowered nature of most trials[61].

CONCLUSION

There has been a steady development of new approaches for treatment of difficult common biliary stones with high success rates and acceptable adverse events rates. Practically, multimodal approaches, especially combination between newer techniques and conventional methods yield better results in complete stone clearance. Various factor; such as the characteristics of the stones, anatomy, history of prior attempts to remove the stones, comorbidities, as well as the availability of experienced operator and resources need to be considered in creating individualized treatment strategies for managing difficult biliary stones.

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MINIREVIEWS

Gastrointestinal endoscopy in cirrhotic patient: Issues on the table

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Abstract

Patients with liver cirrhosis are fragile and present specific clinical hallmarks. When undergoing to gastrointestinal (GI) endoscopy, these subjects require an individual pre evaluation, taking into account: Level of haemostasis impairment, the individual risk of infection, the impact of sedation on hepatic encephalopathy and other factors. The overall assessment of liver function, employing common scoring systems, should be also assessed in the preprocedural phase. Beside some common general problems, regarding GI endoscopy in cirrhotic subjects, also specific issues are present for some frequent indications or procedures. For instance, despite an increased incidence of adenomas in cirrhosis, colon cancer screening remains suboptimal in subjects with this disease. Several studies in fact demonstrated liver cirrhosis as a negative factor for an adequate colon cleansing before colonoscopy. On the other hand, also the routine assessment of gastroesophageal varices during upper GI endoscopy presents some concern, since important inter-observer variability or incomplete description of endoscopic findings has been reported in some studies. In this review we discussed in details the most relevant issues that may be considered while performing general GI endoscopic practice, in patient with cirrhosis. For most of these issues there are no guidelines or clear indications. Moreover until now, few studies focused on these aspects. We believe that targeting these issues with corrective measures may be helpful to develop a tailored endoscopic approach for cirrhosis, in the future.

Key Words: Gastrointestinal endoscopy; Cirrhosis; Sedation; Infection; Gastroesophageal varices; Colonoscopy; Bowel cleansing; Liver transplantation

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Core Tip: In this minireview, we discuss some issues that are encountered while performing general gastrointestinal endoscopy in cirrhotic patients. The solution of these aspects may increase, in the future, the yield of this technique in subjects with significant liver disease.

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INTRODUCTION

The definition of liver cirrhosis refers to a typical anatomopathological liver change characterized by diffuse fibrosis and regenerative nodules as a result of a chronic immunoinflammatory process[1]. Hepatic architecture distortion gives rise to: (1) A reduced liver blood outflow thus determining portal hypertension and; and (2) An impairment of liver cells activities. These changes may lately determine the typical complications of the disease such as: Ascites, hepatic encephalopathy, hepatorenal syndrome and bleeding after gastroesophageal varices (GEVs) rupture. Therefore, the term cirrhosis does not define a specific clinical condition. In this setting, physicians identify a "compensated" or a "decompensated" form of cirrhosis for medical purposes [2]. In the first case, the cirrhotic patient does not exhibit significant symptoms of the disease, and the diagnosis may be ruled out for tests prescribed for other reasons. In the latter case (decompensated cirrhosis), the subject shows the typical complications of the disease. So, it seems wise before approaching a cirrhotic patient with either diagnostic or therapeutic procedures (including the endoscopic ones) to gain the best information on its function.

In this setting, however, the binary classification into compensated or decompensated cirrhosis remains too broad, thus requiring specific scoring systems, such as Child-Turcotte-Pugh[3] or model for end stage liver disease (MELD)[4] score to properly delimit the condition of the individual patient[5].

During their illness, cirrhotic patients may undergo repeated gastrointestinal (GI) endoscopic procedures. For instance, upper GI endoscopy is suggested by United States guidelines as soon as the diagnosis of cirrhosis is achieved, in order to assess for the presence of esophageal varices. In case of absent or small varices, the procedure should be repeated within 2 or 3 years in compensated cirrhosis and yearly in decompensated cirrhosis[6-8].

The British Society of Gastroenterology guidelines recommend screening with slight modification: On an every 3 year basis if no varices were present and annual screening for small varices[6]. Despite the proposal of alternative tests to rule out the presence of varices (such measuring the degree of hepatic stiffness by elastography), the lack of reliability of these techniques still supports the need of upper endoscopy for a definitive diagnosis in the majority of patients[5,9]. Nonetheless, the general use of GI endoscopy has been expanded to also include the cirrhotic population for colon cancer screening, for the advent of ultrasound endoscopy and for the treatment of benign or malignant diseases of the biliary tract. Finally, a specific endoscopy based careful assessment of neoplastic or preneoplastic GI luminal lesions (frequently involving subjects with severe hepatic dysfunction) is required for liver transplant listing.

Given the increased demand of GI endoscopy in cirrhosis and in the attempt to move toward a tailored rather than a general approach in these subjects, in this review, we discuss the possible pitfalls/issues of these procedures in the patient with liver impairment.

COMMON GENERAL PROBLEMS WHILE APPROACHING THE CIRRHOTIC PATIENT WITH GI ENDOSCOPY

Sedation

Routine sedation, in the course of GI endoscopy, has increased significantly in the last decades, being applied in 60% to 100% of cases, depending on the procedures and practice of the center[10]. Characteristics of most used drugs for sedation in endoscopy are reported in Table 1. Although it is widely considered that any endoscopic examination can be more effectively conducted under sedation[5,11], not all endoscopists consider it mandatory in every situation. In fact cardio-vascular or respiratory complications may occur also for low-grade sedation and according to baseline patient conditions or type of endoscopic procedure, as extensively reported by some reviews on this issue[12,13].

Table 1 Characteristics of most used drugs for sedation in endoscopy (the corresponding antidote is also reported when available)

Drug	Onset of effect (min)	Effect duration (min)	Usual dose	Adverse events
Benzodiazepines				
Midazolam	1-2	15-80	1-6 mg	Respiratory depression, disinhibition
Flumazenil (Benzodiazepines Antidote)	1-2	60	0.1-1 mg	Agitation, withdrawal symptoms
Opioids				
Alfentanyl	< 1	30-60	0.250-2 mg	Respiratory and cardiovascular depression
Fentanyl	1-2	30-60	50-200 μg	Respiratory depression, vomiting
Pethidine	3-6	60-180	25-100 mg	Respiratory depression, vomiting
Naloxone (Opioids antidote)	1-2	30-45	0.2-1 mg	Narcotic withdrawal
Anestethic				
Propofol	< 1	4-8	40-400 mg	Respiratory and cardiovascular depression

In compliance with the American Society of Anesthesiology, sedation should be classified as minimal, moderate or deep, according to a decrease in the consciousness of the patient and depression of effective spontaneous respirations[14]. Minimal and moderate sedation are by far the most adopted solutions in routine GI endoscopy and these are usually achieved by the administration of benzodiazepines (diazepam or midazolam) and/or opioids (meperidine or fentanyl)[15]. Unfortunately, both of these categories of drugs have a delayed metabolism in patients with significant liver impairment, thus possibly exposing them to complications, such as hepatic encephalopathy[16-18]. In this perspective, the use of propofol seems to be superior and safer. A meta-analysis on cirrhotic patients undergoing upper GI endoscopy and comparing midazolam to propofol sedation demonstrated a reduced induction time, shorter time of recovery and most prompt discharge with propofol sedation[19]. The same study reported a worsening of minimal encephalopathy with midazolam, even if a meta-analytic confirmation was not possible, because of the different testing strategies among studies.

Differences between these two drugs may be explained while examining their metabolism. In fact, midazolam is eliminated almost exclusively through the liver, while propofol is eliminated by the kidney after conjugation in hepatic and extra-hepatic tissues[20,21]. So, as a rule of thumb: (1) Propofol is usually administered following the same therapeutic scheme used for non-cirrhotic patients and; and (2) The midazolam dose is adjusted according to the metabolic liver impairment[6,17-24].

However, it should be underscored that propofol, differently from benzodiazepines and opioids, does not have a pharmacological antagonist able to counteract possible adverse events. This has given rise the controversial question whether direct administration of propofol by the endoscopist should be considered safe or an anesthesiologist would always be required[25]. On the other hand, despite the fact that adverse events were recorded with similar prevalence employing either propofol or a benzodiazepine plus an opioid, it is questionable that the endoscopist alone can simultaneously induce sedation, supervise the patient and devote himself/herself to the examination.

However, it is evident that this issue remains unsolved and should be approached according to the clinical context, the patient's condition and possibly on the basis of guidelines produced by the local institution[6,10,17,19,20,23,26].

In many countries, the administration of propofol for sedation, as well as the monitoring during the examination and the evaluation of the restoration to a full state of consciousness, remains to be conducted by a specialist in anesthesiology.

Hemostasis impairment

Normal hemostasis implies the coordinate contribution and activation of cells and blood proteins[27]. During liver disease, impairment of this machinery can occur at different times and with different severity. Therefore, any invasive procedure requires a prior evaluation of clotting performance.

Impaired hemostasis in the cirrhotic patient may not be interpreted as the simple deficiency of a coagulation factor. Instead, an imbalance of the entire coagulation cascade (certainly dependent on hepatic pathology), which also involves vascular, renal and medullary dysfunctions, is present[5,16,28]. As a result, cirrhotic patients,

besides the increased risk of hemorrhagic complications, may also frequently experience thromboembolic events, since there is a concomitant deficit of anticoagulant factors[29].

In this perspective evaluation of these subjects on the basis of routine tests, such as prothrombin time and international normalized ratio, could be suboptimal[6,30,31], and a hypercoagulable, hypocoagulable or pro-fibrinolytic status should be ruled out just before employing thromboelastography[5,32].

Moreover thrombocytopenia is frequently observed in cirrhosis, further complicating the evaluation of the net clotting performance in the patient with liver disease. Reduced numbers of platelets, in the past, were thought to be mainly dependent to spleen sequestration[33]; however, concurrent bone marrow depression and reduced thrombopoietin production may also have an important role in determining this occurrence[34].

In clinical practice, the treatment of coagulopathy in cirrhotic patients is less standardized in comparison with other subjects[35]. Expert opinions suggest avoiding transfusions of fresh frozen plasma and instead to correct fibrinogen levels in cirrhotic patients undergoing invasive or surgical procedures[36]. Platelet administration is usually considered when the count is $< 50 \times 10^9$/L. However, one should consider that platelet transfusions are generally afflicted by an increased risk of adverse reactions as compared with the administration of either frozen plasma or red blood cells[37], while platelet refractoriness (lack of increase in platelet count after their administration) is not rare[38]. In this perspective, the new thrombopoietin receptor agonists avatrombopag and lusutrombopag, specifically tested in patients with chronic liver disease undergoing invasive procedures, are of major interest[39,40]. However, despite the good results of these molecules in increasing platelets count, they cannot be considered in urgent situations since they require several days (> 5/8) to achieve a therapeutic effect.

The problem of infections in the cirrhotic patient

Transmission of infections during GI endoscopy represents an issue that has stimulated the development of specific guidelines for prevention and processing of instruments[41,42]. Despite its rarity, endoscopy-driven infection is also of concern for the possible transmission of antibiotic resistant strains in hospital based units. On the other hand, bacterial infections are responsible for significant morbidity and mortality in cirrhotic patients, also leading to acute-on-chronic liver failure. Moreover, hepatic diseases are known to predispose to infection for several reasons, such as increase intestinal permeability, reduced immunologic defense, portal shunting with peripheral circulation and others[42].

In this perspective, prevention of infections in the cirrhotic patient (also during endoscopy) must always be pursued. While performing endoscopy and with regard to infection prevention, it is necessary to distinguish the compensated cirrhotic patient from the decompensated cirrhotic patient and who is in a state of emergency with bleeding from esophageal or gastric varices.

In the case of a compensated cirrhotic patient undergoing elective endoscopy, no convincing evidence is available on the utility of routine antibiotic prophylaxis, since endoscopy-associated bacteremia does not seem to be relevant[43].

Also, in decompensated cirrhosis with ascites of varying degrees, there is insufficient evidence that colonoscopy can trigger subsequent bacterial peritonitis (frequently these subjects are already under long-term antibiotic prophylaxis), which remains a fairly rare event. Therefore, evacuative paracentesis before endoscopy is also not recommended[5,43].

Conversely, any episode of upper GI bleeding marks a significant event in the patient's medical history. This event can precipitate decompensation, especially in patients with advanced disease or hepatocellular carcinoma. In such situations, bleeding can be fatal in up to 20% of cases[44].

The guidelines strongly recommend, together with prompt endoscopic examination/treatment, antibiotic prophylaxis. In fact, this strategy often prevents subsequent infections and also reduces mortality and the risk of relapse[26,38]. Fluoroquinolones are the usual first choice. They are safe and provide broad-spectrum prophylaxis against various pathogens of intestinal origin. In the case of resistance to fluoroquinolones (or if the patient is already taking them for primary prophylaxis of spontaneous bacterial peritonitis), the choice may entail a third generation cephalosporin[44]. Antibiotic therapy should be initiated as soon as possible in conjunction with acute bleeding and continued for at least 5-7 d[44].

DIAGNOSTIC OR PROCEDURAL ISSUES IN THE CIRRHOTIC PATIENT WHILE APPROACHING SPECIFIC ENDOSCOPIC INDICATIONS

Colorectal cancer screening

Screening need in cirrhotic patient: Since the relevant prevalence of colorectal cancer (CRC), accounting for the third most frequent malignant tumor worldwide[45], screening adoption has been suggested by several guidelines[46,47]. Colonoscopy and fecal occult blood immunologic testing are usually regarded as the first-choice strategy [46]. However, the endoscopic colon examination presents several advantages such as: (1) Easy detection of minimal lesions as sessile serrated adenomas; (2) Removal or biopsy of suspected lesions during examination; (3) Is a single-step procedure (achieving the diagnosis without further investigation); and (4) If negative do not require any additional screening assessment within the next 10 years. Patients with liver disease should not be exempt from CRC screening, because they seem to have twice the prevalence for this cancer, in comparison with the general population[48]. On the other hand, liver cirrhosis has long been recognized as an important independent risk factor for colonic adenomas[48], and this finding was recently expanded by the observation that this is also valid for patients with chronic non-cirrhotic liver disease[49]. Given the increased prevalence of preneoplastic colonic lesions and frequent occurrence of chronic low-grade blood loss (because of impaired hemostasis and portal hypertension-related GI abnormalities)[49], the use of fecal occult blood immunologic testing for CRC screening in cirrhotic patients does not seem appropriate compared to that in the general population. Moreover, cirrhotic patients undergoing liver transplantation should be submitted to careful scrutiny and removal of luminal lesions, since immunosuppression may increase the risk of development of CRC after transplant[50]. In this perspective, colonoscopy seems to respond better for the CRC screening needed in patients with significant liver disease. However, the execution of a screening colonoscopy in a cirrhotic patient poses some additional issues in comparison with the general population. Some of these, such as sedation, hemostasis, and infection prevention, were already discussed in the previous paragraphs. Nevertheless, the possible major factor flawing the quality of screening colonoscopy in cirrhosis is represented by bowel cleansing. In fact, among the factors ensuring the good quality of a CRC screening program, adequate bowel cleansing is included, and it should be achieved in at least 90% of subjects[47]. In fact, poor bowel preparation is a well-known predictive factor for missed or delayed cecal intubation and of incomplete colonoscopy[51]. Moreover, it could affect the detection of small preneoplastic luminal lesions, while the detection of a large tumor is usually not impaired[52,53].

Data on bowel cleansing in cirrhotic patient: Optimal colon preparation is a hard task to obtain in patients with severe liver disease. A prospective study examined the predictive factors of inadequate bowel cleansing in 2811 patients undergoing colonoscopy[54]. Liver cirrhosis represented an important contributing factor in the failure to achieve adequate colonic preparation together with body mass index, age and diabetes. In order to further evaluate this issue, our group conducted a prospective observational study comparing normal and cirrhotic patients undergoing screening colonoscopy[55]. Cirrhotic patients completed the prescribed bowel preparation at a similar rate in comparison with the normal control, even if they in general reported a high level of difficulty in assuming the prescribed 4 L standard polyethylene glycol-electrolyte lavage solution. In spite of this, colonic cleansing was inadequate in 49% of cirrhotic patients in comparison with 5% of normal patients ($P < 0.001$). This statistically impacted the time to reach the cecum and endoscope withdrawal time, while the cecal intubation rate was similar between the two groups. The adenoma detection rate was decreased by liver disease (cirrhosis/normal; 19% *vs* 27%) but without statistical significance. In another study, differently from our results, a reduced ciecal intubation rate was observed in cirrhosis as a function of ascites volume, but data regarding bowel preparation were not reported in detail[56]. Finally, a further study retrospectively assessed the quality of bowel cleansing between patients with cirrhotic and non-cirrhotic liver disease[57]. This research provided evidence that just cirrhosis and not chronic liver disease was a risk factor for incomplete colonic lavage; however, poor cleansing did not affect the polyp detection rate nor was it a function of severity of cirrhosis as assessed by the MELD score. In conclusion, adequate bowel cleansing seems to be a difficult task to reach in cirrhotic

patients. Several gray areas remain to be explored with regard to this issue, such as: (1) The reasons for an impaired lavage in cirrhosis remains unclear; (2) The possibility of improvement with alternative tailored schemes is unexplored; and (3) The net effect of impaired cleansing on diagnostic yield is undefined. Nonetheless, it should be considered wise to specify (also in the informed consent) this with cirrhotic patients, since their colonic cleansing might be suboptimal for an adequate endoscopic diagnosis.

Finally, other groups consider the need for CRC screening marginal in cirrhotic patients or at least in those undergoing liver transplantation. In fact, a study on 808 cirrhotic patients undergoing CRC screening before liver transplant showed a limited diagnostic yield (0.2% of CRC and 5.4% of significant adenomas), but at the same time, an increased risk of significant complications (kidney dysfunction and GI bleeding) in the 30 d following endoscopy was recorded[58].

Endoscopic assessment of portal hypertension in cirrhosis

Perhaps the most frequent reason for endoscopic examination in cirrhotic patients is evaluation and monitoring of endoscopic signs of portal hypertension. GEVs are present in a large portion of cirrhotic patients (60%-85%) and may cause significant bleeding and death[59,60]. While some noninvasive tests may rule out the presence of GEVs in well-selected patients, upper GI endoscopy remains the gold standard to accurately define the extent of individual risk, to attain surveillance and to manage acute bleeding[61]. Adequate assessment of GEVs is of crucial importance to prevent variceal rupture and hemorrhage. Bleeding prevention may be obtained by endoscopic band ligation, use of beta blockers or TIPS placement. These measures are usually adopted in subjects exhibiting large varices with red signs (primary prophylaxis) or in those with a previous bleeding episode (secondary prophylaxis). While the GEV bleeding-related deaths remain significant, accounting for 15%-20% of cases[62,63], endoscopy practice in the real world presents some weaknesses. First of all, while some guidelines suggest valid strategies and timing to assess GEVs[7,64], these indications are frequently neglected. A survey in the United States was conducted in order to assess clinical practice in the screening for GEVs[65].

A questionnaire was administered to hepatologists and gastroenterologists throughout the country. Only 60% of the interviewed physicians prescribed upper GI endoscopy at the first diagnosis of cirrhosis. The surveillance timing, as suggested by guidelines, was fulfilled in less than 50% of cases. A cohort study, in the same country, reported an even worse picture[66]. Among 4230 hepatitis C virus cirrhotic patients, just 54% underwent an upper GI endoscopy in a 6-year follow-up, and the examination was performed within 1 year of the diagnosis in only 33.8% of patients. The reasons for this suboptimal standard of care in GEV assessment are not clear. Multiple factors may contribute to this picture, such as: (1) Limited knowledge of GEV management; (2) Overestimation of clinical parameters for predicting portal hypertension; and (3) Racial disparities for management of cirrhosis in some countries [67]. Of concern, even after GEV bleeding, the subsequent surveillance and treatment is seldom observed. In a study among 99 subjects undergoing endoscopic band ligation for acute variceal bleeding, just one-third of subjects followed an endoscopic GEV eradication protocol and 46% did not have any further endoscopic examination after hospital discharge[68]. Beside the scarce adherence to GEV endoscopic diagnosis and surveillance, another factor that may impair the appropriate clinical management of portal hypertension in cirrhosis is the lack of an adequate and unequivocal description of endoscopic findings. More than three decades ago, an Italian study assessed the reliability of upper GI endoscopic examination in cirrhotic patients, comparing the reports of six experts on the same patients[69].The agreement between endoscopists was fair, in the majority of cases, and poor with regard to some variceal features (blue color and extension of red color sign). Excellent agreement (k index > 75) was not recorded for any of the GEV endoscopic features examined. This study underscored, for the first time in the era of flexible endoscopy, the possible operator-dependent limits in the endoscopic assessment of GEV. More recently, our group evaluated the diagnostic accuracy of upper GI endoscopy in cirrhotic patients during common clinical practice[70]. Endoscopic reports (n = 120), coming from different institutions within our regional area, were retrieved and evaluated by eight independent experts (four endoscopists and four hepatologists). While endoscopists evaluated 41% of the reports as incomplete, the hepatologists considered more than one-third of the examinations (36%) inadequate to make decisions on patient management.

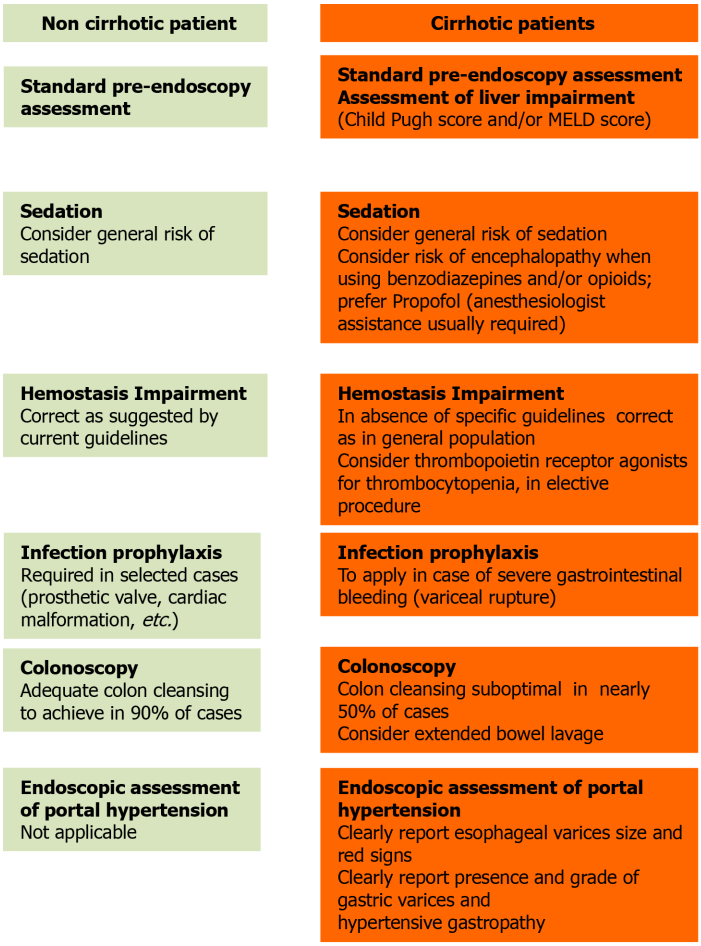

Figure 1 Some tips to consider, while approaching cirrhotic patients (orange boxes) with gastrointestinal endoscopy, are reported in the figure in comparison with general population (green boxes). These indications (in the majority of cases) are mainly desumed by small volume studies and are not intended as evidenced-based guidelines. MELD: Model for end stage liver disease.

Examining all of the above mentioned studies, it comes clear as upper GI endoscopy is not so frequently or adequately performed as usually required in liver cirrhosis. Possible corrective measures may include: (1) Enhanced diffusion of practice guidelines; (2) Identification of a simplified univocal system for GEV endoscopy reports; and (3) Referral of cirrhotic patients to a dedicated GI endoscopic service. In the meantime, the suboptimal endoscopic approach to GEV likely contributes to the significant bleeding-related mortality in cirrhotic patients.

CONCLUSION

Flexible GI endoscopy has undergone exceptional development and diffusion in the last 70 years[71]. Wide application of endoscopic examination has revealed some definite patient-related issues. Specific guidelines have been produced, for instance, with regard to inflammatory bowel disease[72], for patients on anticoagulant or antiplatelet agents[73] or for bowel cleansing in subjects with chronic kidney disease [74]. These indications were generated in the attempt to move toward the concept of a patient-tailored endoscopy. Several endoscopic guidelines have also been produced for cirrhotic patients, but they mainly focus on prevention and treatment of GEV bleeding, as well as the important associated mortality[7,61,64]. However, other clinical issues may be encountered while approaching a cirrhotic subject with GI endoscopy, and in this review, we attempted to focus on the main ones. In Figure 1 are summarized some tips to consider while approaching the cirrhotic patient with GI endoscopy. As we reported earlier, for the larger part of these, there are no guidelines or even clear indications. Besides, just a marginal part of published literature specifically examined these problems in liver disease patients. In this uncertainty, our manuscript seems novel since it focused on some overlooked aspects of endoscopy in

cirrhotic patients, stimulating further research on these issues. On the other hand we attempted to give some practical (even if not conclusive) tips for the everyday clinical activity. Finally, we claim that further studies and collaborative work within experts should be pursued to design cirrhosis-tailored endoscopic behaviors in order to improve routine practice, diagnostic yield, safety and procedure outcomes in these subjects.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic hemostasis makes the difference: Angiographic treatment in patients with lower gastrointestinal bleeding

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Abstract

BACKGROUND

The large majority of gastrointestinal bleedings subside on their own or after endoscopic treatment. However, a small number of these may pose a challenge in terms of therapy because the patients develop hemodynamic instability, and endoscopy does not achieve adequate hemostasis. Interventional radiology supplemented with catheter angiography (CA) and transarterial embolization have gained importance in recent times.

AIM

To evaluate clinical predictors for angiography in patients with lower gastro-

disclose.

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intestinal bleeding (LGIB).

METHODS

We compared two groups of patients in a retrospective analysis. One group had been treated for more than 10 years with CA for LGIB (n = 41). The control group had undergone non-endoscopic or endoscopic treatment for two years and been registered in a bleeding registry (n = 92). The differences between the two groups were analyzed using decision trees with the goal of defining clear rules for optimal treatment.

RESULTS

Patients in the CA group had a higher shock index, a higher Glasgow-Blatchford bleeding score (GBS), lower serum hemoglobin levels, and more rarely achieved hemostasis in primary endoscopy. These patients needed more transfusions, had longer hospital stays, and had to undergo subsequent surgery more frequently (P < 0.001).

CONCLUSION

Endoscopic hemostasis proved to be the crucial difference between the two patient groups. Primary endoscopic hemostasis, along with GBS and the number of transfusions, would permit a stratification of risks. After prospective confirmation of the present findings, the use of decision trees would permit the identification of patients at risk for subsequent diagnosis and treatment based on interventional radiology.

Key Words: Lower gastrointestinal bleeding; Endoscopy; Angiography; Embolization; Computed tomography angiography; Intervention

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Core Tip: Transarterial embolization enables the clinician to control gastrointestinal bleeding with high rates of technical and clinical success. We still do not know when the clinician should conclude endoscopic procedures to control gastrointestinal bleeding. This retrospective study compared patients with conservative treatment and patients who underwent catheter angiography. Patients in the catheter angiography group had a higher shock index, a higher Glasgow-Blatchford score and more rarely achieved hemostasis in primary endoscopy. These patients needed more transfusions, had longer hospital stays and had to undergo subsequent surgery more frequently. Endoscopic hemostasis proved to be the crucial difference between the two patient groups.

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INTRODUCTION

Flexible endoscopy is the gold standard for the diagnosis and treatment of gastrointestinal bleeding. The majority of lower gastrointestinal bleedings (LGIB) subside spontaneously without intervention. An analysis of 2528 patients revealed that a quarter of the patients received transfusions and 10% needed more than four red cell concentrates[1]. Endoscopy discloses the bleeding in no more than 40% of cases[2]. Diverticular bleeding is the most frequent cause of LGIB, accounting for 30%-65% of all cases. As many as 80% of these subside spontaneously[3]. Further frequent causes of bleeding are angiodysplasia and hemorrhoids, as well as cancer[2,4]. Once the bleeding is identified on endoscopy, more than 90% of these can be treated successfully. The appropriate time point of diagnostic endoscopic investigation is still

not clear, because approximately 85% of LGIB can be managed by supportive treatment without any major threat to the patient's health. Guidelines recommend diagnostic endoscopy within 12-24 h[3-7].

Especially in cases of severe bleeding not amenable to endoscopic treatment, surgery serves an additional invasive therapy option[2,4]. Besides, interventional radiology has emerged as an important alternative in the last few years. A repeated bidirectional endoscopy of flawless quality does not enhance the diagnostic yield. In fact, it delays the course of treatment because the interval between the potential bleeding event and subsequent investigations is prolonged. Thus, further radiological investigation and treatment are obviously needed.

In cases of uncontrollable bleeding or recurrent non-varicose gastrointestinal bleeding, the German guidelines for gastrointestinal bleeding recommend early transfer of the patient to a center that provides the option of interventional radiology [8]. Determining the ideal time point for this measure in the course of a patient's treatment appears to be of crucial importance.

Currently, radiological diagnostic investigation and treatment are largely oriented to local facilities. These include, in particular, the availability of therapeutic endoscopy and interventional radiology[2]. Interdisciplinary cooperation between gastroenterologists and radiologists is obviously a crucial factor. Prior to catheter angiography (CA), it would be advisable to perform a computed tomography angiography (CTA). The latter is propagated as an effective method for the localization of bleeding, as well as pre-interventional viewing of vascular anatomy and the detection of relevant additional findings[9].

Given the high sensitivity and specificity of CTA for the detection of active gastrointestinal bleeding, this procedure is recommended in the guidelines[10]. Once CTA has provided evidence of bleeding, CA with transarterial embolization (TAE) is currently the method of choice for controlling an acute LGIB[10,11]. TAE enables the clinician to control gastrointestinal bleeding with high rates of technical (90%-100%) and clinical success (50%-90%), low complication rates of 1%-5%, and improved long-term survival rates[4,7,12-16].

We still do not know when the clinician should conclude endoscopic procedures to control gastrointestinal bleeding, whether CTA has an effect on the outcome, and whether patients with no or a negative CTA should also be scheduled to undergo angiography. In view of these facts, the present retrospective study was performed in a large German single-center patient population at a maximum care hospital. We assessed the course of treatment in patients with LGIB who had undergone interventional radiological treatment. We focused on the identification of variables that raised the likelihood of further radiological diagnosis (CTA) and treatment (CA/TAE) in the course of disease.

MATERIALS AND METHODS

Patient groups

All patients with LGIB who had undergone a CA (CA-LGIB-group) at a maximum care hospital from 1 January 2007 to 31 March 2018 were included in a retrospective analysis. There were no exclusion criteria. The reference group included patients with suspected LGIB who had undergone treatment from 1 January 2015 to 31 December 2016 (reference group with LGIB, K-LGIB). Patients already recorded in the CA-LGIB registry were excluded from the K-LGIB group. One hundred and twenty variables were registered in the K-LGIB registry, and 110 variables in the CA-LGIB registry. Based on clinical estimates, we selected 20 common variables from both groups for the purposes of the present study. The Glasgow-Blatchford bleeding score (GBS)[17], the course of treatment, and the duration of hospitalization were also registered.

Endoscopy

Endoscopic diagnostic investigation and treatment were performed exclusively by investigators who had several years of experience in endoscopic treatment. The data were extracted from a reporting program named E&L (Clinic WinData, Nuremberg) and the hospital information system (SAP, Walldorf). In endoscopic therapy, the absence of hemostasis was defined as persistent bleeding under direct endoscopic visual control, clinically persistent bleeding after the intervention, or persistent clinical bleeding with a drop in hemoglobin levels.

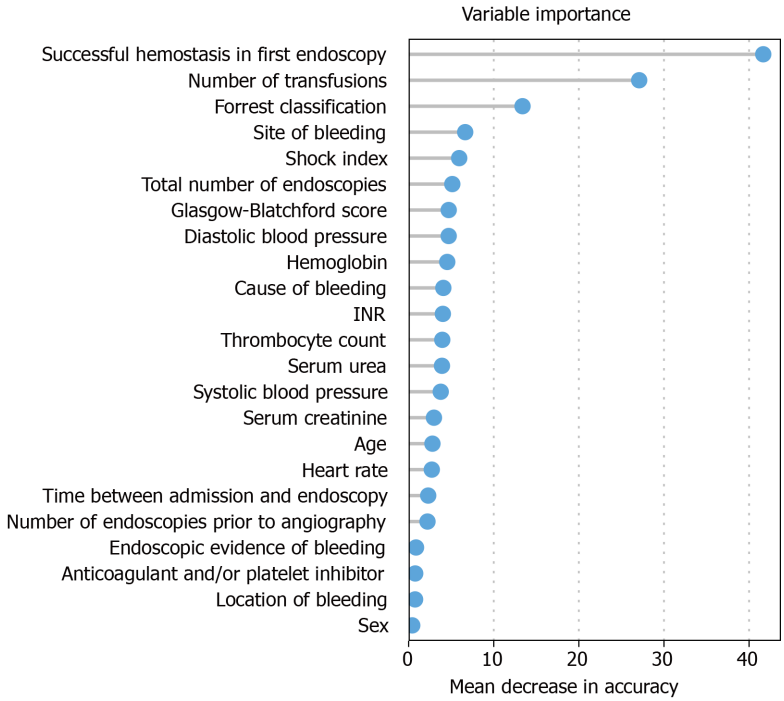

Figure 1 Variable importance.

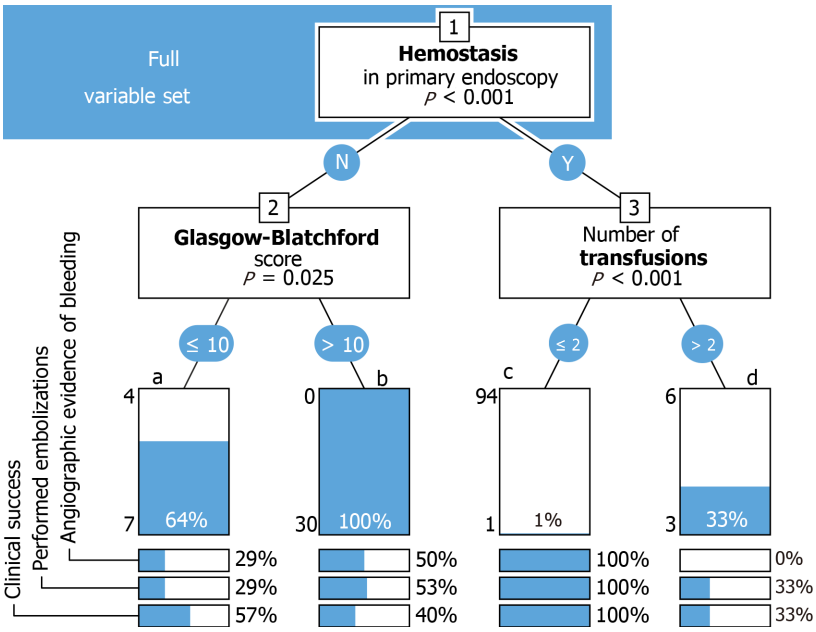

Figure 2 Full variable set for endoscopic hemostasis and the course of further treatment until angiography.

Radiology

All CTA investigations were performed on a Siemens CT Somatom 128 device. A standardized protocol was not used. Over the entire study period, the CA's were performed by five radiologists with several years of experience in interventional radiology. In most cases we used a transfemoral access with a 5/6 French sheath, a guiding catheter, and a microcatheter. Embolization was achieved with various materials, such as coils, polyvinyl alcohol particles (PVA), or n-butyl cyanoacrylate (NBCA). The technical success of CA was defined as the visualization of a suspected bleeding vessel without extravasation or localization of the bleeding vessel and performing TAE. Clinical success was defined as the absence of any complication after 30 d. The absence of complications included no repeat angiography, no surgical intervention, or discharge of the patient. Hemodynamic instability was defined as a

systolic blood pressure below 100 mmHg, a positive shock index, or transfusion of four or more red cell concentrates in 48 h[18].

Statistical analysis

Data analysis was performed using R v3.6.1[19]. For two-sample comparisons (Table 1), Wilcoxon's rank sum test was used for continuous data, circumventing the requirements for normality of the *t*-test. Fisher's exact test was used for categorical data. Variable importance (Figure 1) was determined with the randomForest package v4.6.14[20], and decision trees (Figures 2 and 3) were constructed using the party package v1.3.4[21]. The decision trees were based on the set of all variables, or a reduced set composed of variables with assumed clinical relevance, using conditional inference trees. This algorithm recursively applies binary partitions to the dataset, splitting it by the most informative variable, as determined by Bonferroni-adjusted Monte Carlo p-values. The partitions are applied until further splitting of the dataset would not increase the predictive power of the tree any further (see stop criterion in the package reference manual).

Variable importance (Figure 1): This bar chart shows the variable importance of all features considered for the construction of the decision trees (Figures 2 and 3). Based on the randomForest package for R[20], missing values were first imputed using rfImpute, followed by the construction of a randomForest classifier. The shown metric is the mean decrease in accuracy[22]. Such importance measures serve to identify relevant features and perform variable selection.

Decision tree (Figures 2 and 3): Decision trees were constructed using the party package for R[21], applying conditional inference trees either to the complete dataset (Figure 2), or to a set of variables selected for assumed clinical relevance (Figure 3). Each binary split (shown as a numbered box) is annotated with its corresponding p-value. Each terminal node (shown as a bar) represents the percentage of angiography-positive cases, with the individual numbers of positive and negative cases to the left. Percentages of cases with angiographic evidence of bleeding, performed embolizations, and clinical success are given below each node.

Ethics vote

The study protocol conformed to the ethical guidelines of the 1975 Declaration of Helsinki, and was approved by the ethics committee of the Regional Medical Society of Hessen (Landesärztekammer Hessen), approval number 2016/2017, on 31 August 2017. Written informed consent was obtained from each patient included in the registry.

RESULTS

Description

Forty-one patients with LGIB underwent CA between 1 January 2007 and 31 March 2018. Diverticular bleeding (Figure 4) was the most common suspected cause of bleeding (14/41, 34.1%). Endoscopic investigation demonstrated blood in the lower gastrointestinal tract in 17/41 cases (41.5%). The exact site of bleeding could not be localized in endoscopy in 23/41 patients (56.1%). Primary hemostasis in endoscopy was achieved in 4/41 patients (9.8%). In the K-LGIB group, primary endoscopic hemostasis was achieved in 88/92 cases (95.7%).

Seventeen of 41 patients underwent a CTA investigation prior to angiography. CTA revealed extravasation of contrast medium, and therefore a suspected active bleeding, in six cases. CA showed active bleeding in two of the six cases (Table 2). The cross-sectional images yielded significant additional data, especially incidental evidence of tumor, in 13 of 17 cases (76.5%).

An average of 2.2 d elapsed from the index endoscopy to the CA (minimum 0 days, maximum 11 d). The time period from admission to the hospital until CA was on average 3.0 d. Twenty-five patients (61.0%) were given anesthesia during the angiography, and 16 (39.0%) were intubated for the intervention. Angiography yielded evidence of bleeding in 18/41 patients (44.0%). In three of these patients, provocative catecholamine therapy was used to demonstrate bleeding. All cases with contrast extravasation received TAE. A superselective embolization could be performed in 16/18 cases (88.9%), and the TAE was successful in 16/18 patients (88.9%). Hemostasis could not be achieved by angiography in two patients. One of these underwent surgical treatment subsequently, and the other was discharged without further treatment.

Table 1 Selected variables for catheter angiography group and reference group with conservative treatment

	CA-LGIB	K-LGIB	*P* value
General data			
Number of patients (*n*)	41	92	
TAE performed, *n* (%)	20 (48.8)	0	
Age (yr)	72.8	73.2	0.4254[1]
Sex (%)			0.182[2]
Male	29 (70.7)	54 (58.2)	
Female	12 (29.3)	38 (41.8)	
Clinical data			
RR sys (mmHg)	103	124	**≤ 0.0001**[1]
HR (bpm)	97	82	**≤ 0.0001**[1]
Shock index	1	0.7	**≤ 0.0001**[1]
Transfusions (*n*)	7.44	0.55	**≤ 0.0001**[1]
Anticoagulants (%)			0.12[2]
Yes	22 (53.7)	63 (68.5)	
No	19 (46.3)	28 (30.4)	
BFS	11.49	8.28	**≤ 0.0001**[1]
Hb (mg/dL)	7.98	10.7	**≤ 0.0001**[1]
Thrombocytes (10^3/μL)	189	265	**≤ 0.0006**[1]
Creatinine (mg/dL)	0.98	1.24	**0.0255**[1]
INR	1.27	1.29	0.1632[1]
Endoscopic data			
Endoscopies prior to CA (*n*)	2.07	2.12	0.92[1]
Hemostasis achieved in primary endoscopy, *n* (%)			**≤ 0.0001**[2]
Yes	4 (9.8)	88 (95.7)	
No	37 (90.2)	3 (3.3)	
Location of bleeding, *n* (%)			**≤ 0.0087**[2]
Ambiguous	7 (17.5)	43 (46.7)	
Jejunum/ileum	4 (10)	1 (1.1)	
Colon	28 (70)	45 (50)	
Others	1 (2.5)	2 (2.2)	
Follow up			
Duration of hospitalization (d)	19.44	9.79	**≤ 0.001**[1]
Discharge, *n* (%)	25 (61.0)	83 (90.2)	**≤ 0.0001**[2]
Surgery, *n* (%)	13 (31.7)	4 (4.3)	
Death, *n* (%)	3 (7.3)	3 (3.3)	

[1]Wilcoxon's rank sum test.
[2]Fisher's exact test for count data.
LGIB: Lower gastrointestinal bleeding; CA: Catheter angiography; TAE: Transarterial embolization; CA-LGIB: Catheter angiography group; K-LGIB: Reference group with conservative treatment; BFS: Glasgow-Blatchford bleeding score; HR: Heart rate; INR: International normalized ratio.

Coils were the most frequently used material for embolization (13/20). Due to the absence of any evidence of bleeding, no embolization was performed in 21 cases (51.2%). A prophylactic embolization was performed in two cases (4.9%). The average

Table 2 Evidence of bleeding with reference to computed tomography angiography

LGIB (*n* = 17)	CA: Bleeding, *y* (%)	CA: Bleeding, *n* (%)
CTA: Bleeding *y* (%)	2 (11.7)	4 (23.5)
CTA: Bleeding, *n* (%)	4 (23.5)	7 (41.3)

LGIB: Lower gastrointestinal bleeding; CA: Catheter angiography; CTA: Computed tomography angiography.

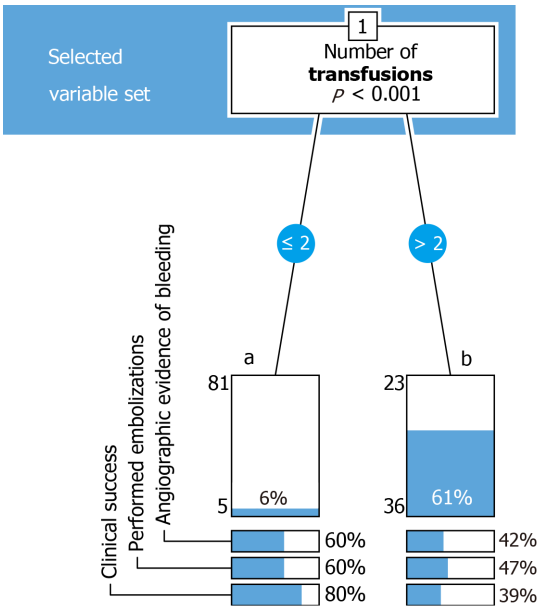

Figure 3 Course of treatment until angiography with reference to the number of transfusions.

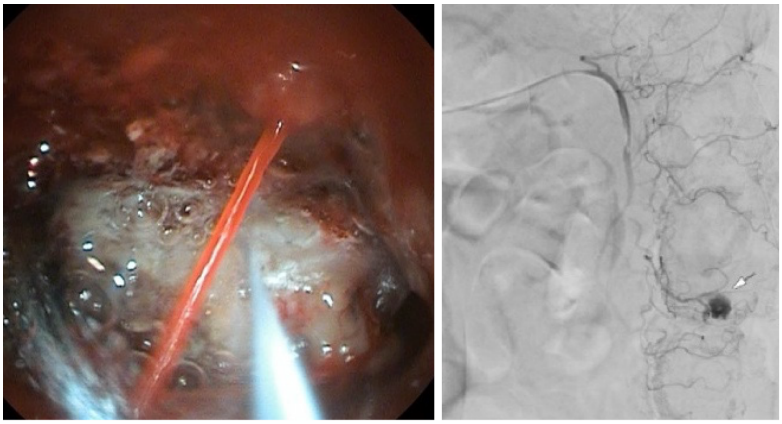

Figure 4 Lower gastrointestinal bleeding which failed endoscopic therapy and was controlled by transarterial embolization sucsessfully.

duration of angiography was one hour, and the overall duration of fluoroscopy 22 min. The median dose area product was 24662 cGy/cm². One patient died during the angiography due to hemorrhagic shock. In three cases the investigation was discontinued by the patients.

Twenty-two patients (53.6%) underwent a control endoscopy. Of these, 13 (59.1%) had a normal report. One patient (4.5%) had necrosis due to ischemia, and 5/22 (22.7%) experienced renewed bleeding. In the CA group, 13/41 (31.7%) patients underwent surgery, three (7.3%) died, and 25 (60.1%) could be discharged. Among patients who underwent TAE, the procedure was clinically successful in 11/20 patients (55%).

The K-LGIB group consisted of 415 treated cases, of whom 92 had LGIB. Table 1 summarizes demographic data, laboratory values, endoscopic findings, and the outcome of treatment in both groups.

Courses of treatment

Weighting of variables for further differentiation was performed with the aid of variable importance (Figure 1). Successful hemostasis in primary endoscopy, the number of transfusions, and the site of bleeding were the major parameters.

All patients with failed primary hemostasis and a GBS >10 in either group underwent angiography (n = 30). The latter investigation yielded evidence of bleeding in 15 patients (50%). Embolization was performed in 16 (53%) patients and was successful in 12 (40%), (Figure 2). Only one patient who achieved hemostasis in primary endoscopy and needed less than two transfusions was scheduled for angiography. Three of nine patients (33%) who needed more than two transfusions underwent angiography, which yielded no evidence of bleeding in any case (Figure 2).

Angiographies were performed in 5/81 patients (6%) who received less than two transfusions regarding both groups (K-LGIB and CA-LGIB), and yielded evidence of bleeding in three cases. Of patients who were given more than two transfusions, angiographies were performed in 36/59 patients (61%), revealed bleeding in 42%, and the treatment was successful in 39% (Figure 3).

DISCUSSION

Despite high rates of endoscopic hemostasis and spontaneous hemostasis, a small number of patients with severe LGIB require additional treatment after endoscopy[2]. CA and TAE have been established as successful treatment modalities for these patients over the last few years. Surgery is needed in a small number of exceptional cases[7]. In our retrospective analysis, we examined patients with LGIB who had undergone CA over a period of 10 years.

Not surprisingly, endoscopic hemostasis was successful in just a small number of patients in the CA group, but in as many as 88 patients (94.7%) in the reference group. These data confirm the success of endoscopy for the management of bleeding[4,23]. In endoscopic diagnostic investigation, hemostasis is a crucial factor to be considered prior to CA (Figure 2). Our data analysis revealed that the failure to achieve primary hemostasis in endoscopy was a major difference between the investigated groups. In patients who had undergone CA, we also identified other parameters that might justify the involvement of interventional radiology for the purpose of diagnosis and therapy early in the course of the patient's treatment. Specifically, these parameters are the shock index, GBS, and the number of transfusions.

In accordance with published guidelines, patients in our study underwent endoscopic investigation within a day after admission[8,24]. Diverticular bleeding was suspected in a large number of those who underwent angiography. Localization of bleeding and the achievement of endoscopic hemostasis are both particularly difficult in patients with diverticular bleeding[25]. In cases of severe disease, it would be advisable to consider angiography at an early point in time.

In our patients, pre-interventional diagnostic CTA investigations did not possess sufficient sensitivity or specificity to predict the outflow of contrast medium on CA. This contradicts published data, which consider CTA possibly even superior to colonoscopy for acute diagnostic investigation[26]. The probability of contrast medium outflow in the CTA is maximized in patients who receive a CTA < 60 min earlier. However, the time period between the primary investigation and angiography had no significant impact on the demonstration of contrast medium outflow[27].

In the published literature, CTA has been described as a useful procedure in planning angiography as well[28]. In our retrospective analysis, a non-standardized CTA investigation over a period of 10 years was a limiting factor in regard of the outcome. As Table 2 shows, CTA yielded poor values for the quality criteria (sensitivity, specificity, positive/negative predictive value). A diagnostic CTA examination was only performed in about 40% of patients, and only a third of cases were investigated with the specific aim of achieving morphological evidence of bleeding on radiological investigation.

An adequately performed CTA investigation, as described by Bruce and Erskine[29] (non-contrasted phase, arterial phase and late venous phase, prompt availability of embolization facilities), is essential to ensure the high sensitivity and specificity of CTA. Early diagnostic investigation by radiological procedures appears to be justified

in hemodynamically unstable patients with no hemostasis in primary endoscopy. In cases of proven bleeding, a CA should be performed immediately after the CTA[27]. When CTA shows no evidence of bleeding, the decision to perform a CA should be made individually in each patient, because a CTA may yield false-negative findings in rare cases[28]. Especially in clinically unstable patients with bleeding on endoscopy, in whom CA is the last option before definitive surgical treatment, an angiography may be meaningful even in the presence of a negative CTA report. Recommendations issued so far suggest that all options to localize the source of bleeding should be exhausted prior to CA, but the decision to perform a CA should not be dependent on previous evidence of bleeding[11]. In the absence of bleeding on CA, a prophylactic TAE or provocation of bleeding should be performed on an individual basis, and might be justified as a means of preventing recurrence.

Published studies recommend superselective embolization for angiographic localization of bleeding[30]. We used this approach in about 90% of our patients. The choice of embolization material[31] is not important; it depends on the investigator's preference. We used coils in the large majority of cases. Published reports recommend the use of other materials such as NBCA[30]. Adequate prospective studies on the subject are lacking.

The high degree of technical success we achieved with CA is in line with published data[16]. The detection of bleeding in a little less than a half of the patients has also been confirmed in other studies[1,32]. Finally, our data revealed clinical success in about one half of cases. Retrospective data concerning TAE show similar rates of clinical success (46%-95%)[10,16,33]. Only 3% of patients with LGIB have symptoms of shock and more than 50% have hemoglobin levels in excess of 12 mg/dL[1]. Thus, a positive shock index may be a predictor of angiographic treatment after failed endoscopic therapy. Our analysis revealed that the shock index was a significant variable importance measure. Patients in the CA group had a significantly higher shock index than those who had undergone conservative treatment and were given, on average seven transfusions, which is a predictor of increased 30-d mortality[32,33]. Thus, TAE permitted successful treatment with a minimally invasive procedure in approximately one half of critically ill patients. Surgery and further increases in morbidity and mortality rates could thus be avoided.

Despite primary endoscopic investigation and treatment, angiographies were performed on average within three days. In view of the fact that the patients usually underwent two diagnostic endoscopies, this time interval is indicative of smooth cooperation between the involved specialties, although the published guidelines provide no recommendations about the ideal time point for CA[8]. Interestingly, and analogous to endoscopic investigation, bleeding is detected on angiography more easily when the examination is performed early after the detection of bleeding on CTA [27].

A rising number of transfusions was shown to be a predictor of clinical failure in the treatment of LGIB[11,33]. Furthermore, the probability of detecting bleeding on angiography is significantly higher[27]. Not surprisingly, the number of transfusions is an important parameter of variable importance and was of crucial significance in our results. The GBS is also an extensively investigated factor in the treatment of gastrointestinal bleeding. Although the GBS was actually developed for upper gastrointestinal bleeding, it reduced hospital-based interventions and mortality rates in LGIB as well[34,35]. Besides, we established GBS as a positive predictor in the demonstration of bleeding on angiography.

Our retrospective data analysis served as a basis for the calculation of variable importance. Subject to a prospective multicenter validation, our data provide potential evidence of optimized treatment after failed endoscopic therapy. To our knowledge, such courses of treatment have not been published so far. In addition to previously published flow charts[2], these courses of treatment might serve as a crucial basis for making decisions about CA. Depending on the parameters registered in our courses of treatment (no hemostasis in primary endoscopy, more than two transfusions, BFS > 10), the clinician should consider the option of interventional radiological procedures.

Limitations

Contrast medium extravasation in TAE should be used as an endpoint in future studies in order to validate the clinical parameters that indicate extravasation. This aspect was not adequately registered in the present study. However, an important point is the changing character of LGIB, which may mask bleeding. Besides, our assumptions need to be validated prospectively. As mentioned earlier, a further limitation of the present study is the use of a non-standardized computed tomography (CT) protocol, which probably led to the selection of patients for angiography on the

basis of certain clinical factors. In the future, a CT for the purpose of detecting an LGIB should always be performed in accordance with the above mentioned model and if possible in the acute phase of bleeding in order to ensure adequate selection of patients for CA.

CONCLUSION

Although LGIB's do subside spontaneously, or can be reliably and successfully treated by endoscopy, the data reported in the present study are relevant for a small number of patients. Angiography has undoubtedly gained increasing precedence over surgery for the treatment of gastrointestinal bleeding. Further prospective analyses will be needed to answer questions about the appropriate time point and the appropriate radiological procedure for diagnosis and treatment. Following confirmation in prospective investigations, our selected predictors and the retrospective courses of treatment derived from these may contribute to the development of future decision trees.

ARTICLE HIGHLIGHTS

Research background

The large majority of lower gastrointestinal bleedings (LGIB) subside on their own or after endoscopic treatment. A small number of these may pose a challenge in terms of therapy when endoscopy does not achieve hemostasis. Based on what we know, transarterial embolization (TAE) enables the clinician to control gastrointestinal bleeding.

Research motivation

The timing and value of computed tomography angiography (CTA) and catheter angiography (CA) after failed primary hemostasis in endoscopy should be given greater attention in the course of treatment. The use of easily determined diagnostic and treatment parameters for identifying the best time point of escalation therapy in terms of angiography is the principal motivation in this field of science.

Research objectives

The aim was to evaluate clinical predictors for CA in patients with LGIB and create a practical decision-making aid based on these. It was shown that endoscopic hemostasis in primary endoscopy, along with GBS and the number of transfusions, were the most important factors in predicting CA.

Research methods

We performed a retrospective analysis of all patients with LGIB who received CA over a 10-year period in a maximum-care hospital (CA-LGIB group). A group of patients with LGIB who underwent conservative treatment served as the reference group (K-LGIB group). We used mean decrease in impurity, a random forest-based metric for variable importance, to assess the suitability of the collected data. Conditional inference trees were employed to build decision-making aids based on binary splits.

Research results

Most patients with LGIB and no hemostasis received angiography within three days after admission. We designed the treatment on the basis of the most important clinical parameters [Glasgow-Blatchford bleeding score (GBS), shock index, and serum hemoglobin levels]; these should help the clinician in making decisions about early radiological treatment with CA and TAE. Endoscopic hemostasis proved to be the crucial difference between CA and conservative treatment.

Research conclusions

Primary endoscopic hemostasis, along with the GBS and the number of transfusions, could permit a stratification of risks. Courses of treatment might serve as a crucial basis for making decisions about scheduling a patient to undergo CA. The present data are intended to enhance the clinician's awareness of angiographic diagnostic investigation and treatment after or during failed endoscopic treatment.

Research perspectives

The timing of the CTA, the procedure for a negative CTA in hemodynamically unstable patients and the benefits of provocative CA should be investigated further. Contrast extravasation in CA and subsequent TAE should be the endpoint of future prospective studies. Hospitals will need strategies to transfer people with failed hemostasis in primary endoscopy to interventional radiology.

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CASE REPORT

Visibility of the bleeding point in acute rectal hemorrhagic ulcer using red dichromatic imaging: A case report

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Abstract

BACKGROUND

Red dichromatic imaging (RDI) is a novel image-enhanced endoscopy expected to improve the visibility of the bleeding point. However, it has not been thoroughly investigated.

CASE SUMMARY

A 91-year-old man developed a sudden massive hematochezia and underwent emergent colonoscopy. An ulcer with pulsatile bleeding was found on the lower rectum. Due to massive bleeding, the exact location of the bleeding point was not easy to detect with white light imaging (WLI). Upon switching to RDI, the bleeding point appeared in deeper yellow compared to the surrounding blood. Thus, RDI enabled us for easier recognition of the bleeding point, and hemostasis was achieved successfully. Furthermore, we reviewed endoscopic images and evaluated the color difference between the bleeding point and surrounding blood for WLI and RDI. In our case, the color difference of RDI was greater than that of WLI (9. 75 *vs* 6. 61), and RDI showed a better distinguished bleeding point from the surrounding blood.

CONCLUSION

RDI may improve visualization of the bleeding point by providing better contrast in color difference relative to surrounding blood.

Key Words: Red dichromatic imaging; Image-enhanced endoscopy; Acute hemorrhagic rectal ulcer; Gastrointestinal hemorrhage; Endoscopic hemostasis; Case report

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Core Tip: Red dichromatic imaging (RDI) is a novel image-enhanced endoscopy presumed to improve the visibility of the bleeding point but has not yet been fully explored. We present a case in which RDI effectively identified the bleeding point in an acute hemorrhagic rectal ulcer lesion with an analysis of color difference compared to white light imaging. RDI may enable easier recognition of the bleeding point by enhancing the color contrast of the bleeding point relative to the surrounding blood.

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INTRODUCTION

Endoscopic hemostasis of acute gastrointestinal bleeding is sometimes a challenging task, especially when pulsatile bleeding from the artery impedes clear visibility of the bleeding point. Red dichromatic imaging (RDI) is a new endoscopic technology using three types of wavelength (540 nm, 600 nm and 630 nm) lights[1]. It is integrated as a new function in the latest endoscopic system (EVIS X1, Olympus Co., Tokyo, Japan) from April 2020. An endoscopist can quickly switch from white light imaging (WLI) to RDI, a modality that visualizes blood in yellow, during an endoscopic intervention. Recently, RDI has been found to be effective in the identification of bleeding point in endoscopic hemostasis during endoscopic submucosal dissection or hemorrhage from upper gastrointestinal ulcer[2-5]. In this report, we describe an impressive case in which RDI effectively identified the bleeding point in an acute hemorrhagic rectal ulcer lesion *via* analysis of the color difference between the bleeding point and surrounding blood.

CASE PRESENTATION

Chief complaints

A 91-year-old man hospitalized with pneumonia was referred to our department due to sudden massive fresh hematochezia on the 13th day of hospitalization.

History of present illness

At admission, a right femoral neck fracture was also found and required bed-rest as a nonoperative treatment.

History of past illness

He had a history of pneumonia and hypertension.

Personal and family history

He had smoked 2 packs-per-day of cigarettes for over 30 years but quit 40 years ago and was a social drinker. His family history was unremarkable.

Physical examination

He presented signs of hypovolemic shock with low blood pressure (BP of 79/38 mmHg) and tachycardia (101 bpm). The vital signs were stabilized after a rapid infusion of 1000 mL of lactated Ringer's solution. His abdominal examination was normal with no tenderness.

Laboratory examinations

His hemoglobin level dropped from 11.5 to 7.2 g/dL.

Imaging examinations

Contrast computed tomography revealed extravasation in the lower rectum (Figure 1).

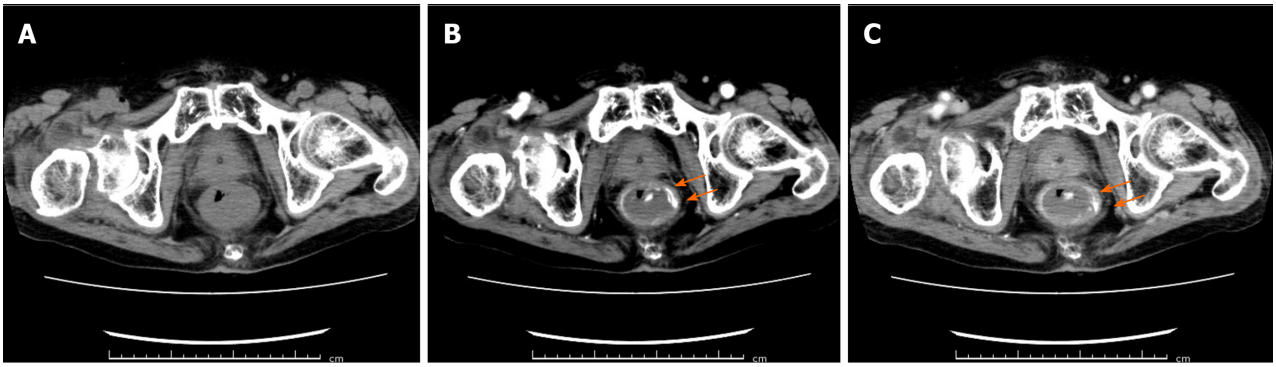


Figure 1 Computed tomography scan images of the pelvis. A: Plain; B: Arterial phase; and C: Delayed phase; Contrast extravasation is observed in the lower rectum on the arterial phase with further pooling of contrast on the delayed phase (orange arrow).

After computed tomography, we promptly performed an emergent colonoscopy using a prototype endoscope (GIF-Y0058; Olympus Co., Tokyo, Japan) instrumented with RDI mode, and an ulcer accompanied with a pulsatile bleeding was found on the lower rectum.

FINAL DIAGNOSIS

The patient was diagnosed with acute hemorrhagic rectal ulcer, likely caused due to being bed-rest status and constipated.

TREATMENT

Followed by endoscopic observation, we went on to achieve hemostasis. However, massive bleeding with pooled blood hindered observation of the bleeding point with WLI (Figure 2A). Thereby, we switched to RDI, and the bleeding point was clearly identified as it was displayed in deeper yellow compared to the surrounding blood (Figure 2B). The bleeding vessel was coagulated with hemostatic forceps (Coagrasper; Olympus Co., Tokyo, Japan) in soft coagulation current (effect 5, 50 W) using an electrosurgical system (VIO300D; ERBE, Tübingen, Germany), and hemostasis was obtained successfully (Figure 2C).

OUTCOME AND FOLLOW-UP

After the achievement of endoscopic hemostasis, his anemia improved after receiving 4 units of packed red blood cells. No further bleeding was noted for a month until the patient was discharged to another hospital for rehabilitation.

DISCUSSION

When attempting endoscopic hemostasis for active bleeding with acute hemorrhagic rectal ulcer using WLI, we often encounter with pooled blood hindering the detection of bleeding points in a similar shade of red. The patient may even need to be repositioned to facilitate the detection of the bleeding point when the bleeding point is located at the gravity side. RDI may overcome this problem as it can enhance the bleeding point in the presence of pooled blood and eventually facilitate the endoscopic hemostasis. The key mechanism of RDI that enables clear visualization of the bleeding point in the presence of pooled blood is the difference in blood concentration and/or blood volume. The narrow-band light of 600 nm wavelength highlights the difference in blood concentration and/or its volume because of the light absorption features of the hemoglobin. The center and circumference of the bleeding point appears in clear contrast because they contain different amounts of hemoglobin and accordingly absorb and reflect differential levels of 600 nm light[6,7]. This means that more light is

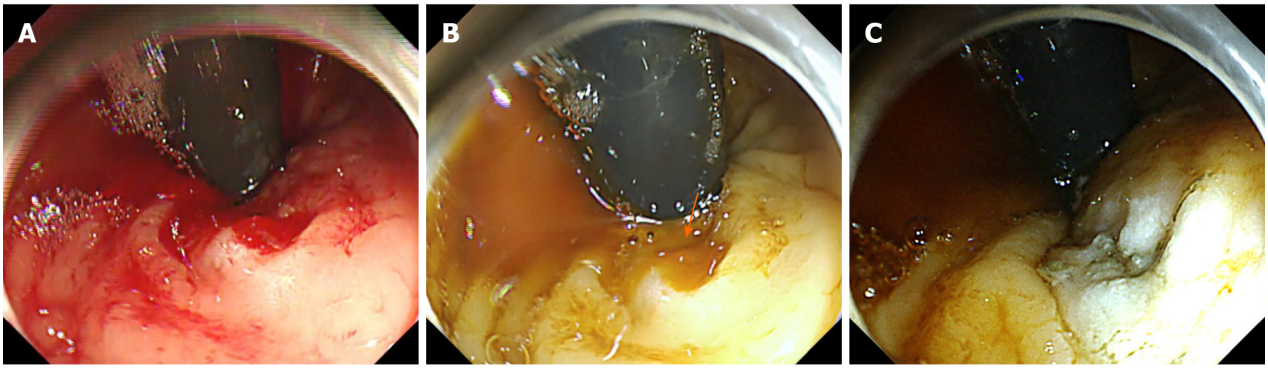
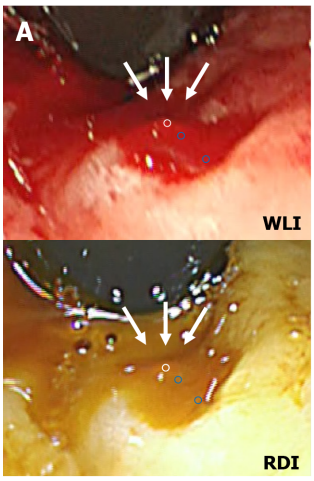


Figure 2 Endoscopic images of emergent colonoscopy. A: Massive pulsatile bleeding from the ulcer on the lower rectum hindered the detection of the bleeding point with white light imaging; B: After switching to red dichromatic imaging, the bleeding point was observed as deep yellow (orange arrow) compared to surrounding blood, and that allowed us to recognize it precisely; and C: The bleeding vessel was coagulated, and hemostasis was achieved successfully with red dichromatic imaging.



B

Bleeding point	Surrounding blood
L^1 59.2	L^1 58.3
a^1 47.2	a^1 52.0
b^1 45.7	b^1 50.1
ΔE: 6.61	

Bleeding point	Surrounding blood
L^1 72.2	L^1 78.0
a^1 9.20	a^1 4.33
b^1 49.3	b^1 55.4
ΔE: 9. 75	

Figure 3 Color values and color differences between bleeding point and surrounding blood. A: The regions of interests (ROIs) were located in the bleeding point and at two selected points in surrounding blood (one was just next to outside of the bleeding point and the other was just inside the surrounding blood), avoiding areas with halation. Each ROI was set approximately in the same region for white light imaging and red dichromatic imaging. The white and blue circles indicate the ROI of the bleeding point (white arrow) and surrounding blood, respectively. The color values were defined as the median color value in each ROI; and B: The ΔE based on color value change between the ROI of the bleeding point and surrounding blood. WLI: White light imaging; RDI: Red dichromatic imaging; ΔE: Color difference.

reflected from the center and less from the circumference. We speculated that this mechanism produces a larger color difference between the bleeding point and surrounding blood, resulting in easier detection of the bleeding point.

Therefore, we investigated the visibility of the bleeding point by evaluating the color difference between the bleeding point and surrounding blood for WLI and the corresponding RDI images in still pictures of this case. The color difference was evaluated by comparing the color values of regions of interest (ROI) for the bleeding point and surrounding blood using Adobe Photoshop Elements 2020 (Adobe Systems Inc., CA, San Jose, United States). The details for the setting of ROI are shown in Figure 3A. The color values were defined as the median color values in each ROI (24 × 24 pixels) according to the Commission Internationaled'Eclairage $L^1a^1b^1$ (L^1 = black to white; 0 to + 100, a^1 = green to red; -128 to + 127, b^1 = blue to yellow; -128 to + 127) color space[8]. The color difference was calculated by the following equation: $\Delta E = \sqrt{(\Delta L)^2 + (\Delta a)^2 + (\Delta b)^2}$. In the present case, the color difference with WLI and RDI was 6.61 and 9.75, respectively (Figure 3B). Thus, RDI differentiated the bleeding point from surrounding blood better than WLI based on color difference.

This report is the first of its kind to use the color difference as an objective indicator for the investigation of the visibility of bleeding point with RDI. Subsequent to this research, we are now conducting a larger study by comparing the visibility of the bleeding point including the evaluation of the color difference between WLI and RDI

for acute gastrointestinal bleeding.

CONCLUSION

Our case of acute hemorrhagic rectal ulcer demonstrated the usefulness of red dichromatic imaging for achieving endoscopic hemostasis by improving the detection of the bleeding point. Red dichromatic imaging may be useful for recognition of the bleeding point by offering good contrast in color difference relative to surrounding blood.

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REVIEW

Six intragastric balloons: Which to choose?

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Abstract

Endoscopically placed intragastric balloons (IGBs) have played a significant role in obesity treatment over the last 30 years, successfully bridging the gap between lifestyle modification/pharmacotherapy and bariatric surgery. Since they provide a continuous sensation of satiety that helps the ingestion of smaller portions of food, facilitating maintenance of a low-calorie diet, they have generally been considered an effective and reversible, less invasive, non-surgical procedure for weight loss. However, some studies indicate that balloons have limited sustainable effectiveness for the vast majority attempting such therapy, resulting in a return to the previous weight after balloon removal. In this review we try to summarize the pros and cons of various balloon types, to guide decision making for both the physician and the obese individual looking for effective treatment. We analyzed the six most commonly used IGBs, namely the liquid-filled balloons Orbera, Spatz3, ReShape Duo and Elipse, and the gas-filled Heliosphere and Obalon - also including comments on the adjustable Spatz3, and the swallowable Obalon and Elipse - to optimize the choice for maximum efficacy and safety.

Key Words: Obesity; Intragastric balloon; Fluid-filled balloons; Gas-filled balloons; Swallowable balloons

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Core Tip: Intragastric balloons have played a significant role in the management of obesity. Their easy application, reversibility and good short-term results have led to the development of a wide variety of balloon types. However, long-term results are not as good, and concerns about complications have also arisen. We tried to analyze the characteristics and effectiveness of the 6 most popular balloon types, in order to

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provide guidance in choosing the most appropriate balloon for each patient.

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INTRODUCTION

Obesity, defined as an excess of body weight, and particularly of body fat, and associated with an increased number of co-morbidities, remains a considerable threat to human health, due to the high prevalence of morbidity and mortality, both from the syndrome itself and the related co-morbidities. Lifestyle modification, covering the combination of energy restriction, physical exercise, and behavioral changes is widely recommended as a stepwise approach to control/treat obesity. However, this measure usually leads to a modest decrease in weight, with a short success time - somewhat similar results to that of pharmacotherapy[1-8].

Although the pathophysiology of obesity is complex, the excess in calorie intake lies at the root of the weight gain mechanism[9]. One of the factors associated with greater calorie intake is definitely the greater fasting gastric capacity[10]; thus, an obvious solution would be the reduction of gastric capacity: either by surgery (resection or bypass procedures) or by placing a space-occupying device, mimicking a bezoar[11].

Bariatric surgery is generally effective, but always carries the risk of complications as well as low patient acceptance. It is estimated that less than 1% of obese patients who qualify for bariatric surgery opt for this procedure, mainly for fear of perceived risks of postoperative complications and mortality and, among others, the high surgical costs, and the lack of access to surgery. Furthermore, surgery is not indicated for overweight and obese class I patients[12-17].

Therefore, endoscopic bariatric and metabolic therapies have emerged over the years, to provide less invasive options beyond lifestyle modifications, pharmacotherapy and surgery, for patients who have failed with conservative treatment and are not or not yet surgical candidates, or refuse surgery because of its invasiveness and fear of complications[12,18]. According to the Statements after the Brazilian Intragastric Balloon Consensus, held in Sao Paulo, Brazil, in June 2016, obese individuals who are candidates for balloon implantation must be over 12 years of age, with established puberty, while there is no maximum age limit, each patient being evaluated individually. The minimum body mass index (BMI) is 25 kg/m^2, after failure of clinical treatment, with no influence of BMI on the choice of balloon type, this being at the discretion of the physician. It is common sense that the presence of an active gastric ulcer, or in any other location, of gastric or esophageal varices, of a hiatal hernia longer than 5 cm as well as previous gastric surgery, are all considered as absolute contraindications[19]. Intragastric balloons (IGBs)-based on the philosophy of restrictive surgical procedures – are space-occupying devices, first described by Niebeb in 1982[11]. They are the most extensively studied and the most commonly used endoscopic "therapies" for obesity, due to their great efficacy and safety. Five years later, in 1987, the consensus meeting of international experts in Tarpon Springs, Florida[20], defined a number of specifications for a balloon to be considered suitable for use and primarily safe: It must (1) have a smooth surface with low potential for causing erosions, ulcers or obstructions; (2) be constructed of durable materials that do not leak; (3) be filled with liquid and not air; (4) be marked with a radiopaque marker that allows proper follow up of the device in case of deflation; and (5) have the capability of being adjusted to various sizes.

Mathus-Vliegen *et al*[18] who have been studying their mode of action for more than a decade, considers IGBs to mediate satiety both peripherally, by being a physical impediment to food intake, by reducing the gastric capacity and by delaying gastric emptying, and centrally, by activating gastric stretch receptors that transmit signals *via* afferent vagal nerves, the solitary tract and paraventricular nuclei, to the ventromedial and lateral hypothalamus[21-23].

In the intervening decades these devices have evolved to become more functional, effective and safe and the whole procedure less invasive, while keeping the

advantages of being reversible and not altering the gastrointestinal anatomy[12,24,25].

Currently, there are many IGB designs, with little variation between them, several of which are now available in clinical practice, but few of which have gained Food and Drug Administration (FDA) approval. They may differ in relation to the method of insertion and removal, the filling volume, adjustability and duration of implantation, while still adhering to the main idea of the artificial bezoar that occupies space in the stomach causing mechanical gastric distention, and providing a continuous sensation of satiety, and thus reduction in food intake, finally resulting in weight loss[12,26,27].

In an effort to facilitate physician choice, the present study attempts to describe the technical characteristics of FDA and European Community (CE)-approved balloons, providing information on their effectiveness and safety, based on the large-scale clinical studies of the last decade.

BALLOON DESCRIPTION

Orbera IGB

Orbera IGB (Apollo Endosurgery, Austin, TX, United States), formerly BioEnterics IGB (BIB, Inamed Corporation, Santa Barbara, CA, United States) was the first of the new generation of balloons which appeared in 1991, following the Tarpon Springs Consensus meeting[20]. To date, it is the most popular and most commonly used endoscopic device for weight loss, having also the most historical data supporting its use; all the other balloons, which follow chronologically, are practically based on the same idea and, unavoidably are comparable to it[4,5,27-29].

The FDA-approved Orbera (2005) is a single spherical silicone-made balloon of about 13 cm in diameter, arriving commercially compressed and impacted at the end of a filling tube attached to a radiopaque self-sealing valve (Figure 1). After an initial diagnostic endoscopy, the balloon placement assembly is inserted orally into the gastric fundus and a volume of 500 to 700 mL saline solution - at the discretion of the physician - is used for balloon inflation through a closed infusion circuit, the whole procedure being performed under direct endoscopic supervision[13,30,31]. After completion of inflation, the infusion system is closed, creating a sudden vacuum resulting in the valve self-sealing and allowing the easy release of the filling tube, which is then gently pulled out through the mouth, leaving the balloon in the fundus, but floating freely in the stomach[32,33].

According to manufacturer, the Orbera balloon could safety remain implanted for up to a maximum of 6 mo, because of the increasing risk of perforation and sudden emptying thereafter, which might allow the balloon to migrate towards the gut and possibly obstruct the bowel[5,13]. It requires sedation and endoscopy for deflation and removal; a double-channel endoscope and two long-jaw rat-tooth forceps may facilitate the procedure[4,13].

For the last two years a balloon which can remain in situ for 12 mo has also been available; the second generation "Orbera365", having almost exactly the same characteristics[34].

Heliosphere balloon

Over the years, it has become obvious that the excess weight of a liquid-filled balloon is the cause of an increased rate of nausea, vomiting and epigastric pain in the days immediately following balloon placement; thus, the air-filled Heliosphere balloon, known as the Heliosphere bag (Helioscopie Medical implants, Vienne, France) was developed to circumvent this disadvantage, and was introduced into clinical practice in 2004[35,36].

It is a single spherical high-volume-capacity, air-filled, polyurethane balloon weighing less than 30 g and is enclosed in a silicone envelope. It requires endoscopy for positioning and is loaded with a simple inflation system, allowing 900-1000 mL of air, within a median time of 12 min[30,37-40]. The balloon is generally well-tolerated during the 6 mo implantation period. However, its use has raised several concerns about procedure-related complications due to technical difficulties in balloon passage through the cardia and the upper esophageal sphincter–large size, low pliability, high failure rates for positioning and spontaneous deflation[28,36,38]; similar difficulties have also been referred to during endoscopic removal, leading, in a few cases, to surgical removal or to the use of a rigid endoscope[35], thus, the use of a two-claw forceps for catching it in the valve is advised. The whole procedure generally takes longer than that for other balloons, including the Orbera, and results in more discomfort, making deep sedation a prerequisite for both patient and endoscopist[41].

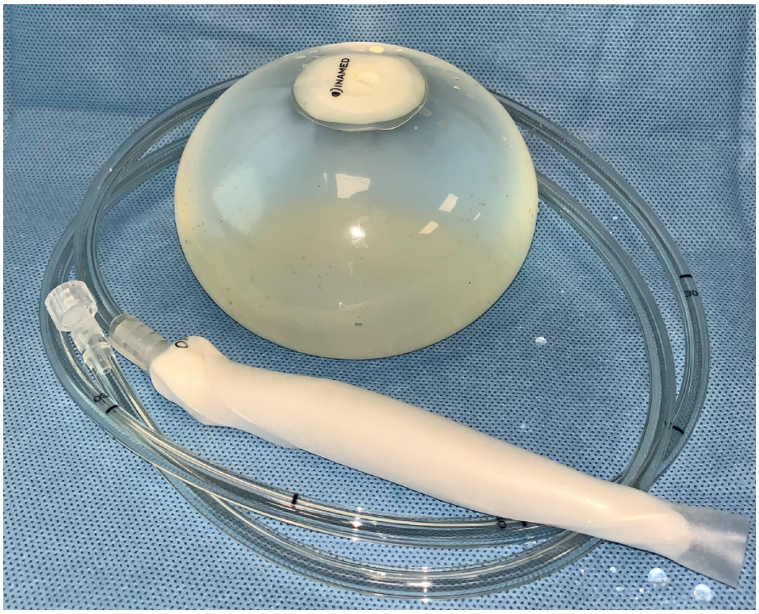

Figure 1 Orbera balloon. (This photo is from our personal photo-archive).

A severe warning for those candidates for gas-filled-Helioshere balloons is to totally refrain from scuba diving and travelling in unpressurized airplane cabins[5].

Spatz3® balloon

Spatz3® balloon (Spatz3; Spatz FGIA, Great Neck, NY, United States) is the 3rd generation Spatz device manufactured with the first criterion of the Tarpon Springs Conference requirements in mind –*i.e.*, its volume can be adjusted - increased or reduced - throughout the treatment period and not only initially at the time of inflation[20]. Additionally, it is the first balloon that can safely remain in the stomach for 360 d, thus facilitating sustained weight loss for one full year, as well as leaving more time for the patient to undergo feeding re-education and lifestyle modification. However, it has the serious disadvantage of not having a completely smooth surface, since the site for insertion of the filling valve forms a sort of 'tail'[42,43]. On the other hand, according to the manufactures, this 'tail' may prevent or delay a deflated balloon from passing through the duodenum. To date it has received the European Union CE mark but not yet gained FDA approval[42,44,45].

It is a spherical silicone, saline-filled balloon, with the unique feature of an extractable, thin, filling catheter with a valve at the end, which enables saline to be added or removed in situ, thus adjusting the intragastric volume according to patient tolerance and the desired weight-loss outcome. The system consists of 3 parts: the balloon; a silicone covered anchor, with an internal network, to facilitate balloon insertion and removal and prevent migration; and the silicone filling tube, able to stretch to modify the fluid volume of the balloon and shrink back into the stomach[35,43,44] (Figure 2).

The Spatz3 is designed to be inserted with a well-lubricated endoscope. The balloon is mounted on the tip of the scope by the use of a type of 'condom'. After visual confirmation that the whole balloon and its apparatus is fully within the gastric cavity - so avoiding the risk of inflation within the esophagus - balloon inflation is carried out under direct view, with 400-700 mL of saline. After inflation, the filling catheter is pulled up until its valve reaches the patient's mouth. Then the catheter is disconnected from the valve, which is closed with its cap, which has a blue nylon loop. Holding the loop, the valve is gently pushed back towards the oropharynx and the gastroscope facilitates the correct positioning of the valve in the gastric fundus[45].

For balloon deflation, in the case of intolerance in the early days - excessive and/or persistent vomiting for more than 7 d - the blue nylon loop is grasped endoscopically by foreign body forceps and pulled up to the mouth. At this level the previous mentioned filling catheter is adjusted and, by aspiration of 100 to 300 mL, the balloon volume is appropriately reduced. The same process is followed, usually 3 mo after implantation when the patient stops or has minimized weight loss, or should he/she report a decrease in satiety, to increase the balloon volume by a standard volume of 250 mL[43,46]. At the end the 12-mo implantation period, the balloon must be

Figure 2 Spatz-3 balloon. [Courtesy of Ms Ariel Nezry (VP Marketing, Spatz FGIA Inc)].

removed endoscopically after emptying by standard balloon needle or deflation utilizing the valve, by the same process as for insertion. However, its size and the described irregular morphology make the endoscopic extraction more difficult and laborious, and thus anaesthesia is absolutely necessary[30,35,38,44].

ReShape Duo integrated dual balloon system

ReShape Duo integrated dual balloon system (ReShape Medical, Inc, San Clemente, CA, United States) consists of two independently filled silicone spheres joined by a central, short, non-communicating flexible silicone shaft. The main idea behind this system design is to decrease the chance of balloon intestinal migration should one of the balloons accidentally deflate. Additionally, this flexible configuration, according to the manufacturers, allows the balloons to conform to the natural contours of the stomach[5,30,47-49].

The ReShape Duo balloon, FDA-approved system is inserted transorally and advanced into the stomach by means of an endoscopic guidewire. Each is filled separately with up to 450 mL of saline (maximum total volume 900 mL), although a smaller volume is recommended for individuals less than 64.5 inches in height[47-51]. When inflated, it occupies a significant portion of the stomach (900 mL), while maintaining the natural gastric anatomy. For balloon system deflation and removal, after a maximum 6 mo period, anaesthesia and endoscopy are definitely required[5,49,52].

As of December 2018, Apollo Endosurgery (Apollo Endosurgery, Austin, TX, United States) purchased ReShape Medical and will focus exclusively on its own Orbera balloon going forward. With this transaction, the ReShape balloon will be phased out[53].

Obalon®

The Obalon® (Obalon Therapeutics Inc, Carlsbad, CA, United States) is a new thin-walled, 250 mL gas-filled, swallowable IGB, designed to allow easy gastric volume titration, by using additional balloons. It is an FDA-approved device, consisting of a series of three individual balloons, equating to a total volume of 750 mL that can be consequently swallowed one month apart, and is relatively well-tolerated by most patients[54].

Each balloon is compressed, folded, and fitted into a 6 g dissolvable gelatin capsule, which is swallowed under fluoroscopic visualization to verify that the entire capsule has entered the stomach[40,54,55]. A thin, 2 fr catheter is attached to the balloon and once the capsule reaches the stomach the other end of the catheter, which extends outside the mouth, is used for remote, automated balloon inflation to a maximal volume of 250 mL, using a canister filled with a proprietary air mixture that is mostly nitrogen based. The procedure is relatively easy and executable by a single operator. After balloon inflation, the catheter is detached and removed, allowing the balloon valve to safely self-seal[5,54-56].

The balloons can remained implanted for up to 6 mo and require endoscopy only for deflation and removal of all 3 balloons at the same time. The balloons are punctured and then grasped by forceps for extraction under general anaesthesia[40,54,56].

Recently, the FDA also approved the Obalon navigation system. It utilizes magnetic resonance to provide a real-time image of the Obalon on a computer screen instead of fluoroscopy to confirm balloon positioning. This technology, besides minimizing the exposure of patient and personnel to radiation and decreasing the cost of radiography, makes the procedure itself relatively easier. The Obalon has been used in pediatrics with promising results[54-56]. In Europe, the Obalon, rather than other balloons, is indicated for use for individuals with a lower BMI (27 kg/m^2)[5].

Elipse balloon

The Elipse balloon (Elipse; Allurion Technologies, Wellesley, MA, United States) is a non-FDA-approved IGB, similar in size, shape and function to the most widely used and endoscopically placed Orbera balloon. However, this is the first intragastric device not requiring anaesthesia, or an invasive endoscopic procedure, either for placement or removal[36,57,58]. It thus represents an innovative option for weight loss, minimizing the costs and the complication risks of the endoscopic procedure for insertion or removal and hence offers an option to obese individuals feeling uncomfortable with endoscopy and/or at risk for anesthesia[36,44]. However, by omitting the pre-implantation endoscopic surveillance of the stomach, the possibility of recognizing mucosal lesions (erosions or ulcers) or anatomical abnormalities (hiatus hernia), which could, theoretically, lead to unexpected complications at the time of balloon remaining in the stomach, is lost[57].

The balloon, made from a thin polymer film without rigid parts, is enclosed, well compressed, inside a small, swallowable vegetarian capsule attached to a thin catheter 75 cm long and 1.3 mm in diameter, *via* a self-sealing valve, and is designed to deploy spontaneously in the stomach. The capsule is as easily swollen with water as a pill, but in the case of difficulty, a stylet can be fed through the catheter to stiffen it, allowing the physician to gently push the capsule during swallowing. Once swallowed, its proper position in the stomach is confirmed through x-ray visualization of the balloon's radiopaque ring-shape marker; after which, the balloon is filled with 550 mL of fluid, consisting of distilled water with potassium sorbate preservative, through the catheter which is then removed by simply pulling it back[58-60]. Placement is performed in a 20 min outpatient visit.

After a 4 mo period, the device is designed to spontaneously empty; the reabsorbable material, remaining closed inside the sealing balloon valve, completely degrades, leaving the device to self - deflate and then naturally pass - thanks to its construction from a thin film without rigid parts-through the gastrointestinal tract and be excreted[35,36,46,57,58].

The ease of insertion and self-removal enables many physicians who do not perform endoscopy to use the balloon and this is expected to lower the total cost of diet programs. However, this may lead to its inappropriate implantation in unsuitable individuals and thus to increased risks of intolerance. Another cause of increased intolerance may be the absence of endoscopic surveillance of the stomach for any pathology prior to its insertion (Table 1).

EFFECTIVENESS FOR BODY WEIGHT LOSS

The first balloon fulfilling the Tarpon Springs Consensus standards was the Bioenterics IGB (Inamed® Corporation, Santa Barbara, CA, United States) now available as Orbera commercially available since 1991. For more than a decade it remained unique in the market, and thus, inevitably, is the subject of many observational and randomized published studies, analyzing its effectiveness, which, in most studies, was impressive. Today, almost 30 years later, the idea of using a balloon as a space-occupying device in the stomach to give the feeling of fullness, still remains not only attractive, but also effective, as demonstrated by the multiple attempts to copy, with modifications, the original idea, many of which have been considered successful and become commercially available. This chapter aims to show in numbers - through meta-analysis and large series - studies published in recent years - the effectiveness in weight loss of the IGBs now in use in clinical practice. For comparison and homogeneity of expression the parameters of percentage total body weight loss (%TBWL), percentage excess weight loss (%EWL) and BMI are used[51,61] (Table 2).

Table 1 Summary of Intragastric balloon characteristics

		FDA/CE approved			CE approved	
Balloon type	**Orbera**	**ReShape Duo**	**Obalon**	**Heliosphere**	**Spatz**	**Elipse**
Manufacturer	Apollo Endosurgery	ReShape Medical	Obalon Therapeutics	Helioscopie Medical Implants	Spatz FGIA	Allurion Technologies
Filled with	Saline	Saline	Nitrogen gas	Air	Saline	Liquid
Capacity (mL)	400-700	450 × 2	250 × 3	900-1000	300-900	550
Number of balloons	1	2	Up to 3	1	1	1
Insertion	Endoscopy	Endoscopy	Swallowed	Endoscopy	Endoscopy	Swallowed
Removal	Endoscopy	Endoscopy	Endoscopy	Endoscopy	Endoscopy	Natural pass
Duration	6	6	6	6	12	4
Adjustable	No	No	No	No	Yes	No

FDA: Food and Drug Administration; CE: European Community.

Table 2 Representative studies of the effectiveness of intragastric balloons

Ref.	Study type	Cases	Balloon type	Mo	Mean BMI loss kg/m²	Mean BWL kg	%TWL	%EWL
Genco *et al*[64], 2005	Observational	2515	Bioenterics	6	4.9 ± 12.7			
Kotzampassi *et al*[13], 2012	Observational	500	Bioenterics	6	7.39 ± 3.57	21.19 ± 10.3		38.09 ± 20.18
Lopez-Nava *et al*[67], 2011	Observational	714	Bioenterics	6	6.5 ± 12.7	18.8 ± 9		41.6 ± 21.8
Fittipaldi-Fernandez *et al* [68], 2020	Observational	5874	air-filled	6		19.13 ± 8.86	18.42 ± 7.25	65.66 ± 36.24
Abu Dayyeh *et al*[71], 2019	Observational	187	Spatz3	9			14.9 ± 7.2 plus 4.7*	
Fittipaldi-Fernandez *et al* [45], 2020	Observational	180	Spatz3	7.12 ± 1.63	6.18 ± 4.07	17.51 ± 11.67	16.22 ± 9.74	56.68 ± 40.12
Schwaab *et al*[72], 2020	Cross-sectional	360/144	Orbera/Spatz3	6 up to 12			15.4 ± 7/15.5 ± 9.6	
Sullivan *et al*[73], 2018	RCT	185/181	Obalon/sham	6			6.6 ± 5.1/3.4 ± 5.0	
Ienca *et al*[58], 2020	Observational	1770	Elipse	4	4.9 ± 2.0	13.5 ± 5.8	14.2 ± 5.0	67.0 ± 64.1
Genco *et al*[59], 2018	Observational	38	Elipse	4	4.2	12.7	11.6	26
Taha *et al*[77], 2020	Observational	96	Elipse	4	4.9 ± 2.0	11.2 ± 5.1	12.1 ± 5.2	
Ponce *et al*[47], 2015	RCT	187/139	ReShapeDuo diet/exercise	6				25.1 ± 1.6/11.3 ± 1.9
Agnihotri *et al*[50], 2018	Observational	202	ReShapeDuo	6		11.7 ± 7.3	11.4 ± 6.7	29.9 ± 18.2

BMI: Body mass index; %TWL: Percentage total weight loss; %EWL: Percentage excess weight loss; RCT: Randomised controlled trial.

Classical Orbera

In 2016 Moura *et al*[62] analyzed 9 out of 12 collected randomised controlled trials (RCTs), all between 1990 and 2014, in an effort to assess the effectiveness of the Orbera IGB-plus-diet against sham balloon-plus-diet. This meta-analysis found the balloon/diet treatment to be more effective than the sham/diet; the former obese patients experienced a higher BMI loss, with a mean difference of 1.41 kg/m² (95%CI: -2.17 to –0.64, P = 0.0003) and a higher weight loss with a mean difference of 3.55 Kg (95%CI: -6.20 to -0.90, P = 0.009). Regarding %EWL, a higher %value was found by the

Student's *t* test in balloon groups, with a mean difference of 14.0% compared to the sham group; however, no significant difference was found between the groups by quantitative analysis, due to a significant heterogeneity of the studies. Furthermore, there are some serious limitations in the study: besides the long period of time covered by the collected RCTs, the main problem is that some of these studies were conducted in the early years of Orbera use; the second is the small number of patients (from 8 to 31 per study group) in all studies except one, which included 187 patients and 139 controls.

Since it is recommended that the Orbera IGB be filled with a volume, ranging between 400 and 700 mL of saline, Kumar *et al*[63] decided to correlate the balloon filling volume to clinically relevant endpoints, namely weight loss outcomes, balloon tolerability, and adverse events. This review, by the inclusion of 44 studies (5549 patients) demonstrating a low risk of publication bias, remains by far the largest meta-analysis of studies dealing with only Orbera balloons. Meta-analysis did not reveal any statistically significant association between filling volumes, between 400 and 700 mL, the percentage of TBWL being 13.2% (95%CI: 12.3–14.0) at 6 mo for all patients. The authors attributed the negative findings to the relationship between balloon size and volume: the diameter of a 400-mL saline-filled balloon is 9.14 cm, while those of a 700-mL is only 20% wider at 11.0 cm. Similarly, there was no association between balloon filling volume and early removal rates (P = 0.1), gastroesophageal reflux symptoms (P = 0.64), or gastric ulcer rates (P = 0.09). However, they recommend the balloon be inflated with a volume of 600–650 mL, since such a volume–inexplicably–re-duces esophagitis: 9.4% *vs* 2.4% for a volume higher than 600 mL (P < 0.001), and migration rates: 2.26% *vs* 0.5% for a volume higher than 600 mL (P = 0.004).

Additionally, Yorke *et al*[64] reported, in their systematic review which included 26 studies (6101 patients), a reduction in body weight of 15.7 ± 5.3 kg and of BMI of 5.9 ± 1.0 kg/m^2, although 25 of the 26 are case series and not RCTs. Furthermore, they presented a percentage of 23.3% of patients experiencing nausea and vomiting, and 19.9% epigastric pain; the incidence of mortality was 0.05%, the 0.1% attributed to gastric perforation.

Although meta-analyses are certainly considered more reliable because they provide cumulative information from RCTs well-controlled for their reliability, there are many serious problems in the subject analyzed: (1) randomized studies of balloon treatment against sham treatment are very few and with a small number of cases; (2) not all studies included in a meta-analysis provide the same information regarding weight loss assessment parameters; and (3) studies comparing balloon types are also few, for two reasons: there are even now no observational studies with a large number of patients and no follow-up for most of the new balloons. The Orbera balloon, on the other hand, has a long history of clinical application and is thus considered trustworthy and reliable by the clinician, deterring many clinicians from changing from the well-known and safe Orbera just for the sake of a study. Thus, observational studies with a large number of patients were unavoidably used in the present analysis.

The most populated retrospective study (2515 patients) from the data-base of the Italian Collaborative Study Group, Genco *et al*[65] in 2005 reported a mean BMI reduction of 4.9 ± 12.7 (range, 0–25 kg/m^2) at 6 mo; from 44.4 ± 7.8 (range, 28–79.1 kg/m^2) to 35.4 ± 11.8 (range, 24–73 kg/m^2), and a mean EWL from 59.5 ± 29.8 (range, 16–210 kg) to 33.9 ± 18.7 (range, 0–87 kg), accompanied by a sign of resolution of diabetes and arterial hypertension in the majority of cases. Intolerance leading to early removal of the Bioenterics IGB was evidenced in 11 out of 2515 (0.44%) patients, while the overall complication rate was relatively low (2.8%).

A case series for 500 consecutive patients treated with the Bioenterics IGB, who were recruited from a single center and followed-up for a 5 year period was reported by Kotzampassi *et al*[13]. There was a mean body weight loss of 21.19 ± 10.3 kg or a 16.79% reduction, a mean BMI reduction of 7.39 ± 3.57 kg/m^2 or 16.89%, and a percent EWL of 38.09 ± 20.18, meaning that a target of more than 20% EWL had been achieved in 83% of patients at the time of balloon removal. At the 60 mo follow-up, a total of 195 patients completed the study and were found to have retained a weight loss of 7.26 ± 5.41 kg, a BMI reduction of 2.53 ± 1.85 kg/m^2, and a %EWL of 12.97 ± 8.54. At this time, 46 out of the 195 (23%) retained %EWL greater than 20%. The authors comment that those obese patients who lost 80% of their total weight loss during the first 3 mo of the 6-mo treatment, succeeded in maintaining a percent EWL of > 20 long-term after BIB removal: more precisely, this cutoff point was achieved in 83% at the time of removal and in 53%, 27%, and 23% at 12-, 24-, and 60-mo follow-up[13]. Quite similar were the results of a meta-analysis of 7 studies (409 patients) reporting a mean weight loss of 12.9 ± 0.8 kg at 3 mo and 16 ± 0.9 at 6 mo, meaning that 80% of the weight loss was achieved within the first 3 mo of treatment[66].

Similarly, in a large series of 714 consecutive Spanish patients treated with the BioEnterics IGB (now Orbera), Lopez-Nava *et al*[67] found their initial mean weight to be 106.3 ± 21.5 kg (range, 68–190), mean BMI 37.6 ± 5.7 kg/m^2 (range, 31–57) and mean EW 56.3 ± 27.1 (range, 16–205 kg). After balloon removal at 6 mo, mean weight was 94.7 ± 22 (range, 52–160 kg); mean BMI 31.1 ± 7.2 (range, 24–48 kg/m^2), mean %EWL 41.6 ± 21.8 (range, 0–77), mean weight loss 18.8 ± 9 (range, 0–45 kg); mean BMI loss 6.5 ± 12.7 (range, 0–21 kg/m^2); and mean %EBL was 44.5 ± 22.6 (range, 0–81).

In 2015 American Society for Gastrointestinal Endoscopy (ASGE)[25] published a meta-analysis of 17 studies with 1638 patients which demonstrated a percentage of excess weight loss of 25.44% (95%CI: 21.47%-29.41%) with the Orbera balloon at 12 mo and a percentage of total weight loss of 11.27% (95%CI: 8.17%–14.36%) at 12 mo after implantation; thus they considered the Orbera balloon an appropriate treatment option since it exceeded the threshold of the preservation and incorporation of valuable endoscopic innovations of 5% TBWL.

In 2018, 39 Brazilian expert endoscopists[19] reached a consensus on guidelines on indications, patient selection, filling volume, techniques of insertion and removal and adverse events, based on their experience with 41.863 balloons-32.735 subjects with the non-adjustable fluid-filled Orbera (78.2%), another 16.9% with similar balloons, such as the Silimed, 1020 patients (2.4%) with the adjustable fluid-filled balloon Spatz and another 2.5% of cases with the Heliosphere air-filled balloon. The mean percentage total weight loss (%TWL) was 18.4% ± 2.9%, ranging from 13% to 25% and the mean BMI reduction was 7.2 ± 3.1 kg/m^2, ranging from 3.5 to 18.0. The total early removal rate due to intolerance was 2.2% (928 cases)-more common with the adjustable balloon (2.5% in 1020 subjects), and rather uncommon (0.8%) with the Heliosphere air-filled balloon. The adverse event rate after the adaptation period was reported at 2.5%, the most common being 0.9% hyperinflation and 0.8% spontaneous deflation of the device. Finally, there were only 3 deaths; a gastric rupture due to overfeeding in a super-obese patient, a pulmonary aspiration with vomiting, and a pulmonary embolism, which may not have been directly attributable to the balloon.

The most recently published study was that from 5 private clinics in Brazil (2000-2017) by Fittipaldi-Fernandez *et al*[68], which included 5874 patients in whom a liquid-filled balloon not named, but having characteristics intimating the Orbera was placed (600-700 mL saline). After 6 to 7 mo, patients were found to have a weight loss of 19.13 ± 8.86 kg, and a %TWL of 18.42 ± 7.25%, treatment success rate, i.e. rate of patients achieving a %TWL over 10%, being 85%. The %EWL was 65.66 ± 36.24%, while BMI also decreased significantly, from 36.94 ± 5.67 to 30.08 ± 5.06 kg/m^2, $P < 0.0001$.

Air-filled heliosphere

Over time, new balloons have been designed, keeping the initial idea of the Orbera-space-occupation in the stomach-but looking to improve the characteristics responsible for the adverse events of nausea and vomiting early after implantation, *i.e.* the combination of large volume and weight of the saline filled balloon. Thus, in 2017 Saber *et al*[69] were the first to introduce the air-filled balloon in their meta-analysis. They analyzed a total of 20 RCTs (13 with the fluid-filled Orbera balloon and 7 with air-filled balloons) involving 1195 patients assessed prior to, at 3 mo after balloon placement, and upon its removal. Unfortunately, from the 7 studies – 190 cases only – relating to air-filled balloons, 6 concluded that the air-filled balloons were not effective. The overall meta-analysis, regardless of the balloon type, revealed a significant reduction of 1.59 and 1.34 kg/m^2 for overall and for 3-mo BMI, respectively; a significant reduction of 14.25 and 11.16% for overall and > 3-mo percentage of excess weight loss, respectively; and a significant reduction of 2.81, 1.62, and 4.09 % for overall, 3-mo, and > 3-mo percent of weight loss, respectively. Overall a significant difference was calculated that favored the fluid-filled over air-filled IGBs; however, data was available only for a 3-mo study period comparison ($P = 0.02$). In general, due to the large heterogeneity within the studies (fluid and air-filled) the efficacy of all IGBs appears to be less impressive. However, generally speaking, the gas-filled balloons have better tolerance after implantation, but result in less weight loss in comparison to the fluid-filled[27].

Along the same line, Bazerbachi *et al*[52] analyzed 15 RCTs involving patients treated with FDA approved, fluid-filled (Orbera; 12 studies, ReShape Duo; 1 study) or air-filled balloons (Heliosphere; 1 study, Obalon; 1 study) for at least 6-mo compared with another balloon, sham-balloon, or open-label control groups, in an effort to assess the effectiveness and tolerability of each. In meta-analysis, the fluid-filled devices were found superior in achieving a significant change of %TBWL, in 96.8% and 96.6% of cases at 6 and 12 mo, respectively: the Orbera resulted in a 6.72% reduction of total body weight (95%CI: 5.55, 7.89); and the ReShape Duo 4% (95%CI: 2.69, 5.31) as

opposed to the air-filled balloons Heliosphere and Obalon, which achieved 6.71% (95%CI: 0.82, 14.23) and 3.3% (95%CI: 2.30, 4.30), respectively. Although the fluid-filled balloons had the greater likelihood of being superior in achieving %TBWL, in the present meta-analysis the Orbera was finally associated with a non-significant difference in relation to the gas-filled Heliosphere 2.20% (-0.76, 5.16); the statistical findings probably relating both to the heterogeneity and small number of studies (Orbera n = 12 *vs* one for each other balloon type) for pair-wise comparisons. Finally, fluid-filled balloons were considered to be associated with a higher rate of intolerance; the combination of their high volume and weight have a profound impact on gastric motility, leading to a delay in gastric emptying of solids and thus to the increased sense of fullness and satiation, and as a result to body weight loss.

Adjustable Spatz

Another requirement in the Tarpon Springs Consensus meeting was that the balloon volume capacity be variable and adjustable, according to patient tolerance and success in losing weight. This was achieved with the Spatz adjustable balloon system by a rather complex and sophisticated mechanism which allows the filling volume to be adjusted, up or down, after implantation. Modifications ultimately resulted in the 3rd generation of adjustable balloons, the Spatz3.

One of the first available comparative studies carried out between 2010 and 2014, was that of Russo *et al*[70]. It comprised a small patient group: 20 elderly patients in whom the BioEnterics IGB was implanted and 10 patients given the Spatz Adjustable Balloon System. The two groups were compared in terms of weight loss, complications, and maintenance of weight after removal. They had a BMI ranging between 37 to 46 kg/m^2 and a weight range of 103 to 165 kg. For both procedures, median BMI at the end of treatment was 32 ± 2 kg/m^2 and the median weight loss was 20 ± 3 kg. At 6 mo follow-up, weight gains were 6 ± 1.5 kg for the 10 patients with the Bioenterics balloon *vs* 6 ± 2 kg for the five patients with the Spatz. In 2 out of each group the balloon was removed early, due to intolerance. In one additional BioEnterics balloon patient the balloon was removed due to deflation; and in 3 additional Spatz patients the balloon was adjusted due to intolerance, but finally two of the latter achieved no significant weight loss.

Abu Dayyeh *et al*[71], at 8 US centers, studied the efficacy and safety of the Spatz3 in 187 patients in relation to lifestyle modification alone for a 32-wk period. Percentage total weight loss was 14.9 ± 7.2% in the treatment group compared to 3.6 ± 5.8% in the control group; an additional 4.7% TBWL was achieved after upward volume adjustment between weeks 18 and 32 and more than 40% of the treatment group had maintained their weight loss at 56wks. Serious adverse events were reported at a rate of 5.3%, 4% of which were attributed to gastric ulcers.

Fittipaldi-Fernandez *et al*[45] presented 180 patients randomly divided into a Spatz3 balloon group in which the balloon was inflated with 600 mL of saline, the volume remaining stable throughout treatment, and a second Spatz3 balloon group in which the balloon volume was adjusted upward with 250 mL more saline. At removal, after 7.12 ± 1.63 mo, BMI was found decreased from 39.51 to 32.84 kg/m^2 (P < 0.0001), body weight from 111.87 to 90.28 kg (P < 0.0001), and excess weight from 41.55 to 22.99 kg (P < 0.0001). The volume adjustment resulted in greater mean weight loss of only 4.35 kg, but no increased %TWL, %EWL, or decrease in BMI compared with the not-adjusted group. The authors conclude that the Spatz3 balloon seems to be an effective weight loss procedure, although it was found to be related to a higher morbidity (16.14%) in relation to traditional balloons.

Schwaab *et al*[72] 2020 published a cross-sectional study of 470 overweight or obese patients who were treated by either a non-adjustable IGB (Orbera), 326 subjects implanted for 6 mo; or an adjustable balloon (Spatz) in 144 subjects for up to 12 mo. A total of 414 out of 470 individuals completed the treatment period. The Orbera-treated patients achieved a %TBWL of 15.4 ± 7% and the Spatz-treated patients 15.5 ± 9.6%. Similarly, 264 Orbera-treated patients (88.6%) against 93 Spatz-treated patients (80.2%) achieved a %EWL over 25%, P = 0.038. However, the balloon volume adjustment seems not to have made a significant difference: within the Spatz group, 67 (85.9%) patients subjected to re-adjustment of balloon volume *vs* 27 (73%) not subjected to re-adjustment achieved a %EWL over 25%, P = 0.203.

Swallowable Obalon and Elipse

The Obalon, the gas-filled, swallowable IGB, designed to allow easy gastric volume titration by using additional balloons was studied against a lifestyle modification-alone group by Sullivan *et al*[73] (the SMART trial). A total of 387 patients were included from 15 centers in United States; 185 patients swallowed at least one Obalon

capsule and 181 a sham capsule. After a 6 mo treatment period, the Obalon resulted in a %TBWL of 6.6 ± 5.1% in relation to 3.4 ± 5.0% in the control group, $P = 0.0354$, the difference being 3.2% (95%CI: 2.2, 4.2); the responder rate was 62.1% in the Obalon group, the end-point being 35% and 30.7% in control group, $P < 0.0001$. At 48 wk, subjects who had achieved a weight loss at week 24, maintained their loss at a rate of 88.5% (7.8 ± 4.4%TBWL at 24 wk and 6.9 ± 6.5% TBWL at 48 wk, $n = 151$). Finally, they presented 0.3% severe adverse events, including one bleeding gastric ulcer.

There are few previously published clinical studies, with only a small number of participants: Mion *et al*[54] in 2013 first reported a pilot study in 17 patients – 43 balloons - to assess the efficacy of the Obalon for weight loss over a 3mo study period. There was a median %EWL of 36.2 (range 0 to 118%) and a BMI reduction from 31.0 kg/m^2 to 28.1 kg/m^2, with no serious side-effects. Similarly, in 17 cases of pediatric/adolescent morbid obesity De Peppo *et al*[56] in 2017 reported a statistically significant decrease ($P > 0.05$) of mean BMI value from 35.27 ± 5.89kg/m^2 to 32.25 ± 7.1 kg/m^2; and a %EWL of 20.1 ± 9.8 (range 2.3 to 35.1) after 3 mo of treatment.

The Elipse IGB is a swallowable fluid-filled balloon, which is spontaneously deflated at week 16 and passes through the gut to be self-removed through the natural orifice; it can thus be considered the 'evolution' of the Obalon, since it is both placed and removed without the need of anesthesia and endoscopy. Recently, Ienca *et al*[58] published the largest trial comprising 1770 consecutive Elipse patients. After 4 mo treatment a weight loss of 13.5 ± 5.8 kg, a %EWL of 67.0 ± 64.1, a BMI reduction of 4.9 ± 2.0, and a %TBWL 14.2 ± 5.0 was reported. Eleven emptied balloons (0.6%) were vomited and another 52 (2.9%) were endoscopically removed due to patient intolerance. Three deflated balloons led to small bowel obstruction, requiring surgical intervention.

The difference in the reliability of the statistical results depends on the number of patients in the study sample, as well as the use of a multidisciplinary approach and counseling for these patients; thus Genco *et al*[59] presenting their early experience with the Elipse balloon in only 38 Italian patients who received a multidisciplinary approach, reported a mean weight loss of 12.7 kg, a %EWL of 26%, a mean BMI reduction of 4.2 kg/m^2, and a %TBWL of 11.6%.

At the same time, Vantanasiri *et al*[74] 2020 published a systematic review and meta-analysis of six prospective studies of the Elipse balloon, involving 2013 patients. The largest study was that already discussed (Ienca *et al*[58]–1770 patients) and the other 5 were small cohort studies (30 to 135 patients) with high heterogeneity. The mean %TWL after completion of treatment (4 to 6 mo) was 12.8% (95%CI: 11.6%–13.9%; I2 = 83%) and at 12 mo 10.9% (95%CI: 5.0%–16.9%, I2 = 98%). However, the long-term effects after the Elipse balloon treatment still remain unclear. Additionally, there is no study comparing the Elipse balloon with any other IGB. A rate of 0.2% of serious adverse events was reported; three patients suffered small bowel obstruction due to a deflated balloon and one experienced gastric perforation, resolved surgically. Although it seems to be safe and easily handled, its application by an inexperienced bariatric endoscopist, as no endoscopy is needed, poses the risk of overlooking or misunderstanding a serious adverse event, as Angrisani *et al*[75] points out in his commentary entitled "the pitfalls of excessive simplicity".

In the same year another meta-analysis of 7 Elipse balloon-studies, involving 2152 patients was conducted by Ramai *et al*[76], with the same disadvantage as the previous one: only Ienca's study[58] had 1770 cases, while all other six studies ranged from 12 to 135 cases, with high heterogeneity. The results, however, were quite similar: %TBWL was 12.2% (95%CI: 10.1-14.3, I2 = 94%) and %EBWL was 49.1% (95%CI: 30.6-67.5, I2 = 97%). Pooled adverse events were 37.5% abdominal pain, 29.6% vomiting, 15.4% diarrhea and 0.5% small bowel obstruction.

Finally, a recent study of 96 patients from Egypt, not included in the previous meta-analyses, was published by Taha *et al*[77], 2020. After the 4 mo period following implantation the %TBWL was 12.1 ± 5.2%, the mean weight loss was 11.2 ± 5.1 kg, and the mean BMI reduction was 4.9 ± 2.0 kg/m^2. The authors also reported 3.1% intolerance, resulting in early balloon removal; one (1.1%) balloon deflated early and was uneventfully passed, and, surprisingly, there were 11.5% attacks of diarrhea and 21.9% of colicky abdominal pain for a week around the time of balloon self-deflation.

Double balloon

Regarding the ReShape Duo IGB, Ponce *et al*[48], 2013 published the first results after its placement in 21 subjects *vs* 9 controls-diet only. These data belong to the phase 1 portion of the REDUCE study, which stopped prematurely to be redesigned, since its primary endpoints seemed to be unachieved. At 6mo these patients presented no significant difference in %EWL, although their findings were not negligible (31.8% ±

21.3% in the balloon group and 18.3% ± 20.9% in the controls, respectively, $P = 0.1371$); a percentage of 64% of balloon-treated maintained their weight loss 6mo after balloon removal.

Two years thereafter Ponce *et al*[47] presented the final results of the REDUCE pivotal trial: the ReShape balloon-treated patients ($n = 187$) had a 25.1 ± 1.6% (mean ± SE) %EWL, 48.8% of cases achieving a %EWL over 25% *vs* 11.3 ± 1.9% in the diet and exercise only control patients ($n = 139$), $P = 0.0041$; sudden balloon deflation occurred in 6% of cases, but no migrations; balloon intolerance led to early balloon removal in 9%. Gastric ulcers at the level of gastric incisura were initially observed in 35% of patients due to pressure of the distal tip of the device. After a minor modification to make it shorter, smoother and with a 50% reduced diameter, the frequency of ulcers dropped to 10%.

Another study with 202 patients in whom the Reshape Duo balloon had been placed was published in 2018 by Agnihotri *et al*[50]. At 6 mo they reported a statistically significant decrease ($P < 0.001$) in BMI values from 36.8 ± 8.4 kg/m^2 in baseline to 32.8 ± 6.7 kg/m^2, a %TBWL of 11.4 ± 6.7% and a %EWL of 29.9 ± 18.2%. The authors also referred to a high rate of nausea, vomiting and abdominal pain in the early days: 66.4%, 49% and 25.2%, respectively, leading to a 6.4% of early balloon removal. Finally, there was only one case of balloon migration, resulting in a small bowel obstruction and requiring surgical intervention.

Finally, Suchartlikitwong *et al*[49] in 2019 presented their experience in 35 cases using the Reshape Duo balloon. They reported a 7% decrease in BMI value, or 2.7 ± 2.9 kg/m^2, $P < 0.001$. Nausea and vomiting presented in 23% of patients, requiring balloon removal in two. 3% of patients suffered gastric erosions, but one patient with a history of ulcer experienced gastric hemorrhage requiring blood transfusion. Finally, one patient required surgery for balloon removal after deflation and distal movement leading to bowel obstruction.

Efficacy and tolerability

Looking for comparative assessment of the efficacy of IGBs, Kotinda *et al*[12] performed a systematic review and meta-analysis of 13 randomized controlled trials (1523 overweight and obese adults) focusing on the efficacy of IGBs for weight loss. Eight studies used the Orbera, one the Orbera or Heliosphere (gas-filled), two the ReShape Duo, and one each the Spatz and theObalon (gas-filled). They found a highly significant difference in mean %EWL of 17.98% (95%CI: 8.37-27.58, $P < 0.00001$) in the balloon group in comparison to the sham/life-style modification group. In the subgroup analysis there was no significant difference between balloon types for this outcome. When assessing data in respect to %TWL, they also found a highly significant difference in mean %TWL of 4.40% (95%CI: 1.37-7.43, $P < 0.00001$), but, in subgroup analysis, this effect was mostly related to the Spatz balloon [11.30 (9.77, 12.83)], although other balloons (Obalon, Orbera, and ReShape Duo) also had favorable outcomes. However, on analysis of the data in relation to BMI loss, a significant difference of 2.13 Kg/m^2 (95%CI: 0.57-3.68, $P < 0.00001$) was found in the balloon group, while in subgroup analysis it was mainly due to the Orbera balloon [2.49 (0.19, 4.80)], although the Obalon, Heliosphere, and ReShape Duo also showed favorable results. They finally analyzed the values of absolute weight loss, not commonly found as a study parameter. From a total of 7 studies (1005 participants), a mean difference of 6.12 kg (95%CI: 3.80 to 8.44, $P < 0.00001$), in favor of the balloon group was evident, mainly achieved by the Orbera balloon [7.88 (3.81-11.95)], although the Obalon and the ReShape Duo also had positive outcomes.

IGBs are space-occupying devices designed to induce satiety and thus reduce food intake, which ultimately results in weight loss; it is reasonable and obvious to expect that the sudden but permanent onset of fullness of the stomach by means of increasing the balloon volume, and, in the case of fluid-filled balloons, of the additional sensation of weight could be 'translated' by the obese as a sense of persistent nausea and/or tendency to vomit, as well as generalized abdominal pain and/or discomfort, back pain, and acid reflux. These accommodative symptoms are common after balloon placement, but are usually self-limiting. In terms of patient tolerance of the IGB, and especially during the first 1-2 wk of placement, Trang *et al*[78] in 2018 conducted a systematic review and meta-analysis of the incidence of nausea and vomiting after IGB placement in bariatric patients. In this review of 10 studies they focused on four types of balloons: the fluid-filled Orbera, the ReShape Duo, the Elipse, and the gas-filled Obalon, and calculated the meta-analytic rates of nausea and vomiting based on adverse event sample size. A total of 564 out of 938 patients reported nausea; 63.33% (95%CI: 61.49%–65.16%), and 507 patients reported vomiting; 55.29% (95%CI: 53.59%–56.99%). Fluid-filled balloons were placed in obese participants in 7 studies:

394 and 434 out of 575 patients experienced nausea and vomiting respectively; rates of 72.99% (95%CI: 69.54%–76.45%) and 76.95% (95%CI: 73.86%–80.05%), respectively. The gas-filled Obalon balloon, was used in 3 studies: 200 and 62 out of 363 patients reported nausea and vomiting, respectively; rates of 55.10% (95%CI: 50.00%–60.00%) and 16.20% (95%CI: 12.43%–19.96%), respectively. Further analysis of fluid-filled balloons, *i.e.* the Orbera, ReShape Duo, and Elipse, revealed that the Orbera balloon caused the highest rates of nausea and vomiting compared to all other balloons. Three studies using the Orbera reported nausea and vomiting in 195 and 177 out of 248 individuals respectively; rates of 81.97% (95%CI: 77.00%–87.00%) and 72.16% (95%CI: 66.65%–77.67%) respectively. Comparatively, 2 studies with the ReShape and another 2 with the Elipse balloons reported nausea and vomiting respectively in 178 and 246 out of 285 patients and in 21 and 23 out of 42 patients; rates of 63.18% (95%CI: 58.00%–69.00%) and 86.42% (95%CI: 82.44%–90.39%) for the ReShape and 51.42% (95%CI: 46.00%–57.00%) and 12.48% (95%CI: 8.51%–16.44%), for the Elipse, respectively. The authors comment that the large variation rate of symptoms, even that of vomiting, [a relatively objective parameter], apart from the type of balloon used, might be related to the type, the dosage and the frequency of medications prescribed during any specific study.

Gastric emptying and weight loss

Based on the general hypothesis that the rates of gastric emptying and the stomach accommodation volume regulate food intake, appetite, satiation and satiety, and are thus associated with postprandial fullness, bloating, and finally weight loss, Vargas *et al*[24] analyzed the changes in time of gastric emptying in 19 studies, after either IGB placement or bariatric surgery. Fluid-filled balloons (3 studies) increased gastric emptying time by 116 min (95%CI: 29.4–203.4 min) as opposed to air-filled balloons (2 studies) which did not result in a statistically significant difference in gastric emptying time [-2.9 min (95%CI: -21.7 to 15.9 min)]. When authors analyzed pooled data of 5 studies, the mean change in gastric emptying time was only 42.7 min, (non-significant); however, meta-regression revealed prolongation of gastric emptying time which was associated with a higher percentage of total body weight lost at 6 mo (P = 0.05). When the association between gastric emptying time and weight loss was analyzed in fluid-filled (Orbera) balloons, the significantly prolonged gastric emptying time led to a greater excess weight loss at 6 mo (P = 0.04), potentially explaining the difference in efficacy and tolerance found across air *vs* fluid-filled balloons[52].

Quality of life and mental health

Gadd *et al*[79] tried to analyze the impact of endoscopic bariatric procedures, IGBs included, in the improvement of quality of life (QoL) and mental health, assessed by using a validated tool. Twenty studies published between 2008 and 2019 with a total number of 876 participants (77% female) were included, evaluating five different endoscopic procedures. Fourteen out of 20 referred to IGBs and finally 9 (371 participants - 350 at 6 to 76-mo follow-up) were included *via* meta-analysis. IGB placement was associated with a significant improvement in QoL (SMD: 0.78; 95%CI: 0.56, 1.00; P = 0.05; I2: 48%). Following sensitivity analysis, IGB placement was associated with a large improvement in post-procedural QoL (SMD: 0.85; 95%CI: 0.69, 1.02; P < 0.00001; I2: 7%). Five studies (367 participants at 6 to 76 mo follow-up) out of the nine were analyzed in respect to mental health, depression, and anxiety, and IGBs revealed a significant improvement (SMD: 0.86; 95%CI: 0.29, 1.42; P = 0.003; I2 = 92%). All studies correlate improvement of quality of life, mental health, depression, and anxiety with significant improvement in obesity related parameters. The two studies (Guedes *et al*[80] and Deliopoulou *et al*[81]) with the largest improvements in mental health also had the greatest weight loss. However, the authors commented that all these patients received multidisciplinary support in the form of unlimited 24-h phone support, follow-up by a dietitian and nutrition counseling, cognitive behavioral therapy, and/or a lifestyle modification programme. The greater the support, the more significant the improvement in mental health and weight loss.

DISCUSSION

The IGB is a well-established therapeutic tool for the treatment of obesity, being the most popular technique of those included under the concept of endoscopic bariatric and metabolic therapies, which have emerged over the years, to provide alternative options beyond lifestyle modifications, pharmacotherapy, and surgery. It is actually a

completely non-invasive endoscopic technique, in the absolute sense of the term, since its leading advantage is that it does not interfere permanently with the anatomy and volume-shaping of the stomach by means of interventions in the gastric wall, such as sutures, stomas, thermal destruction of the mucosa, *etc.*, used by other modern endoscopic techniques.

Thus, IGB insertion represents a generally safe, easy to perform, adjustable, reversible, and reproducible endoscopic gastric restriction procedure, successfully applied for weight loss over the last 30 years. It covers a broad spectrum of indications from the overweight to the obese individual who does not fulfill the criteria for bariatric surgery, up to the morbidly obese, who qualifies for bariatric surgery but has uncontrolled co-morbidities causing her/him to be of high-risk for anesthesia and surgery or denied anesthesia and/or surgery, or its use as a bridge to bariatric surgery, and, finally, to anyone who just needs to achieve limited weight reduction, either prior to surgery of whatever kind and for whatever reason or merely for aesthetic purposes [51,82,83]. Generally speaking, the specific indications for balloon implantation for each candidate for such treatment must be built on the absolute judgment of the treating physician or the multidisciplinary working team; however, the positive response, that is the weight loss, is due exclusively to the responsibility of the patient to strictly adhere to a diet/exercise program and follow-up sessions throughout the treatment period, whatever type of balloon has been used.

To reconfirm the advantages of the procedure, we use the concepts formulated by Fobi and Baltasar to define quality indicators for bariatric surgery procedures which should also be somehow applicable to bariatric endoscopy[84]. According to these criteria any relevant procedure should be: (1) safe, exhibiting a mortality of less than 1%, and a morbidity of less than 10%; (2) effective and long-lasting, with excess weight loss of over 50% in more than 75% of patients at 5 year follow-up; (3) reproducible, so the results of different centers performing the procedure provide a similar, easy learning curve; (4) provide good quality of life; (5) require revisions less than 2%; (6) have minimal adverse effects; and (7) be easily reversible, from an anatomical or functional perspective.

However, IGB effectiveness, as a non-permanent intervention, remains debatable, as there is no consensus on the proportion of weight loss that should be achieved for an endoscopic procedure to be considered effective and thus be recommended for clinical use. The ASGE[25] defined a mean minimum threshold of 25% EWL, measured at 12 mo, for any endoscopic bariatric and metabolic therapy intended as a primary obesity intervention, and 5% of %TBWL as the absolute minimum threshold for any non-primary intervention, such as bridging therapy. It also recommended that the risk of serious adverse events related to the procedure be equal or less than 5%-most of the reported adverse events with IGBs (nausea, vomiting, abdominal pain) are classified as mild to moderate, according to ASGE Quality Task Force recommendations[25].

Today there are already six commercially available balloons, three of which are FDA-approved; some of them having one or more 'clones', available in different parts of the world. Chronologically, the first balloon designed and manufactured according to the Tarpon Springs Directives was the Bioenterics IGB (now available as the Orbera) [20]. Based on the advantages and disadvantages of this balloon, there have been many attempts to develop new balloons, incorporating technical improvements, but without compromising the baseline characteristics of the Orbera, which has long remained at the top of the field.

The main disadvantages of the Orbera balloon, which should be improved, are the following: (1) The balloon placement and removal must be performed by means of endoscopy, and at least the removal to be done under conscious sedation, which increases not only the overall cost of treatment, but also the potential risks of both endoscopy and anesthesia; (2) The first week after balloon placement patients experience some degree of discomfort, in the form of nausea, vomiting and epigastric pain, well-attributed to the 600-700 gr of saline with which the balloon is inflated. This etiology is true for all fluid-filled balloons. On the other hand, this is the feature which makes the fluid-filled devices more effective in weight loss, in comparison to gas-filled balloons; (3) The effectiveness of the Orbera and of other fluid-filled balloons is generally satisfactory, especially when combined with diet and exercise counseling and the patient is under a multidisciplinary assessment group, not excluding, occasionally, psychiatric supervision. After balloon removal, however, the maintenance of good results in weight loss varies in the long-term, depending on many subject-related and not balloon-related factors, as, exactly similarly, occurs in real life; ex-obese individuals must maintain the new habits and lifestyle, feeding re-education and physical exercise, but mainly the behavioral modification and positive psychological state resulting from the changes in their physical appearance (body shape),

physical functioning through improvements in co-morbidities, and social functioning due to increased self-esteem[13,85,86].

Based on this, some argue that a long-lasting balloon such as one with 12 mo lifespan in the stomach (the Orbera365 and the Spatz3) may be more useful since it allows more time for life-style re-education to become habituated[87,88]. On the other hand, it is well known that the greatest weight loss, even up to 80% of the total %EWL, is achieved within the first 3 mo of balloon-life in the stomach; weight loss then continues, but at a reduced percent monthly[13,66,89]. Thus, a 12-mo lifespan balloon probably offers questionable benefits. It might also be suggested that long-term contact with gastric mucosa, especially if the balloon is not totally smooth and spherical (Spatz3), could be more traumatic, possibly resulting in gastric mucosal erosions and bleeding.

The counter-argument would be that the 4 mo life-span of the Elipse could be considered an inadequate time to achieve the desired results. Although the 6 mo balloons achieve the greatest weight loss within the first 3 mo, the additional 3 mo in the stomach is a time during which it works at very least as a space-occupying device preventing excessive food intake and consequently of early weight gain.

Unfortunately, there are no studies at all comparing the weight loss with the classical Orbera against the new Orbera365 - that is 6 mo *vs* 12 mo of the balloon remaining in the stomach. Theoretically, this could be an argument for inserting two consecutive balloons, but there is little evidence of success achieved by the second, which is why some authors recommend a time lapse between the first and second balloon[90,91]. In contrast, the application of the Spatz3 for 12 mo cannot be compared with the Orbera365, since the latter is designed as 'adjustable', meaning that at 3 mo, when the patient stops losing weight quickly, a volume of 250 mL of saline is added, changing both the volume and weight of the balloon, and thus the results. However, when compared, the weight loss between groups in which the Spatz3 balloons was adjusted or not, no significant difference was found[45].

Comparing the filling volume of the various liquid-filled balloons, it is clear that the volume of the balloon does not seem to directly determine weight loss. This was demonstrated in a study in which the Orbera balloon was filled with volumes of 400 mL to 700 mL[63], but also from the results of all studies with various balloons, with more or less the same volumes of saline. Furthermore, it is well known that short-term satiety is primarily affected by gastric distension and gastric volume; as we know from research that mechanical gastric balloon distension to a volume greater than 400 mL during meals significantly reduces oral intake[92,93]. However, it should emphasized that gastric distension and gastric volume are related to the weight and volume of the 'food', rather than its energy content, thus decisions regarding food ingredients has to rely on the patient's choice to comply with dietary rules[23,92].

For this reason all patients must undergo a psychological screening before entering the process of balloon implantation[61,86]. This does not in any way mean that obese patients with bipolar disorders or other psychiatric diseases under medication should be excluded from treatment. On the contrary, it seems that there is a clear improvement in depression status with weight loss and the improvement of their body image[13,85,94], called by Spirou *et al*[95] the "psychological honeymoon period". In our opinion, a key component in their preliminary interview must be for the obese individuals to describe the social and psychological impact of obesity on their life, make a brief statement on their motivation to lose weight (for instance, to alleviate physical symptoms or to become more attractive/marriageable), and to recognize how they are affected by external factors, such as social support and reinforcement. This information – particularly the reason for strongly desiring to lose weight - should then be used at every follow-up session to inspire them to continue the effort towards weight loss or loss maintenance[13].

Another essential tool for achieving a significant and sustainable weight loss is the requirement for the patient to attend follow-up consultation sessions, which also bolster self-confidence. In a study analyzing 583 obese individuals treated with the Orbera balloon in respect to weight loss, the group of successful responders (%EWL more than 50%) and the group of poor responders (%EWL less than 20%) were compared. 85.2% of successful responders, n = 162, had attended the maximum of six interviews, whereas the 83.8% of the 105 poor responders attended fewer than four interviews[13,85,96]. Similar results were reported by Schwaab *et al*[72]: patients with more than four consultations achieved notably higher %EWL values (more than 18%, $P < 0.001$).

As has already been mentioned in the 'drawbacks' to the Orbera, the liquid-filled balloons have a higher rate of intolerance during the first week after implantation; which is why air-filled (Heliosphere bag) or gas-filled balloons (Obalon) were

designed. The Heliosphere has a volume of 550 mL, but a weight of only 30 gr, thus allowing a soft transition to new nutritional status, without nausea and vomiting, but in exchange for less weight loss in some studies. Some difficulty in balloon placement through gastric cardia has also been reported[12]. To overcome the same problem of early intolerance, the Spatz3 was designed with the unique feature of post-implantation volume control, meaning its volume can be reduced in case of early intolerance and, when symptoms cease, the volume can be increased. These procedures do, however, presuppose anesthesia and endoscopy[44,45].

The improvements and advances made in the design of the other balloons (the ReShape Duo, the Obalon and the Elipse) modifying the classic Orbera configuration, could be summarized as follows: The ReShape Dual balloon system[30,47] has been re-designed as two smaller, independent silicone spheres of 450 mL each, joined by a central, short, non-communicating flexible silicone shaft. This flexible balloon configuration allows them to conform to the natural anatomy of the stomach, while decreasing the chance of balloon intestinal migration should one of the balloons accidentally deflate[5,47,56,57]. Unfortunately, Apollo Endosurgery discontinued this product line after purchasing ReShape Medical Inc, CA, in 2018.

The Obalon and the Elipse balloons have the advantage of not requiring endoscopy for insertion and, in the case of the Elipse, for removal too, both being easily swallowable. Nevertheless, fluoroscopy is mandatory for proper positioning, because although the total cost of treatment is significantly reduced, as is the theoretical danger of complications due to anaesthesia and endoscopy, there is still a risk[59]. However, the endoscopy-free insertion carries its own disadvantages: the balloon is placed in a stomach with unknown mucosal pathology, and unknown anatomy, thus all the 'exclusions' described for the other balloons remain obscure (huge hiatus hernia, gastric ulcer/erosions, prior gastric surgery). The Elipse has the additional advantage of being degradable after a 4mo period, when it freely passes through the rectum.

Major complications related to IGB placement include esophageal/ gastric ulcerations and tears due to permanent mucosal irritation by the balloon or iatrogenic trauma and/or perforation during balloon insertion and, mainly, removal; and bowel obstruction, due to balloon self-deflation and migration to the gut[97]. According to the Tarpon Springs directives[20] for "the safe and effective balloon" a balloon must have "a smooth surface having low potential for causing erosions, ulcers or obstructions". The greatest conformity to this description is the Orbera. The early design flaw of the ReShape Duo, with the distal tip, was the cause of gastric ulceration in up to 35% of cases, which, however, dropped immediately to 10% after design modification[48]. Similarly, the Spatz3 balloon, although exactly meeting the criterion of being adjustable, has failed to fulfill the criterion of having a completely smooth surface, since it has a sort of 'tail' at the site of insertion of the filling valve[43]. This balloon has also been implicated in causing acute pancreatitis[98].

In a recent publication Stavrou *et al*[99] systematically reviewed PubMed and Scopus archived publications up to the end of 2018, describing Orbera-related life-threatening visceral complications, *i.e.* perforations and obstructions, and classified them according to blame: the device, the patient or the doctor. In a total of over 277000 balloons implanted worldwide by the end of September 2018, according to Apollo Endosurgery reports[100], 22 cases of gastric perforation, 2 cases of esophageal perforation and 10 cases of bowel obstruction were found. For the gastric perforation the endoscopist was responsible in 9 cases, the patient in 4, and the balloon itself in 9. For the 2 cases of esophageal perforation, the endoscopists were responsible, while for the 12 cases of bowel obstruction, the patient was responsible for 7 and the device for the other 5 cases.

CONCLUSION

As a final comment at the end of this analysis, we must underline that balloon placement, and even more balloon endoscopic removal should not be considered to be, in any way, a simple endoscopic procedure to be carried out by an inexperienced endoscopist. Individual doctors or even institutions without experience, accreditation, or the ability to resolve obesity-related or bariatric surgery-related complications must not undertake such procedures, if we do not want an increase in complications[95,101,102]. This danger increases with the increased availability of swallowable balloons on the market. Their advertising and the ease of use, as presented, can become a disastrous trap if an uncertified and inexperienced doctor dares to use them. The fact that endoscopy is not mandatory and becomes a matter of patient choice removes the

necessity for a doctor with the appropriate training to be able to recognize and deal with any complication which might suddenly occur. This point is further emphasized in the latest published directives of the ASGE: "...training and skill acquisition with endoscopic bariatric techniques and technologies is mandatory before clinical application is undertaken, and should include didactic as well as hands-on practical education". And, furthermore, "...importantly, any practitioner who is interested in performing an endoscopic bariatric procedure should also be educated in the clinical management of obese patients," which means, have the ability to resolve complications[25].

From the above analyses, it is clear that: (1) There are no "good" and "bad" balloons, at first glance; all new balloons must be given an equal chance to be tested by experienced endoscopists before being judged; and (2) There is no special indication for the use of a particular balloon - all fit all stomachs. However, the use of one rather than another of the six balloons mentioned in this review, or between some others of lower cost, or of national manufacturers, relies on the absolute discretion of the physician, and not of the obese patient, and I personally never discuss it.

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REVIEW

Endoscopic retrograde cholangiopancreatography: Current practice and future research

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) has evolved from a primarily diagnostic to therapeutic procedure in hepatobiliary and pancreatic disease. Most commonly, ERCPs are performed for choledocholithiasis with or without cholangitis, but improvements in technology and technique have allowed for management of pancreatic duct stones, benign and malignant strictures, and bile and pancreatic leaks. As an example of necessity driving innovation, the new disposable duodenoscopes have been introduced into practice. With the advantage of eliminating transmissible infections, they represent a paradigm shift in quality improvement within ERCP. With procedures becoming more complicated, the necessity for anesthesia involvement and safety of propofol use and general anesthesia has become better defined. The improvements in endoscopic ultrasound (EUS) have allowed for direct bile duct access and EUS facilitated bile duct access for ERCP. In patients with surgically altered anatomy, selective cannulation can be performed with overtube-assisted enteroscopy, laparoscopic surgery assistance, or the EUS-directed transgastric ERCP. Cholangioscopy and pancreatoscopy use has become ubiquitous with defined indications for large bile duct stones, indeterminate strictures, and hepatobiliary and pancreatic neoplasia. This review summarizes the recent advances in infection prevention, quality improvement, pancreaticobiliary access, and management of hepatobiliary and pancreatic diseases. Where appropriate, future research directions are included in each section.

Key Words: Cholangiopancreatography; Endoscopic retrograde; Cholangioscopy; Cannulation; Endoscopic ultrasound; Disposable duodenoscopes

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Core Tip: Disposable duodenoscopes present a way to eliminate transmission of drug resistant infections. Access to single operator cholangioscopy and panreatoscopy has made complex intraductal assessment and therapy more ubiquitous. Future research will clarify the role of endoscopic ultrasound bile duct access for variant anatomy or failed endoscopic retrograde cholangiopancreatography (ERCP), photodynamic therapy, and indomethacin and pancreas duct (PD) stents in post ERCP pancreatitis prophylaxis.

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INTRODUCTION

This coronavirus disease 2019 (COVID-19) pandemic has changed our collective understanding of infection transmission, vaccine development, and the challenges of providing continuity of care in a rapidly evolving health care crisis. The evolution in endoscopic retrograde cholangiopancreatography (ERCP) has been more gradual, but certainly there have been periods of innovation punctuated by rapid change. Given the global pandemic, an area of interest with accelerated focus is the use of disposable duodenoscopes to break the chain of infection in ERCP. With rising concerns over reusable duodenoscopes implicated in nosocomial outbreaks, the trend toward transitioning to disposable components and completely disposable duodenoscopes has begun.

As highlighted in previous reviews, ERCP has moved from a diagnostic to primarily therapeutic procedure[1]. The therapeutic indications for ERCP include stones in the biliary and pancreatic ducts, benign and malignant strictures, and bile and pancreatic leaks[1]. Despite the near ubiquitous access to advanced radiology and endoscopic ultrasound (EUS) in North America, ERCP still has diagnostic indications in patients with a solitary dilated duct, cholangiocarcinoma, primary sclerosing cholangitis, and autoimmune cholangitis. This article will focus on the current state of practice for diagnosing and managing hepatobiliary and pancreatic disease with ERCP in 2021.

As competency-based training programs have evolved to include EUS and ERCP, hybrid procedures have evolved. Any future textbooks will have to include both procedures given their complementary nature. In addition to the advances made in these hybrid procedures, our focus should remain on clinical success and mitigating risk independent of technical success during a single procedure. This article will review the progress made since the last review in this journal[2] and clarify future research directions in the field.

INFECTION PREVENTION AND QUALITY IMPROVEMENT

Disposable duodenoscopes

While some practice changes in ERCP have been adopted because of an enthusiasm for technologic advance and the opportunity to treat complex problems, this past year was a somber reminder of our oath to do no harm. At no point in our history has there been a greater focus on infection prevention in health care with the ever-present threat of COVID-19. The prevention of transmissible infections has added cost and complexity to the reprocessing of duodenoscopes. Duodenoscopes have a complex design with intricate moving parts, long working channels, and are heat labile which make them difficult devices to disinfect[3]. Contaminated duodenoscopes have been implicated in the spread of multidrug resistant organisms[4-7]. Several measures have been taken to improve the disinfection process to mitigate cross contamination[8]. Along with this, the Food and Drug Administration (FDA) recommended a transition to a newer design of duodenoscopes with disposable components which can simplify the disinfection process[9]. This has also led to innovations in duodenoscope design

which include disposable parts and the development of a completely disposable duodenoscope.

Development of a single-use duodenoscope began in 2017. The challenge was manufacturing a scope comparable in performance and efficacy to a conventional reusable duodenoscope and eliminate the risk of any cross contamination[10]. Although there have been disposable bronchoscopes, nasopharyngoscopes, and ureteroscopes in clinical use, a disposable scope in gastroenterological clinical practice has been unprecedented[10]. In December 2019, the FDA cleared the first fully disposable duodenoscope — EXALT™ Model D Single-Use Duodenoscope (Figure 1), Boston Scientific Corporation (Marlborough, MA, United States)[11]. The endoscope has a 4.2 mm working channel, LED light, and conventional four-way steering. The current model D has a similar elevator lift angle and viewing angle when compared to the available reusable duodenoscopes. Subsequently in July 2020, a second disposable duodenoscope was cleared by the FDA-Duodenoscope model aScope™ Duodeno, Ambu A/S (Ballerup, Denmark)[5].

Advantages of a single-use duodenoscope are that they are sterile with no risk of cross contamination between patients. There is no need for disinfection or reprocessing, and it also eliminates the cost of maintenance and repair. Initial studies with the use of disposable duodenoscopes in a bench model, real patients, and a randomized study comparing with conventional duodenoscopes have shown equivalent performance characteristics compared to reusable duodenoscopes[10,12,13]. The significant disadvantages of the adoption of disposable duodenoscopes are the increased costs and increased environmental waste[14]. Further studies on the safety, efficacy, costs, patient outcomes, and environmental impact will help navigate the transition toward these novel devices.

Periprocedural management: Anesthesia involvement and propofol use in ERCP

ERCP has become safer with better equipment, standardized training programs, and better periprocedural care. As ERCP applications have broadened to include other modalities like EUS, there has been a significant increase in the use of involvement of anesthesia services in endoscopy. The safety of anesthesia-directed sedation in endoscopy is complex to analyze, but now better understood.

Safe sedation is a dynamic process that allows for technical and clinical success. In a United Kingdom study of therapeutic procedures, sedation was deemed inappropriate in up to 14% of cases[15]. Prior to Propofol use and general anesthesia, intolerance of sedation with discomfort was noted in one third to one half of ERCPs[16]. Comorbid patients with higher American Society of Anesthesiologist scores are more likely to have anesthesiologist involvement[17]. The safety of anesthesia service in endoscopy was analysed in a large cross-sectional study using the National Anesthesia Clinical Outcomes Registry. A total of 27721 patients had an ERCP performed with 12 deaths and 1052 anesthesia-related complications reported[17]. In the unadjusted model, ERCP was associated with an elevated odds ratio (OR) of 8.83 [95% confidence interval (CI): 7.70-10.12] relative to colonoscopy, that was not significant in the multivariate analysis.

Propofol is a sedative and hypnotic medication with a shorter duration of action compared to midazolam and fentanyl. Benefits of propofol include improvements in patient satisfaction, procedural outcome, and quicker recovery when compared to procedural sedation[18-20]. Propofol can cause significant hypotension and rapid respiratory depression. Further study was required to clarify propofol's safety in endoscopy. The ProSed 2 study[21] was a large multicenter prospective study reviewing sedation methods and associated complications of which 20967 procedures (6.7%) were ERCPs. The lowest rates of sedation-related complications were in patients receiving propofol monotherapy, and only 5 reported fatalities occurred during these ERCPs. An important point from the study is that their data collection focused on adverse events related to sedation alone, and delayed complications were not included. As with the Lieber study[17], delayed adverse events like post ERCP pancreatitis would not be captured by the author's study design[22]. Respiratory complications are more common in upper endoscopies[17], and the decision to intubate a patient remains individualized to the nature of the intended procedure and the patient's comorbidities. If anesthesia services are involved at our institution, any decision regarding the patient's anesthesia and intubation is collaborative with shared care decision making.

Future directions: Reducing post ERCP pancreatitis

Guidewire cannulation[23], pancreatic duct stents[24], intensive intravenous hydration [25,26], and rectal indomethacin[27] are used to reduce post ERCP pancreatitis[28]. In

Figure 1 The EXALT duodenoscope in use at our center.

the landmark trial published in the NEJM assessing the benefits indomethacin for post ERCP prophylaxis, more than 80% of patients also received a pancreatic duct stent [27]. The dose of rectal indomethacin used in the study was 100 mg. There was a reduction in post ERCP pancreatitis in both patients who received a stent (16.1% to 9.7% P = 0.04) and those who did not (20.6% to 6.3% P = 0.049). Post hoc analysis of this data suggested that the use of rectal indomethacin alone was better than a stent alone or the combination of stent and rectal indomethacin[29]. Despite data to support rectal indomethacin given before the procedure[30], and the double wire technique [31], the current state of practice remains individual to the practitioner. Side effects of long-term nonsteroidal anti-inflammatory drug use include renal impairment and peptic ulcer disease. A single dose of indomethacin did not result in a significant risk of acute renal impairment or clinically significant gastrointestinal bleeding[27]. The stent *vs* indomethacin for preventing post-ERCP pancreatitis (SVI) trial will clarify the value of a prophylactic pancreatic stent when added to rectally administered indomethacin[29] and should help further define standards of practice.

CANNULATION, BILIARY ACCESS, AND ALTERED ANATOMY

EUS assisted biliary access

Cannulation techniques have continued to evolve with advances in equipment[32]. Adding the EUS rendezvous may represent the last advance necessary to achieve 100% cannulation success during the index procedure. However, the additional risk of adding an EUS rendezvous to the index procedure needs to be evaluated prospectively in many centers. Failed cannulations are currently managed with a referral to interventional radiology for percutaneous transhepatic cholangiography (PTC). Biliary access and management would take the form of a combined PTC with ERCP, PTC with formation of an established tract, or antegrade stenting and stone removal[33]. EUS-guided rendezvous was first published in 2004[34]. Technical success has been reported with rates as high as 80% to 81%[35,36] with adverse event rates being 11%. A recent systematic review and meta-analysis reported a technical success of 86.1% (95%CI: 78.4-91) (12 studies reporting a total of 342 patients) and clinical success of 80.8% (95%CI: 64.1-90.8) (4 studies reporting a total of 94 patients)[37]. Consistent with previous reports, the pooled rate of adverse events was 14% (95%CI: 10.5-18.4) (12 studies; 42 events in 342 patients)[37]. At this time, the role of EUS rendezvous in ERCP is still not standardized and has not been compared to PTC in a comparative study[33]. In addition to EUS rendezvous, EUS directed transmural bile duct drainage is an alternate option. Transmural options for biliary drainage include hepaticogastrostomy (for proximal biliary obstruction) and choledochoduodenostomy (for distal biliary obstruction). While hepaticogastrostomy is performed using tubular metal stents, choledochoduodenostomy can be performed using tubular stents or LAMS based on bile duct size. A recent RCT compared EUS guided transmural biliary drainage *vs* ERCP for distal malignant obstruction and reported similar technical and clinical success[38].

Overtube-assisted enteroscopy and laparoscopic surgery-assisted ERCP

Given the burden of obesity and weight loss surgeries, expertise in altered surgical anatomy ERCP is necessary at tertiary referral centers. In a previous systematic review of overtube-assisted enteroscopy (OAE) and ERCP[39], patients with a Roux-en-Y with gastric bypass had a technically successful ERCP in just 70% of cases. Additionally, patients with a Roux-en-Y and either a hepaticojejunostomy (Figure 2) or pancreaticoduodenectomy undergoing ERCP had success in 76% of cases. A systematic review and meta-analysis[40] published in 2020 included 10 studies reporting a total of 398 procedures. The pooled rates of technical success of enteroscopy and OAE-ERCP were comparable at 75.3% (95%CI: 64.5-83.6) and 64.8% (95%CI: 53.1-74.9), respectively. The pooled rate of adverse events was 8.0% (95%CI: 5.2-12.2). The pooled rate of enteroscopy success with a double-balloon enteroscope in the 4 available studies was 83.5% (95%CI 68.3-92.2). Importantly, technical success of double-balloon enteroscopy ERCP (DBE-ERCP) was also higher at 72.5% (95%CI: 52.3-86.4). The pooled rate of adverse events with DBE-ERCP was 9.0% (95%CI: 5.4-14.5)[40].

Another approach to altered anatomy is the laparoscopic surgery-assisted ERCP [41]. At our institution, this surgery involves 4 Laparoscopic ports placed under direct visualization, formation of a gastrotomy, and placement of a rigid 19 mm sigmoidoscope into the gastrotomy. The duodenoscope is advanced through the sigmoidoscope, pylorus, and into the duodenum[42]. A meta-analysis in 2020 found that laparoscopic assisted surgery is significantly more effective than enteroscopy-assisted ERCP[43]. Therapeutic success was defined as completion of the diagnostic or therapeutic indication of the ERCP. The pooled proportion of patients with therapeutic success was higher in the surgery group at 97.9% (95%CI: 96.7-98.7) compared to 73.2% (95%CI: 62.5-82.6) in the enteroscopy-assisted ERCP patients. The benefits were countered by a higher rate of adverse events (19%; 95%CI: 12.6-26.4 *vs* 6.5%; 95%CI: 3.9-9.6) and a longer procedural time (158.5 min SD ± 20 *vs* 100.5 min SD ± 19.2 min).

EUS-directed transgastric ERCP

Given the challenges in managing patients with altered anatomy, EUS-directed transgastric ERCP (EDGE) is a novel way to approach patients with Roux-en-Y gastric bypass (RYGB)[44,45] and avoids the previously described laparoscopic-assisted access into the disconnected portion of the stomach. Importantly, the procedure has gained popularity since 2015[46] because of the ability to use conventional cannulation techniques and equipment. A retrospective multicenter review[47] of 178 patients reported a technical success of 98% (175/178) countered by 4 severe adverse events (SAE) (2.2%) and 10% of patients having a documented persistent fistula (9/90). It has been proposed that the EDGE could be used in patients with a RYGB, of which the details like limb length are unknown, and in patients with a surgically absent gallbladder[48]. A meta-analysis showed comparable rates of success to the laparoscopic assisted ERCP[45]. The significantly higher rates of technical success justify future comparative study of OAE and DBE ERCP with the EDGE procedure. The challenge for any prospective multicenter comparison will be that the EDGE can be done in 2 sessions[45]. The EUS placement of a transluminal stent, and then a second procedure at a follow-up interval to perform the ERCP. Although an EDGE procedure can be done at the time of LAMS placement, stent migration and free perforation can occur and most endoscopists wait 4-6 weeks prior to proceeding to ERCP.

ERCP AND ITS ROLE IN THE DIAGNOSIS AND MANAGEMENT OF BILIARY DISEASE

ERCP in complex bile duct stones

The main indication for ERCP is choledocholithiasis[49] which can cause cholangitis, biliary obstruction, and pancreatitis. For routine stones < 1 cm, a sphincterotomy with stone extraction using a balloon or basket is performed. Large bile duct stones present a particular challenge for safe and complete removal[50]. Recent guidelines have suggested performing a sphincterotomy and then a large balloon dilation over a sphincterotomy alone[51] for large stones. In a systematic review and meta-analysis, patients were more likely to have complete clearance of large stones (≥ 1 cm) OR 2.8, 95%CI: 1.4-5.7, I^2 26% if a balloon dilation was performed after a sphincterotomy (Figure 3).

Cholangioscopy is ideal for complex lithotripsy because of the ability to visualize the stone and introduce either a laser lithotripsy or electrohydraulic lithotripsy

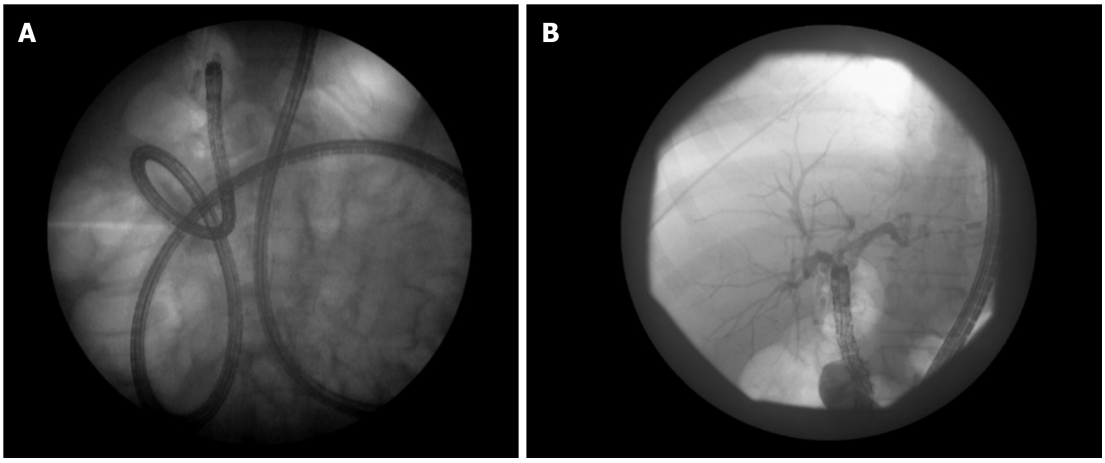

Figure 2 An overtube assisted enteroscopy and endoscopic retrograde cholangiopancreatography performed for a stent exchange and stone extraction. The patient had a Roux-en-Y hepaticojejunostomy after a bile duct injury. A: Stent exchange; B: Stone extraction.

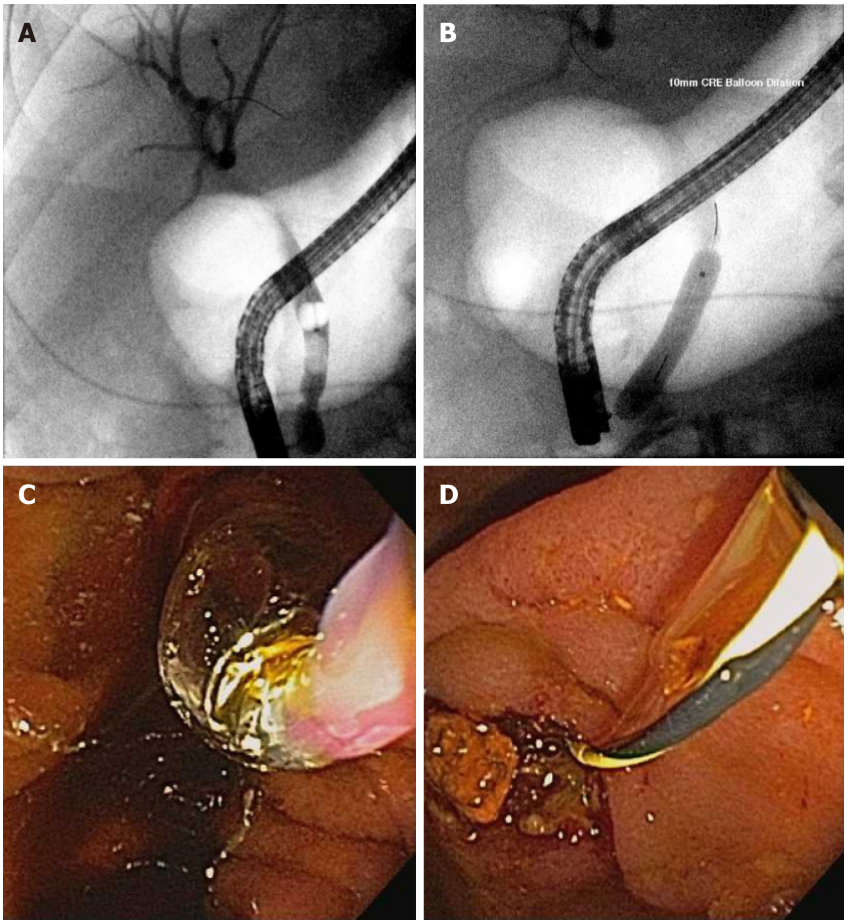

Figure 3 Large bile duct stone extraction. A: Bile duct stone; B-D: Balloon sphincteroplasty performed (B and C) with extracted stone fragment (D).

catheter[52]. Observational studies have reported procedural success in stone cases up to 92% with single operator cholangioscopy[53]. However, prior randomized controlled trials had not shown a significant difference between large balloon sphincteroplasty and cholangioscopy guided lithotripsy[54]. In a randomized comparison of large balloon sphincteroplasty with single-operator cholangioscopy guided lithotripsy, the proportion of ductal clearance was 72.7% and 93.9% in 1 session, respectively[55]. Treatment costs were higher in the cholangioscopy arm with no significant difference in complications. Future directions include standardized training in cholangioscopy and development of treatment algorithms for large bile duct stones[51].

ERCP in strictures and cholangiocarcinoma: Diagnosis and management

Cholangioscopy has progressed significantly since the transition from a dual-operator to a single-operator cholangioscope[52]. With the advent and proliferation of access to single-operator cholangioscopy, sensitivity for diagnosis of obstructive biliary pathology has improved. Cohort studies have shown adequate tissue for diagnostic assessment in 88% of patients with a biopsy performed with cholangioscopy[53]. A recent randomized multicenter trial confirmed higher first sample sensitivity with cholangioscopy compared to standard brushings (68.3% *vs* 21.4% $P < 0.01$) in patients with indeterminate biliary strictures[56]. Their data showed that the addition of the visual impression by digital single-operator cholangioscopy and direct biopsy had the highest likelihood of diagnosing malignancy in an indeterminate biliary stricture (Figure 4). For patients with primary sclerosing cholangitis, additional biopsies for fluorescence in situ hybridization (FISH) has been shown to improve sensitivity of indeterminate biliary strictures[57].

Management of unresectable cholangiocarcinoma has largely been limited to systemic chemotherapy and radiation. Currently, the main role of ERCP in cholangiocarcinoma is treating biliary obstructions with biliary stents. The advent of endoscopic options for unresectable cholangiocarcinoma has provided some hope in this field. Photodynamic therapy (PDT) and radiofrequency ablation (RFA) provide 2 available options for these patients. PDT works to ablate cancer tissue by using a photosensitizer that is activated by laser light. This results in tissue destruction by apoptosis and necrosis[58]. The main adverse event associated with PDT is photosensitivity. A sentinel study showed a survival benefit in patients receiving PDT [59]. A systematic review and meta-analysis published in 2017 by this journal[60] included 10 studies with 402 patients analyzed. The pooled OR for successful biliary drainage, defined as a reduction in bilirubin of 50% or greater at 7 d, was 4.39 (95%CI: 2.35-8.19) when comparing PDT and biliary stenting to biliary stenting alone. Future directions include targeted placement of the photsensitizer. Pullulan acetate-conjugated pheophorbide A is a photosensitizer that was successfully incorporated into self-expanding metal stent[61].

RFA is a local ablative therapy from a bipolar probe using high frequency current. A randomized trial from 2017 compared the outcomes of RFA with biliary stenting or biliary stenting alone[62]. The primary outcome of the study was mean survival time from the first RFA to time of death. In 21 months of follow-up, the mean survival time was significantly higher in the RFA and stent group (13.2 ± 0.6 mo) than if the patient received a biliary stent alone (8.3 ± 0.5 mo, $P < 0.001$). A previous retrospective comparative trial showed no difference between PDT and RFA in terms of survival rates[63]. Despite expected advances, the possible benefit of drug eluting stents remains untested in clinical trials. Vorinostat-eluting nanofiber membranes have showed antineoplastic effects against cholongiocarcinoma[64]. Stents with histone deacetylase inhibitors[65] and stents coated with gemcitabine and cisplatin have been fabricated[66], but neither have been tested in prospective studies.

PANCREATIC DISEASE: PANCREATIC STONES AND PANCREATIC LEAKS

ERCP in the management of pancreatic strictures

Radiological studies like CT and MRI/MRCP are the primary means of diagnosing chronic pancreatitis and strictures in 2021. However, in the early stages of chronic pancreatitis where the structural changes are limited, a combination of EUS, MRCP with secretin, and pancreatic function tests can be done in patients with high suspicion and risk factors[67]. ERCP is an important treatment option for patients with symptomatic chronic pancreatitis and strictures[68], with main pancreatic duct (MPD) strictures as the most likely to be intervened on. ERCP is recommended in patients with symptomatic, dominant strictures. These are defined as upstream MPD dilatation ≥ 6 mm in diameter, prevention of contrast medium outflow alongside a 6-Fr catheter inserted upstream from the stricture, or abdominal pain during continuous infusion of a nasopancreatic catheter inserted upstream from the stricture with 1 L saline over 12-24 h[69]. Stenting across the pancreatic duct stricture using ERCP decompresses the duct, helps relieve pain, and can result in improvement of exocrine pancreatic function [68]. Multiple studies have shown that stenting in chronic pancreatitis with strictures can improve pain[70-73]. A large multicenter study of more than 1000 patients followed up for a mean 4.9 years showed long-term success of endotherapy in 86% of

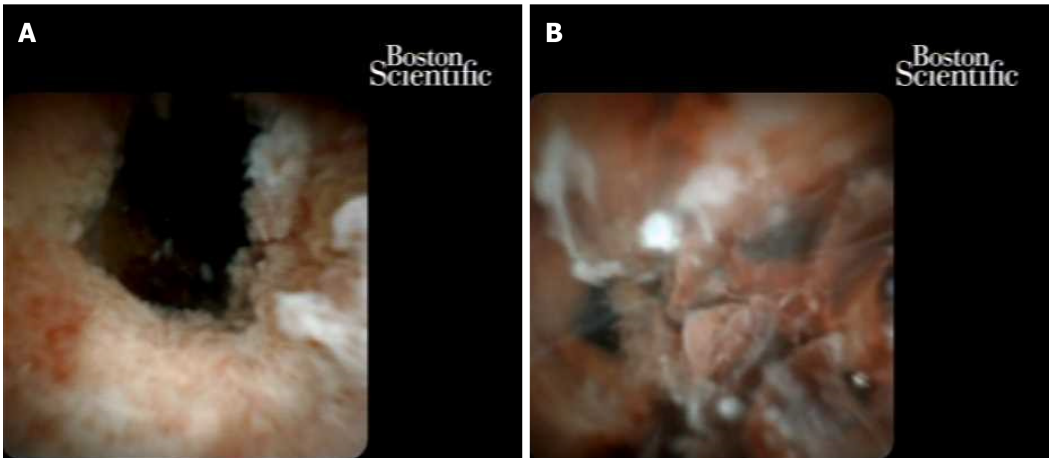

Figure 4 Cholangioscopy: Multifocal intraductal papillary neoplasm of bile ducts with high-grade dysplasia, that became cholangiocarcinoma. A: High-grade dysplasia; B: Cholangiocarcinoma.

patients but was lower at 65% in intention to treat analysis[68]. A large meta-analysis involving 16 studies and 1498 patients showed immediate pain relief in 88% and long-term pain relief in 67%. Complication rates for endotherapy were 7.85%[74]. More recently, rendezvous access using transgastric EUS puncture of the pancreatic duct and guidewire placement through a tight stenosis has allowed treatment of previously inaccessible strictures[75]. This is particularly effective in post Whipple patients with a stenotic pancreaticojejunostomy[76].

Commonly, a single plastic stent is used in pancreatic strictures. Multiple side-by-side plastic stents have also been used in treatment refractory strictures which did not respond to a single stent[77]. Newer stents like the fully covered self-expandable metal stents and a biodegradable noncovered self-expandable stents have been evaluated[78,79]. Preliminary studies with longitudinal follow-up of fully covered self-expanding metal stents (FCSEMSs) in symptomatic main duct pancreatic strictures[79] are promising. In patients with MPD strictures that remained symptomatic after a single plastic stent who were treated with a 6 mm or 8 mm Niti-S Bumpt Stent (Taewoong Medical, Gimpo-SI, South Korea), 89% of patients were asymptomatic after 3 years. Given the technical success of FCSEMS[80] and relative safety[81,82], larger studies with long-term data will be performed. An ongoing trial will look at the degree of pain reduction, SAE, and stricture resolution[83] in patients who received a FCSEMS. To date, SEMS in the pancreatic duct in the United States remains investigational.

Pancreatoscopy, pancreatic stones, and pancreatic leaks

The indications for pancreatoscopy include direct visualization of strictures, filling defects, and to differentiate benign from malignant intraductal pathology. Pancreatoscopy can be helpful in the management of suspected intraductal papillary mucinous neoplasms as it can diagnose and stage the disease prior to surgical resection[84-86]. Per oral pancreatoscopy was first demonstrated in 1970s by Kawai *et al*[87], but required a second operator, and the technology was limited[88-90]. The first digital SpyGlass™ direct visualization cholangiopancreatoscope (Boston Scientific Corporation, Marlborough, MA, United States) was introduced in 2007. This included a working channel for biopsies and allowed for irrigation[91,92]. Further iterations had improved digital image quality[93]. The most recent digital version was launched in 2018 and has increased resolution, improved lighting, a retrieval basket, and a retrieval snare. The primary therapeutic indication of pancreatoscopy is direct lithotripsy for pancreatic duct stones[94]. Complication rates post pancreatoscopy have ranged from 3.8% to 12% and mainly include mild pancreatitis[85,95-97].

Chronic calcific pancreatitis is complicated by intraductal pancreatic stones which can be difficult to manage. In symptomatic patients, preprocedure imaging is mandatory to decide on adding extracorporeal shock wave lithotripsy (ESWL) before ERCP (Figure 5). ESWL is indicated if there are larger stones (≥ 5 mm) with ductal obstruction. Previous studies have shown that adding ESWL significantly decreases pain scores, yearly hospitalizations for pancreatitis, and opioid use[98]. A systematic review and meta-analyses of 22 ESWL ERCP studies noted high rates of complete stone fragmentation at 86.3% (95%CI: 76.0-94.0)[99]. The pooled percentage of patients with complete ductal clearance, however was 69.8% (95%CI: 63.8-75.5). This is a

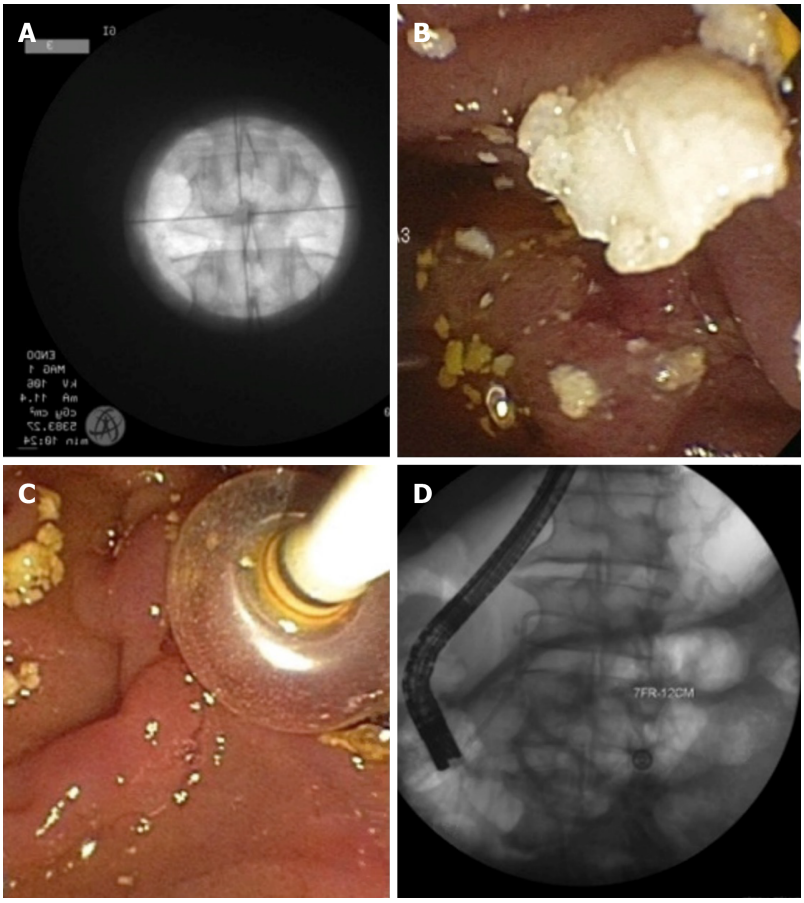

Figure 5 Chronic pancreatitis with a large pancreatic stone. A: Extracorpeal shock wave lithotripsy with stone; B and C: Successful stone extraction; D: Placement of a plastic pancreatic stent.

difficult patient population to manage and overall ESWL resulted in a moderate proportion of patients with complete absence of pain 64.2% (95%CI: 57.5-70.6). At our institution we perform an ESWL and ERCP in the same session (Figure 5). Repeat treatments are arranged based on post treatment symptom burden, interval imaging, and stone burden on repeat pancreatogram.

Pancreatic inflammation can cause a pancreatic duct leak with the unfortunate consequences of peripancreatic fluid collection, pseudocyst, walled-off pancreatic necrosis, pancreatic ascites, and fistula formation[100]. Management of pancreatic duct leaks historically involved conservative management including TPN and octreotide as a bridge to surgery. ERCP allows for diagnosis of the leak, transpapillary stent placement, and avoidance of surgery. Fluid collections from a pancreatic leak can be managed with internal luminal drainage and percutaneous drains[101,102]. Transluminal pigtail stents placed for pancreatic fluid leak in disconnected duct syndrome can be left in indefinitely as removing stents leads to risk of recurrent fluid collection[103].

CONCLUSION

ERCPs are done for multiple important reasons[1]. Although the most common indication remains choledocholithiasis with or without cholangitis[49], evolving indications include cholangiopancreatoscopy with directed diagnostic and therapeutic procedures. Further training and improvements in practice have allowed for the use of over-tube, laparoscopic surgery-assisted, and EUS-facilitated ERCP[104] in patients who have undergone RYGB for morbid obesity. New developments in technology have allowed for the potential use of SEMS for refractory pancreatic duct strictures and the redesign of a duodenoscopes to include marketing of a disposable scopes to mitigate infectious complications from inadequately reprocessed devices. Despite the tumultuous last year and a half, there continues to be hope in the field of ERCP for managing complex disease.

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REVIEW

Indications and outcomes of endoscopic resection for non-pedunculated colorectal lesions: A narrative review

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Abstract

In the last years, endoscopic techniques gained a crucial role in the treatment of colorectal flat lesions. At the same time, the importance of a reliable assessment of such lesions to predict the malignancy and the depth of invasion of the colonic wall emerged. The current unsolved dilemma about the endoscopic excision techniques concerns the necessity of a reliable submucosal invasive cancer assessment system that can stratify the risk of the post-procedural need for surgery. Accordingly, this narrative literature review aims to compare the available diagnostic strategies in predicting malignancy and to give a guide about the best techniques to employ. We performed a literature search using electronic databases (MEDLINE/PubMed, EMBASE, and Cochrane Library). We collected all articles about endoscopic mucosal resection (EMR) and endoscopic submucosal dissection (ESD) registering the outcomes. Moreover, we analyzed all meta-analyses comparing EMR *vs* ESD outcomes for colorectal sessile or non-polypoid lesions of any size, preoperatively estimated as non-invasive. Seven meta-analysis studies, mainly Eastern, were included in the analysis comparing 124 studies and overall 22954 patients who underwent EMR and ESD procedures. Of these, eighty-two were retrospective, twenty-four perspective, nine case-control, and six cohorts, while three were randomized clinical trials. A total of 18118 EMR and 10379 ESD were completed for a whole of 28497 colorectal sessile or non-polypoid lesions > 5-10 mm in size. In conclusion, it is crucial to enhance the preoperative diagnostic workup, especially in deciding the most suitable endoscopic method for radical resection of flat colorectal lesions at risk of underlying malignancy. Additionally, the ESD necessitates further improvement because of the excessively time-consuming as well as the intraprocedural

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technical hindrances and related complications. We found a higher rate of *en bloc* resections and R0 for ESD than EMR for non-pedunculated colorectal lesions. Nevertheless, despite the lower local recurrence rates, ESD had greater perforation rates and needed lengthier procedural times. The prevailing risk for additional surgery in ESD rather than EMR for complications or oncologic reasons is still uncertain.

Key Words: Colorectal cancer; Adenoma detection; High-resolution colonoscopy; Chromoendoscopy; Pit pattern; Dysplasia

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Core Tip: The current unsolved dilemma concerns the necessity of a reliable submucosal invasive cancer assessment system, able to stratify the risk of the post-procedural need for surgery after endoscopic submucosal dissection of colorectal non-pedunculated lesions. It should be capable of selecting the at-risk subgroups of patients in whom endoscopic submucosal dissection could be the most suitable method. Accordingly, this narrative review aims to describe the best diagnostic strategies for predicting malignancy according to current endoscopic technology, to choose wisely among endoscopic mucosal resection, and endoscopic submucosal dissection procedures.

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INTRODUCTION

The Japanese[1,2], European[3], and American[4,5] guidelines recommend that large sessile colorectal polyps and laterally spreading tumor (LST) can be successfully removed by piecemeal endoscopic mucosal resection (p-EMR)[2,3,5,6] if there are no signs of deep submucosal invasion on endoscopic assessment[5-9].

EMR is fast and safe to remove non-pedunculated colorectal lesions sized above 10-15 mm[1-3,5]. However, p-EMR may impair accurate histological assessment and has higher recurrence rates than *en bloc* resection[1-3,5], resulting in a higher frequency of post-procedural surgery[1-3,5].

En bloc EMR (with distinct techniques) for sessile polyps or LSTs ≥ 20 mm has been reported in 16%-48% of cases[10-14], with a success rate ranging from 42.9% to 98.8% and R0 rate between 45.0% to 96.7% cases[15-19]. A 2009 meta-analysis about endoscopic excision of large colorectal sessile polyps and LST lesions, reported an *en bloc* EMR rate of 62.85% and R0 rate of 58.66% on a sample of over 5221 patients[20]. It would be adequate to refer to the recurrence and surgery rates for EMR. Nevertheless, EMR is contraindicated in the presence of signs of deep invasion, like tissue ulceration/hardening, central depression, and non-lifting signs after submucosal injection[1-3,5].

Endoscopic submucosal dissection (ESD) should be preferred over EMR in cases of colorectal lesions greater than 20 mm with signs of superficial submucosal invasive cancer (SMIC), non-granular (NG) surface pattern, or when it could not be radically removed by the conventional procedures[2,5,21].

ESD achieves higher rates of *en bloc* and R0 resection, which translates into more adequate histological assessment and lower rates of local recurrence[1,2,5,22]. The downsides of ESD are longer procedural time and higher intraprocedural complications such as perforation, which of course are lowered by experience[1,2,5,21]. However, a recent systematic review has suggested limiting the indication for ESD because of the high incidence registered of non-curative resection due to a wrong SMIC assessment[2].

Colorectal lesion morphology can predict the risk of SMIC and help to guide the most appropriate endoscopic treatment[3,5,21,23]. Three parameters have to be considered: morphological pattern (MP) according to the Paris 2002 classification[24] and updated for the colon in the Kyoto 2008[25]; glandular pattern [pit pattern (PP)] according to the Kudo classification[26]; and vascular pattern[24,25,27-29]. The assessment of MP requires the use of a high-definition endoscope[21,24,25,27].

Diagnostic performance for the histological prediction of underlying malignancy of colorectal lesions according to their MP, as well as to Kudo PP, narrow-band imaging (NBI) international colorectal endoscopic (NICE), and Japanese NBI Expert Team (JNET) classifications are described in Table 1[6].

Regarding MP, Paris type 0-IIc non-polypoid lesions have a higher risk of SMIC than Paris 0-IIa, 0-IIb, and polypoid lesions[5,21,24,25,27]. Furthermore, the rates of SMIC for granular (G) homogenous, G nodular mixed, NG flat, and NG pseudodepressed LSTs were 4.9%, 15.9%, 3.0%, and 19.4%, respectively[30]. Additionally, the risk of occult SMIC according to colonic lesion morphology and location have been estimated to be 0.8% for 0-IIa G (proximal: 0.7%, distal: 1.2%), 7.1% for 0-IIa + Is G (proximal: 4.2%, distal: 10.1%), 3.7% for 0-Is G (proximal: 2.3%, distal: 5.7%), whereas SMIC risk was 4.2% for 0-IIa NG (proximal: 3.8%, distal: 6.4%), 14.1% for 0-IIa + Is NG (proximal: 12.7%, distal: 15.9%), 15.3% for 0-Is NG (proximal:12.3%, distal: 21.4%)[6]. Though those lesions without these features might still contain SMIC that is not visible on endoscopic inspection, which is defined as covert SMIC[6].

Current guidelines support the use of high-resolution colonoscopy with chromoendoscopy (dye or virtual) and optical magnification to establish the presence of SMIC and the feasibility of resection[24,25,26,31,32]. Virtual chromoendoscopy, by "real-time imaging" modifications (with NBI, flexible spectral imaging color enhancement, or i-Scan), allows the correct evaluation of PP and vascular pattern[5,21,24-26]. Optical magnification endoscopes identify the mucosal surface PP according to the Kudo classification[2,33].

The Japanese usually assess the risk of colorectal lesion infiltration by using chromoendoscopy with indigo carmine or crystal violet. In the Western areas, the reduced spread of magnification (both high costs and long procedural times) has restricted the evaluation of the risk of lesion infiltration to lifting-sign[3,21,26,34].

These techniques have improved the early detection of colorectal cancer (CRC) by characterizing the microscopic appearance of the dimples or furrows that separate the mucosal cells, which change according to the distinct stages of dysplasia and neoplastic transformation[5,21,24,26,34]. Specifically, the sensitivity and specificity for the diagnosis of T1 CRC with deep SMIC by using NBI were 79% and 94%, respectively[35].

NICE CLASSIFICATION

The employment of NBI[36,37] has led to NICE classification[38] that distinguishes among hyperplastic polyps (type 1), adenomas (type 2) with/without superficial SMIC, and cancers with deep SMIC (type 3) based on color features, vessels, and surface pattern[38-40].

Therefore, lesions with glandular distortion but intact vascular structures [Kudo Vi, NICE type 2] are at risk of a superficial SMIC and are suitable for endoscopic *en bloc* resection. Whereas a highly distorted PP or an absence/irregularity of the submucosal vessels (Kudo Vn or NICE type 3) are strongly predictive of deep SMIC. Therefore, after performing biopsies and tattoos of the lesion, surgical treatment should be judged[38].

The sensitivity, specificity, positive predictive value, and negative predictive value of the NICE classification for predicting deep SMIC were 58.4% (95% confidence interval (CI): 47.5%-68.8%), 96.4% (95%CI: 95.5%-97.2%), 41.6%, (95%CI: 32.9%-50.8%), and 98.1% (95%CI: 97.5%-98.7%), respectively[39], whereas 99.1%, 57.7%, 95.4%, and 88.2%, respectively in differentiating neoplastic from non-neoplastic polyps[40]. Interobserver agreement was relevant (kappa: 0.70) for predicting deep SMIC[41]. Also, the sensitivity for the diagnosis of deep SMIC regarding lesions with type 3 of NICE was significantly greater among very expert endoscopists than in the less-experienced ones (91.7% *vs* 83.3%; $P = 0.04$)[42].

Table 1 Diagnostic performance for the histological prediction of underlying malignancy of colorectal lesions according to their morphological pattern as well as to Kudo pit pattern, narrow-band imaging international colorectal endoscopic, and Japan narrow-band imaging expert team classifications

Variables	Sensitivity	Specificity	PPV	NPV	Accuracy
Morphological pattern[1]					
0-IIa G	5.7%	70.0%	1.7%	89.1%	64.6%
0-Is G	11.5%	83.2%	5.8%	91.2%	77.3%
0-IIa + Is G	22.9%	77.4%	8.4%	91.7%	72.8%
0-IIa NG	27.4%	79.5%	10.8%	92.4%	75.2%
0-Is NG	16.6%	95.5%	25.0%	92.7%	89.0%
0-IIa + Is NG	15.9%	94.5%	20.7%	92.6%	88.0%
Kudo pit pattern (NBI)[2]	73.3%-93.7%[3]	89.2%-100%[3]	93.7%-100%[3]	89.2%- 96.4%[3]	92.0%-96.7%[3]
NICE classification[4]					
Type 1	82.1%-84.6%	93.8%-94.9%	65.9%-92.5%	60.4-98.2%	93.9%-97.8%
Type 2	89.8%-91.4%	84.3%-86.3%	89.1%-90.7%	97.3-97.7%	56.6%-61.2%
Type 3	83.3%-91.7%	96.4%-97.0%	96.0%-96.8%	45.8-54.0%	99.4%-99.7%
JNET classification[5]					
Type 1	73.0%-87.1%	96.0%-99.5%	73.4%-92.3%	96%-98.9%	93.0%-98.5%
Type 2A	82.5%-96.0%	70.0%-91.1%	90.3%-96.7%	62.1%-92.1%	84.5%-90.9%
Type 2B	42.0%-75.6%	84.2%-95.0%	26.0%-67.3%	92.2%-98.0%	81.3%-93.0%
Type 3	35.0%-91.7%	98.1%-100%	63.2%-100%	93.8%-99.7%	94.0%-98.0%

[1]Diagnostic performance of lesion classification types according to Paris classification for covert submucosal invasive cancer (SMIC) (SMIC that is not visible on endoscopic inspection).
[2]Narrow-band imaging.
[3]These percentages refer to the ability of preoperative magnifying chromoendoscopy (Kudo pit pattern classification by narrow-band imaging assessment of mucosal surface) to predict depth of submucosal invasion for large colorectal lesions.
[4]Narrow-band imaging international colorectal endoscopic (NICE) classification, NICE type 1: hyperplastic polyps, NICE type 2: adenomas (with/without risk of a superficial SMIC), NICE type 3: strongly predictive of cancers with deep SMIC.
[5]Japan narrow-band imaging expert team classification (JNET), JNET type 1: predictive of hyperplastic/sessile serrated polyps, JNET type 2A: predictive of neoplasia with low/high-grade intramucosal neoplasia, JNET type 2B: predictive of high-grade intramucosal neoplasia/shallow submucosal invasive cancer, JNET type 3: predictive of cancer with deep SMIC. PPV: Positive predictive value; NPV: Negative predictive value; NBI: Narrow-band imaging; JNET: Japan Narrow-band imaging expert team classification; NICE: Narrow-band imaging international colorectal endoscopic; NG: Non-granular; G: Granular.

JNET CLASSIFICATION

The JNET classification consists of four categories and uses vascular pattern and MP to diagnose hyperplastic/sessile serrated polyps (type 1), neoplasia with low/high-grade intramucosal neoplasia (type 2A), high-grade intramucosal neoplasia/shallow SMIC (type 2B), and cancer with deep SMIC (type 3)[42-46]. The interobserver and the intraobserver agreement for the JNET classification were moderate (kappa: 0.52) and excellent (kappa: 0.88), respectively. Type 2B lesions included a variety of colorectal tumors, including those with high-grade dysplasia, with superficial and deep SMIC [45]. Both non-expert/expert endoscopists had similar specificity, negative predictive value, and accuracy (> 90%) for 1/2B/3 types and sensitivity and positive predictive value above 90% for type 2A, whereas type 2B exhibited a sensitivity of only 42%[44].

Colorectal polyps exhibiting ulceration, excavation, defined deep depression, Paris IIc and IIa+c, mucosal friability, convergent plicae, and Kudo type V PP most likely correspond to SMIC. Therefore, they are at high risk for lymphovascular invasion and lymph node metastasis[48-52].

Additionally, superficial SMIC (sm1 and sm2, involving the upper and middle level of the submucosa, respectively)[25] was not closely associated with non-lifting signs because underlying undamaged submucosa may still expand, unlike deep SMIC (sm3, involving the lower level of the submucosa)[25,53-55]. Accordingly, when deep SMIC

is suspected or proven, in addition to excision of the lesion, the removal of the loco-regional lymph nodes is necessary, which can only be achieved by surgery[5,21,26,25,52].

Moreover, staging even with echoendoscopy and magnetic resonance imaging can be considered for rectal tumors with endoscopic features suspected for SMIC and eventually lymph node staging[56,57]. Colorectal surgery is recommended for lymphovascular invasion, SMIC deeper than sm1, positive/non-evaluable vertical margins, or poorly differentiated tumor[8,21,26,24,25]. When a positivity of horizontal margin is shown without additional high-risk criteria, endoscopic surveillance/re-treatment could be weighed instead of surgery[21,26,24,25].

EMR en bloc or piecemeal: indications, efficacy, and safety

On the other hand, colorectal lesions without SMIC-suggestive features have a high likelihood of being radically removed by endoscopic techniques and should not be referred for surgery without primary estimating the possibility of a polypectomy/EMR at an expert endoscopy center[58]. Moreover, it should be avoided to perform biopsies in such lesions because it can produce submucosal fibrosis, not allowing the lifting process[5,21,25,26,34]. Indeed, in a study[59] of 36 patients with 38 large polypoid lesions, negative for cancer who were referred from a colorectal surgeon to an EMR expert, 79% of the lesions were successfully treated endoscopically, thus avoiding unnecessary surgery in 71% of cases.

EMR encompasses different techniques (*i.e.* inject and cut, with either cold or hot snare; cap-assisted; underwater; hybrid)[32,60-63]. Various studies have proved that *en bloc* or p-EMR can radically and safely remove most colorectal sessile or non-polypoid lesions[13-16,64].

En bloc or p-EMR resections aim particularly at a resection with a histologically confirmed negative resection margin. Particularly, *en bloc* R0 resection, together with the absence of undifferentiated adenocarcinoma, deep invasion (submucosal invasion > 1000 μm), and lymphovascular invasion excludes the risk of lymph node metastasis [2,3,5,7,8,10-16,52,64].

Specifically, *en bloc* EMR has been reached in 47.2%[15], 53.5%[11], 66.3%[14], 91.3%[17], and 98.8%[16] of procedures, whereas R0 was achieved in 45%[14], 88.9%[15], 89.2%[10], 91.0%[11], and 96.7%[18] of events for colorectal sessile polyps and/or LSTs [14,15,17,18] or for recurrent adenomas after p-EMR[11] of various diameters (≥ 10/20 mm[10,14,17], ranging 8-100 mm[11], 10-50 mm[18], or 20-50 mm[14]).

According to current guidelines, p-EMR is mainly employed for treating large non-malignant colorectal sessile or non-polypoid lesions[3,63,65]. To be optimally performed, it requires the resection to be completed by a limited number of pieces and adequate margins[2,3,5].

However, according to a meta-analysis published in 2016[65] including 6442 patients and 6779 large colorectal polyps, successful endoscopic resection (independently from surgery following endoscopy and, in some events, to histology) by any endoscopic technique, post-endoscopic resection bleeding, perforation, and mortality occurred in 96.3% (95%CI: 96.0%-97.0%), 6.5% (95%CI: 5.9%-7.1%), 1.5% (95%CI: 1.2%-1.7%), and 0.08% cases (95%CI: 0.01%-0.15%), respectively, after resection. A rate of 8% of patients (95%CI: 7%-10%, I^2 = 78.6%) underwent surgery due to non-curative endoscopic resection and 1.0% (95%CI: 0.7%-1.4%, I^2 = 0%) due to adverse events[65].

Other studies have also reported various percentages of post-EMR bleeding in 0% [14,16,19], 1.75%[18], 2.8%-3.1%[13], 6.2%[66], 9.8%[11], and 10.8%[12] after the resection of large colorectal lesions.

The efficacy and safety of hot and cold snare EMR for non-pedunculated colorectal adenomas < 20 mm has been evaluated in few studies, which suggested a capacity for resectability improvement and for delivering better histopathological evaluation especially with the cold snare technique[15,67-69].

Besides, a Japanese single-armed multicenter prospective trial[67] of 624 patients undergoing standard EMR of non-pedunculated polyps with a diameter ≤ 20 mm, successful *en bloc* and R0 resection rates of 93.3% and 78.3%, respectively, were observed. Postoperative rates of bleeding and perforation were 1.1% and 0%, respectively[67].

Another Japanese multicenter randomized controlled trial (Yamashina *et al*[68], 2019) showed for 102 sessile lesions ranging between 10-20 mm and treated by standard EMR (with electrocautery) an *en bloc* resection of 75% (95%CI: 65%-83%), R0 resection of 50% (95%CI: 40%-60%), with a median procedure time of 175 s, and adverse events were reported in 2% of cases.

A Japanese prospective, observational study[69] assessing an overall 80 non-pedunculated adenomas measuring 10-14 mm and treated with cold snare EMR

reported *en bloc* and R0 resection rates of 82.5% and 63.8%, respectively. No post-procedural adverse events occurred.

Otherwise, in a retrospective, single-center study[15] analyzing 44 EMR salvage procedures (following the previous p-EMR) of polyps whose median size was 14 mm, *en bloc* resection rate was 15.9%, R0 resection rate was 31.8%, and intraprocedural argon plasma coagulation (APC) ablation of visible residual was 65.9%. Bleeding occurred in 4.5%, and there were no perforation events[15].

Among the studies evaluating EMR for colorectal lesions < 20 mm, the majority did not analyze the recurrence rates[67-69], but only one reported a 39.4% of recurrence at surveillance[15].

Hot snare EMR is the conventional technique employed for resection of large (≥ 20 mm) non-malignant sessile colonic polyps, although severe adverse events can occur mainly due to electrocautery application.

Cold snare p-EMR of sessile colonic polyps or LSTs ≥ 20 mm represents an alternative technique feasible, efficient, and secure in many cases, although large randomized/prospective trials to strengthen the results and to define which polyps are rightly suitable for this method are needed. Furthermore, the adverse event and polyp recurrence rates are usually low.

A retrospective study[70] reported similar technical success for both cold snare p-EMR and standard EMR employed for 156 and 406 sessile serrated lesions sized ≥ 20 mm (100% *vs* 99%; *P* = not significant), respectively. While cold snare p-EMR was not associated with adverse events, delayed bleeding and deep mural injury were observed in 5.1% and 3.4%, respectively, following EMR[70].

A retrospective Australian study[71] of 186 patients treated by cold snare p-EMR for 204 sessile polyps ≥ 20 mm reached a median interval of 150 d of residual/recurrent polyp in 5.5% of cases, whereas at a median interval-time of 18 mo registered a 3.5% late residual/recurrent polyp. Bleeding occurred throughout the p-EMR in 2.2% of cases, whereas post-EMR bleeding occurred in 3.8%[71].

In a prospective observational cohort study[72], the risk of residual or recurring adenoma after p-EMR of large non-pedunculated polyps was 10.8% (mean size, 31.6 ± 10.1 mm)[72].

A prospective and multicenter Australian study[73] on 1178 LSTs ≥ 20 mm removed by p-EMR showed a recurrence rate of 19.4%[73]. In detail, LST size ≥ 40 mm [odds ratio (OR) = 2.47; *P* < 0.001], the intraprocedural bleeding (OR = 1.78; *P* = 0.024), and high-grade dysplasia (OR = 1.72; *P* = 0.029) were independent predictors for polyp recurrence[73].

Indications, outcomes, and adverse events of underwater EMR

Principal boundaries with conventional EMR involve high percentages of polyp recurrence and low *en bloc* resection rates, especially for lesions sized above 20 mm. Underwater EMR (U-EMR) represents an alternative method for *en bloc* resection of more extensive lesions. Comparison studies showed the feasibility and safety of U-EMR that is associated with higher *en bloc* and R0 resection rates for colonic lesions compared to standard EMR[62].

Previously, Binmoeller *et al*[13], in a prospective observational study, reported a 100% R0 resection concerning U-EMR for large sessile polyps, and delayed bleeding occurred in 5%[13].

In a multicenter randomized controlled trial[68], U-EMR for polyps with intermediate-size (10-20 mm in diameter) demonstrated higher *en bloc* and R0 resection rates as compared to conventional EMR [89% (95%CI: 81%–94%) *vs* 75% (95%CI: 65%–83%), *P* = 0.007; and 69% (95%CI: 59%–77%), *vs* 50% (95%CI: 40%–60%), *P* = 0.011, respectively]. There was no significant difference in prevalence of adverse events in the U-EMR group (2.8% *vs* 2.0%, *P* = not significant)[68].

In a meta-analysis of American and European studies[74], the U-EMR technique exhibited an R0 resection rate of 96.36% (95%CI: 91.77%-98.44%). Also, *en bloc* resection rate was described in 57.07% (95%CI: 43.20%-69.91%) for sessile polyps and non-polypoid lesions (mean size range, 15.0-33.8 mm). Adverse events occurred in 3.31% (95%CI: 1.97%-5.52%) and late bleedings in 2.85% (95%CI: 1.64-4.90%), in the absence of perforation[74].

In a recent systematic review and meta-analysis[75], U-EMR has shown a higher *en bloc* resection rate than conventional EMR for removing polyps > 20 mm in size (OR = 1.9; 95%CI: 1.0-3.5; *P* = 0.04), whereas R0 resection (OR = 3.1; 95%CI: 0.7%-12.6%; *P* = 0.14), piecemeal resection (OR = 3.1; 95%CI: 0.7%-12.6%; *P* = 0.13), and diagnostic accuracy for CRC (OR = 1.1; 95%CI: 0.6%-1.8%; *P* = 0.82) were similar. There were lower rates of recurrence (OR = 0.3; 95%CI: 0.1%-0.8%; *P* = 0.01) and incomplete resection (OR = 0.4; 95%CI: 0.2%-0.5%; *P* = 0.001) with U-EMR. The two methods

produced equivalent procedural times and safety profiles.

Indications and outcomes of cap-assisted EMR and EMR with a ligation device

The cap-assisted EMR (C-EMR) and EMR with a ligation device (EMR-L) in the colon have limited indications, especially for R0 resection of small rectal neuroendocrine tumors (NETs) because their radical removal can be difficult to achieve with standard endoscopic resection techniques due to the frequent involvement of the submucosal layer[76,77].

Some articles have described the usefulness of a distally attached cap during colonoscopy for shortening cecal intubation, decreasing patient discomfort, improving adenoma detection rate, and simplifying mucosal resection of non-pedunculated lesions[81-85]. Moreover, C-EMR can resect more adequately complex and large interplicae non-polypoid lesions, especially those located in the right colon[18].

A 2011 single-center prospective, randomized, controlled trial[86] showed during C-EMR/colonoscopy of 166 patients a significantly reduced procedural time (3.5 ± 4.5 *vs* 4.2 ± 5.1 min, $P = 0.010$), a higher polyp detection rate (3.4 ± 2.7 *vs* 2.7 ± 1.9, $P = 0.003$), and a lower rate of missed polyps (1.1 ± 1.5 *vs* 0.8 ± 0.9, $P = 0.024$) than patients undergoing conventional colonoscopy[86].

As reported in a retrospective study[87], C-EMR was feasible for resection of small rectal NETs. This study analyzed a total of 34 rectal NETs that were removed by C-EMR, reaching a higher R0 resection rate (94.1% *vs* 76.8%, $P = 0.032$) and a higher tendency of frequency of intraprocedural bleeding (8.8% *vs* 0%, $P = 0.051$) than standard EMR ($n = 56$); the procedural time was significantly shorter in the C-EMR group (3.9 ± 1.1 *vs* 19.0 ± 12.1 min, $P < 0.001$) than the ESD group ($n = 32$)[87]. For NETs ranging 6-8 mm in size, there were no differences in the adverse events or R0 resection rates between the C-EMR group and ESD group.

A review[88] suggested that C-EMR is effective and safe when polyp removal is challenging *via* standard EMR technique. Specifically, this study described a rate of 100% R0 resection after C-EMR of 21 ileocecal valve polyps (median size, 15 mm), and late bleeding occurred in 4.8%[88].

On the other hand, a Japanese and retrospective study[89] evaluating 22 colorectal carcinoid tumors (mean size, 6.2 mm) that were treated by EMR-L reported *en bloc* and R0 resection rates of 73% and 50%, respectively, for EMR-L. Perforation and bleeding did not occur[89].

Finally, the authors of a recent retrospective Korean study[90] deduced that EMR-L may be the preferred treatment method for small rectal NETs, considering the higher *en bloc* resection rate in the EMR-L group than C-EMR one (100% *vs* 92.9%, $P = 0.003$). Though only a superior trend for R0 resection rate was observed in the former group (92.5% *vs* 83.3%, $P = 0.087$), and there were no differences in intraprocedural adverse events ($P = 0.870$)[90].

Risk factors for adverse outcomes and recurrences after EMR of colorectal lesions > 20 mm

The factors that limit EMR[91] are resection technique[92,93], polyp size[94,95], previous removal attempts[96], location[97], endoscopist experience, and patient comorbidities[91,95,96,97].

Indeed, the risk factors for post-procedural hemorrhage included polyp location in the proximal tract[66,98,99,100] and particularly those larger than 40 mm[101,102]. Perforation occurred unusually (0.36%-6.30%)[12-14,98,103] and was higher particularly for lesions of the transverse colon with underlying high-grade dysplasia, SMIC, and after *en bloc* resection[3].

In detail, the perforation event has complicated endoscopic procedures in 0%[12,13], 0.36%[11], 1.4%-1.5%[98,103], 1.75%[18], 1.5%-1.9%[16], 2.9%[19], and 6.3%[14] of cases, with a negligible procedure-related fatality (< 0.1%)[12-14,18,19]. Late bleeding was usually endoscopically managed, while prophylactic coagulation of visible vessels or clip use did not lessen the risk of bleeding[1,3,6,50].

Also, complex lesions located at the ileocecal valve (single and both lips) were associated with resection failures (OR = 12.2; 95%CI: 1.64%-90.50%; $P = 0.002$) as well as in cases of terminal ileal involvement (OR = 121.3; 95%CI: 1.52%-84.00%; $P = 0.002$)[97]. The appendiceal orifice, the anorectal junction, and the peridiverticular sites have also been considered challenging to remove the lesions safely[2,3,5,10,98].

Additionally, an American study identified the previous resection attempts as a significant risk factor for failure of complete excision (OR = 0.024; $P = 0.001$) and for achieving a successful resection without applying thermal ablation of residual (OR = 0.081; $P < 0.001$)[96].

Moreover, no study has defined the threshold extent for which *en bloc* EMR is unsafe. *En bloc* EMR is generally limited to lesions sized up to 20 mm, while the larger usually require ESD or surgery for local radicality[5,7,21,20,32]. Specifically, for sessile polyps and flat lesions, the maximum size to perform safely *en bloc* excision was 15-20 mm proximal to the splenic flexure where the risk of perforation is the greatest and 20-25 mm in the sigmoid/rectum tract for anatomic reasons[3,5,20,32].

Interestingly, the circumferential incision of lesions with hybrid ESD methods (*i.e.* cap-assisted or precut-EMR) can allow the extension of the size threshold for complete resection while reducing the risk of perforation[19,99,104,105].

Hence, the cases including sessile colorectal polyps ≥ 20 mm (Paris classification 0-IIa, 0-Is, 0-Isp), LSTs, lesions located in difficult areas, or colitis-associated dysplasia have been judged amenable to be referred to experienced endoscopists in a high volume tertiary referral center before surgical option[2,3,5,11].

The EMR treatment for large colorectal sessile or non-polypoid lesions is associated with heterogeneous rates of adenoma recurrence/persistence that range between 0% and 39.4%[74,106-108], depending on the EMR technique (*i.e.* standard, hybrid, cap-assisted, or underwater), polyp size/histology, a higher number of resected pieces, previous attempts of resection, and surveillance period (3-6 mo or ≥ 12 mo)[19,61,63,96,109].

Recurrence rates succeeding cold snare p-EMR were similar to standard EMR at two consecutive surveillances (4.3%/2.0% *vs* 4.6%/1.2%, respectively)[70].

Previously, Kikuchi *et al*[106] evaluated the risk of recurrence even in patients with CRC and SMIC of any size following EMR; none of the 17 patients with superficial SMIC registered localized recurrence or lymph node metastases.

Bergmann and Beger[18] showed a 3.3% local recurrence after treating lesions with sizes ranging from 10-50 mm. Notably, Masci *et al*[16] described an approximately 15% recurrence rate of the lesions either in high- or low-volume centers.

Specifically, a meta-analysis[65] including 6442 patients treated with endoscopic resection of 6779 large polyps found an endoscopic recurrence in 13.8% of cases.

Moss *et al*[17], Conio *et al*[12], and Buchner *et al*[11] showed adenomatous recurrence at the resection site in 16%, 21.9%, and 27%, respectively, for large sessile polyps or LST lesions, referred to using EMR.

Pohl *et al*[109] reported a 17.3% incomplete resection by using hot snare EMR for large lesions. On the other hand, Thoguluva *et al*[64] observed after cold snare EMR of intermediate-size non-polypoid lesions an overall residual disease in 4.1%, whereas Muniraj *et al*[63] reported 20% of recurrences at 6 mo. Additionally, Rex *et al*[108] displayed a comparable residual polyp rate after the EMR of large sessile serrated adenoma/polyps or traditional adenomas (8.7% *vs* 11.1%, respectively).

Non-standard EMR techniques have reported favorable outcomes regarding reducing residual or recurrence lesions[15,74,87,107]. Indeed, Hong *et al*[14], reported no recurrence after EMR with circumferential incision for the treatment of large sessile polyps and LSTs. Yang *et al*[87] observed no recurrence in the C-EMR group after resection of 34 small rectal NETs. Binmoeller *et al*[13] and Spadaccini *et al*[74] showed a recurrence rate of 1.8% and 8.8%, respectively, using U-EMR for sessile polyps and non-polypoid lesions at surveillance program. In contrast, Kim *et al*[15] displayed a significantly lower recurrence in the U-EMR group than the standard EMR (10.0% *vs* 39.4%). Instead, a 4% recurrence was described after the employment of C-EMR for sessile lesions (or LSTs) over 1 year of surveillance[107].

P-EMR has been judged as an independent risk factor for recurrence after endoscopic resection of non-pedunculated colorectal adenomas and early carcinomas [110].

In detail, Kim *et al*[111] observed at surveillance following the previous p-EMR of large non-pedunculated adenomas, a second and third recurrence in 34% and 20% among 70 recurrent lesions, respectively. Nevertheless, another study[19] recorded a surprisingly higher recurrence rate for standard EMR than p-EMR (25.9% *vs* 3.2%). Moreover, Kim *et al*[96] presented significantly diverse recurrence rates in the patients without any prior manipulation (7.7%), with previous biopsy sampling (40.7%), and with advanced manipulation (53.8%) identifying previous resection attempts as a significant risk factor compared with non-manipulated lesions (OR = 18.8; P = 0.001). Besides, Nanda *et al*[97] showed for the lesions located in technically complicated sites such as ileum with/without valve involvement, an early and a late recurrence in 17.5% and 4.5% of patients, respectively.

Fortunately, most of such events are not an overwhelming barrier because they can be managed with further endoscopic therapy[107,112-115] when it is carried out with a regular surveillance program (3-6 mo) following the index endoscopy[3,5,32]. These relapses have been removed even with a 93% success rate for advanced colonic

adenomas up to 120 mm in size after conventional or wide-field EMR[10,17].

Thermal ablation/APC of margins at the resection site can be either an adjuvant treatment to clean suspicious margins to reduce recurrences or a subsequent therapeutic aid to eliminate the visible residual unremoved after index EMR[21,23,114,115].

Renewed endoscopic treatment of recurrences is correlated with high curative rates, low complication rates, and a low risk of malignant evolution[111,112,115].

Brooker *et al*[112] showed a decrease of 50% of early relapse of large colorectal sessile polyps after combining EMR treatment with APC. The study by Kim *et al*[111] analyzing 70 recurrent lesions after the previous p-EMR of large non-pedunculated adenomas reported that 1 patient underwent surgery for an adenoma involving the ileocecal valve and another one underwent curative surgery for a deep SMIC. The rest of the patients were successfully managed endoscopically.

Furthermore, a recent large Australian randomized multicenter study (390 patients) of tertiary centers[115] confirmed reduced adenoma recurrence rates at early follow-up in patients treated with thermal ablation of the resection margins after the EMR of large LSTs as compared to controls without additional treatment (5.2% *vs* 21.0%, respectively). Otherwise, a small cohort Polish study[114] reported similar recurrence rates for large sessile polyps treated with both p-EMR and APC than those treated with only p-EMR (14% for both groups).

ESD: Indications, efficacy, safety, and recurrences

The endoscopic eradication of colorectal preneoplastic and neoplastic lesions has continuously changed and evolved in the last decades to develop ESD[116-119], a more challenging technique[5,21,26,91,120]. The ESD method was initially developed in Japan in the early 2000s for the resection of superficial carcinomas of the upper digestive tract[121-124], whereas Western areas used ESD especially for treating colorectal lesions[4,5,21,26,91]. However, the technical difficulty, the necessity for a lengthy training of the medical/nursing team, and the higher complication rate than conventional EMR have hampered widespread adoption in Western countries[1,2,5,21].

ESD can have both a diagnostic and therapeutic intent, although due to higher rates of perforation the diagnostic intent in the colon is limited[1,2,5,21]. This procedure aims at the *en bloc* and deep removal of large non-pedunculated lesions with a high potential of malignancy. These lesions need an accurate histological assessment for the risk of lymph node metastases, and *en bloc* R0 is mandatory in these cases with high suspicion of superficial submucosal invasion[5,21,22,52].

ESD uses dedicated needles that by cutting the mucosa and submucosa can enable an almost surgical resection of lesions > 20 mm that are otherwise not radically removable or only in several fragments, providing a lower recurrence rate of the lesions[1,2,5,21].

The Japan Gastroenterological Endoscopy Society[21], European Society of Gastrointestinal Endoscopy[2], and American Society for Gastrointestinal Endoscopy [5] guidelines were endorsed to provide specific recommendations on the appropriate use of ESD. These guidelines strongly advise ESD instead of EMR in the following cases[1,2,5,21,106]: for the removal of large sessile or non-polypoid tumors (including LST G and nodular mixed types) assumed to have superficial SMIC, carcinoma with shallow T1 SMIC, depressed or irregular type tumors, LSTs (pseudo-depressed) with an NG surface pattern, Kudo Vi-type PP, when regardless of the size a lesion is radically unremovable with snare EMR, tumors with submucosal fibrosis, local residual or recurrent early carcinomas after inefficacious endoscopic resection, or non-polypoid dysplasia/sporadic tumors in patients with inflammatory bowel disease.

Some studies have documented the efficacy and safety of ESD for treating sessile or non-polypoid lesions of any size, especially in Asian countries[5,123,125].

However, ESD has been complicated by late bleeding in 2%[123], 5%[125], 5.1%, and 13%[127] and by perforation in 2.5%[123], 3.2%[126], 4%[125], 7%[125], and 18%[127] of the procedures. Recurrence occurred in 4%[125], 7%[123], 7.5%[126], and 13.8%[65] of cases.

Specifically, a systematic review by Repici *et al*[128] evaluated, among 22 studies (91% Asian), the outcomes of 2841 sessile lesions or LSTs of any diameter [median of mean size, 32.4 mm (range 6.2-43.6 mm)] following ESD treatment. The *en bloc* and R0 rates were 91.6% and 88%, respectively, and significantly higher for Asians than Europeans (88% *vs* 65%, respectively) with a good safety profile (4% and 2% of the procedures were complicated by perforation or late bleeding, respectively). Furthermore, ESD showed a relapse rate of < 0.1%, whereas the estimation of surgery for complications was 1%[128].

A retrospective Japanese study[123] analyzed 1017 ESD procedures performed for sessile or non-polypoid lesions (mean size, 38 mm). *En bloc* resection was successful in 90% while R0 in 77% of cases[123]. Perforation and delayed bleeding rates were 2.5% and 2.0%, respectively. Relapses occurred in 7.5%[123]. A small prospective study[127] evaluating ESD outcomes in a French cohort of 45 patients (treated for sessile rectal tumors or LSTs ≥ 10 mm) showed fair *en bloc* resection rates (64%) as well as low curative R0 (53%). The complication rate was high (18% for perforation and 13% for late bleeding), while 7% relapsed during surveillance[127].

Another Japanese study[126] suggested the safety of ESD for treating early CRC; among the 373 analyzed patients, 82.4% had non-polypoid lesions and 17.3% sessile lesions (sized 28.6 ± 14.2 mm). Post-procedural perforation and bleeding rates occurred in 3.2% and 5.1% of cases, respectively.

A retrospective Japanese study[93] compared EMR and ESD techniques for treating 189 large tumors (including LST-G/LST-NG, and depressed/protruded lesions). Despite the ESD group had significantly larger tumor sizes (31.6 ± 9.0 *vs* 25.5 ± 6.8 mm, $P < 0.001$), longer procedural times (87.2 ± 49.7 *vs* 29.4 ± 26.1 min, $P < 0.001$), and higher perforation cases (5.9% *vs* 0%, $P = 0.04$), there occurred higher *en bloc* resection rates (83.5% *vs* 48.1%, $P < 0.001$) and fewer recurrences (1.2% *vs* 15.4%, $P = 0.002$) than EMR. Postoperative bleedings were similar in the two groups (2.4% *vs* 2.9%, P = not significant)[93].

A systematic review[125] of 15 European studies determined the efficacy and safety of ESD for treating 1404 cases with large and complex lesions [mean size, 40 mm (range 24-59 mm)]. The *en bloc* resection rate was 83%, and the R0 rate was 70%[125]. Perforation and bleeding rates were 7% and 5%, respectively. The recurrence rate was 4% in a year of surveillance time[125].

Notably, in the presence of residual or locally recurrent lesions after previous EMR, a new variant of the ESD technique using double clip and rubber band traction has shown promising results, either for removing LSTs deeply invading appendiceal orifice[129-131] or recurrent sessile serrated adenomas invading the site of previous appendectomy[132,133]. Indeed, in a retrospective French study[129], ESD with double clip and rubber band traction of 53 residual/locally recurrent colonic lesions achieved *en bloc* and R0 resections in 92.5% and 79.2%, respectively. Intraoperative perforations and late bleeding occurred in 7.5% and 1.9%, respectively, although they were endoscopically managed. No complications requiring surgery occurred[129].

Nevertheless, following the limited ESD indications[1,2,5,21] and the greater attention on the indiscriminate use of this procedure are the results of the systematic review by Fuccio *et al*[22] published in 2018 of mixed Asian and European (51 included) studies[22]. Of the 11260 lesions treated with ESD, 82.2% were adenomas with low or high-grade dysplasia. Submucosal cancers were in 15.7% of cases, but only 8% had superficial SMIC. This percentage was reduced to 6% when the analysis was limited to oncologically curative events, with no statistically significant difference between the European and Asian studies. Therefore, most lesions could have been radically resected, even with p-EMR. This study considered even the clinical outcomes of standard ESD performed on 18764 lesions (of 97 studies). The rates of *en bloc* resection and R0 were 91% and 82%, respectively, with a 2% recurrence rate[22]. European studies, as compared to Asian ones, displayed lower R0 rates (71.3% *vs* 86.6%) and a higher incidence of adverse events. Late bleeding and perforation occurred in 4.2%/8.6% *vs* 2.4%/4.5%, respectively, thus confirming greater expertise of Eastern endoscopist[116].

Therefore, the unsolved question concerns the necessity of a reliable SMIC assessment system, able to stratify the risk of the post-procedural need for surgery after ESD. In other words, it should be capable of selecting the at-risk subgroups of patients in whom ESD could be the most suitable method. Accordingly, this narrative review aims to describe the best diagnostic strategies for predicting malignancy based on the morphologic features of colorectal non-pedunculated lesions according to current endoscopic technology, to wisely choose among EMR and ESD procedures.

Inclusion criteria

We included studies that assessed the morphological and imaging patterns predictive of SMIC of non-pedunculated colorectal lesions of any size before choosing among EMR or ESD procedures. We also included those studies comparing the two strategies, regardless of the techniques or devices employed.

Exclusion criteria

We excluded studies including colorectal lesions removed in patients with inflammatory bowel disease and those using surgery as a control group.

EMR vs ESD: Systematic reviews and meta-analyses

***En bloc* and R0:** As shown in Table 2, a systematic review and meta-analysis[134], including four retrospective studies and 243 Asiatic patients, reported a significantly higher percentage of *en bloc* resection for sessile polyps (rectal carcinoids < 15 mm) in ESD than EMR group (100% *vs* 92%, respectively) and also a higher R0 of 87.7% than 69.1% (OR = 0.29; 95%CI: 0.14–0.58; $P < 0.001$), respectively.

A meta-analysis of six case-control studies[135] of Asian populations, including 893 patients treated for sessile or flat lesions ≥ 10 mm, reported a higher *en bloc* resection rate in the ESD group than the EMR group (87.9% *vs* 44.5%, respectively; OR = 7.94; 95%CI: 3.96-15.91; $P < 0.001$). Also, the ESD and EMR groups did not significantly differ in terms of R0 resection rates [83.8% *vs* 65.5 %, respectively; OR = 1.65; 95%CI: 0.29-9.30; P = not significant].

A systematic review and meta-analysis of four retrospective studies[136] enrolled 216 patients of Asian populations endoscopically treated for rectal carcinoids of size ≥ 10 mm. A non-significant difference of *en bloc* resection (90.6% *vs* 93.6%; OR = 0.82; 95%CI: 0.25-2.70; $P = 0.74$) and R0 (79.4% and 78%; OR = 1.53; 95%CI: 0.62-3.73; $P = 0.35$) between ESD and EMR methods was shown.

Another meta-analysis of seventeen heterogeneous retrospective Chinese studies [137], evaluating the endoscopic outcomes of 2003 sessile polyps (≥ 5 mm) (mostly carcinoids), revealed a significantly higher *en bloc* resection rate (92.0% *vs* 89.8%, respectively; OR = 2.81; 95%CI: 1.39-5.70; $P = 0.004$) using ESD than EMR as well as higher R0 rates (86.5% *vs* 61.4%, respectively; OR = 2.81; 95%CI: 1.39-5.70; $P < 0.004$) for the ESD group.

Moreover, a meta-analysis of eight Japanese studies[103], including six cohort studies and two case-control series for a total of 1262 patients, compared endoscopic resection of sessile lesions of variable size and confirmed the highest percentages of *en bloc* resection (91.7% *vs* 46.7%; OR = 6.84; 95%CI: 3.30-14.18; $P < 0.001$) and R0 resection (80.3% *vs* 42.3%; OR = 4.26; 95%CI: 3.77-6.57) using ESD than EMR.

A systematic review with meta-analysis[138] related to eleven retrospective studies (eight of them evaluating sessile polyps and three of any LST ≥ 20 mm) including 4678 Asian and French patients, displayed higher rates of *en bloc* resection (89.9% *vs* 34.9%; OR = 1.93; 95%CI: 1.46-2.54; $P < 0.001$) and R0 resection (79.6% *vs* 36.2%; OR = 2.01; 95%CI: 1.76-2.29; $P < 0.001$) for ESD than EMR.

Finally, in a systematic review of 66 Western and Asian studies[107] evaluating a total of 13659 sessile polyps/LST lesions, the percentage of *en bloc* resection was 90.5% after ESD and 62.8% following EMR (OR = 0.18; 95%CI: 0.16–0.2; $P < 0.001$]. Notably, the R0 curative rate was higher after EMR (92.0% *vs* 82.1%; OR = 2.5; 95%CI: 2.2–2.7; $P < 0.001$).

Tumor size: The tumor size was larger in the ESD group as compared to EMR in the three meta-analyses of Chao *et al*[137] (mean size not specified, OR = 3.09; 95%CI: 1.54-4.63; $P < 0.001$), Fujiya *et al*[103] (mean size was reported only for three studies, OR = 7.38; 95%CI: 6.42-8.34), and Arezzo *et al*[138] (33.7 mm *vs* 27.4 mm, OR = 7.36; 95%CI: 6.27-8.45; $P < 0.001$). The size of lesions in the other three studies was similar for all groups[134-136].

Adverse events: The perforation rate was higher in the ESD group, whereas the delayed bleeding rate was similar to the EMR group in the four studies of Chao *et al* [137] (5.9% *vs* 1.5%; OR = 5.27; 95%CI: 2.75-10.08; $P < 0.001$ and 3.7% *vs* 3.3%; OR = 1.34; 95%CI: 0.81-2.20; $P = 0.25$), Fujiya *et al*[103] (8.5% *vs* 0%; OR = 4.96; 95%CI: 2.79-8.85 and 2.0% *vs* 3.5%; OR = 0.85; 95%CI: 0.45-1.60), Arezzo *et al*[138] (4.9% *vs* 0.9%; OR = 3.19; 95%CI: 2.14–4.77; $P < 0.001$ and 1.9% *vs* 2.9%; OR = 0.68; 95%CI: 0.44–1.03; $P = 0.070$), and De Ceglie *et al*[107] (4.8% *vs* 0.9%; OR = 0.19; 95%CI: 0.15–0.24; $P < 0.001$ and 2.04% *vs* 2.27%; OR = 1.1; 95%CI: 0.9–1.4; $P = 0.3$), respectively.

Moreover in the study of De Ceglie *et al*[107], there was no meaningful difference in bleeding risk for ESD and EMR procedures. Also, ESD showed similar rates of post-procedural bleeding (3.6% *vs* 8.0%) and perforation (0.7% *vs* 8.0%) than the EMR group according to Zhong *et al*[134] and similar overall complication rates as observed by Wang *et al*[136] (18.3% *vs* 10.3%; OR = 0.67; 95%CI: 0.26-1.69; $P = 0.40$) and by Wang *et al*[135] (8.9% *vs* 5.8%).

Recurrence: ESD was associated with a lower recurrence rate than EMR in the six studies of Wang *et al*[135] (0.98% *vs* 12.70%; OR = 0.09; 95%CI: 0.04-0.19), Wang *et al* [136] (0.9% *vs* 6.4%; OR = 0.15; 95%CI: 0.03-0.87; $P = 0.03$, when using the fixed-effect model), Chao *et al*[137] (1.0% *vs* 9.9%; OR = 0.14; 95%CI: 0.06-0.30; $P < 0.001$), Fujiya *et al*[103] (0.9% *vs* 12.2%; OR = 0.08; 95%CI: 0.04-0.17), Arezzo *et al*[138] (0.7% *vs* 12.7%;

Table 2 Characteristics of the seven included systematic reviews and meta-analyses on the comparison between the outcomes for endoscopic mucosal resection and endoscopic submucosal dissection procedures

Ref.	Study	Nations	N patients/lesions	Type of colorectal lesions	Lesion size	Procedural time[1]	*En bloc* resection[1]	R0[1]	Perforation[1]	Bleeding[1]	Surgery[1]	Recurrence[1]
Zhong *et al* [134], 2013	Systematic review with meta-analysis of 4 retrospective studies	Japan, Korea, China	243 patients/245 lesions (EMR: 106; ESD: 139)	Sessile (carcinoids)	< 15 mm	19.1 ± 11.1 *vs* 8.1 ± 9.4	92% *vs* 100%	69.1% *vs* 87.7%	2.8% *vs* 0.7%	2.8% *vs* 3.6%	0.7% *vs* 0%	2.9% *vs* 0%
Wang *et al* [135], 2014	Meta-analysis of 6 studies (case-control)	Japan, Korea	893 patients/1642 lesions (EMR: 866; ESD: 776)	Sessile or flat	≥ 10 mm	Range, 29.0-29.4 *vs* 87.2-108.0 min	44.5% *vs* 87.9%	65.5% *vs* 83.8%	5.8% *vs* 8.9% (overall complications)		NA	12.70% *vs* 0.98%
Wang *et al* [136], 2016	Systematic review with meta-analysis of 4 retrospective studies	Brazil, Korea, Japan, China	216 patients/216 lesions (EMR: 109; ESD: 107)	Rectal carcinoids (lesion morphology not specified)	≥ 10 mm	(150.0 ± 66.3/116.0 ± 58.5 ± 3.6/63.0 ± 54.0/50.0 ± 589.2) *vs* (133.0 ± 94.8/84.0 ± 51.2/131.0 ± 100.0/78 ± 176.7) min	93.6% *vs* 90.6%	78% *vs* 79.4%	10.3% *vs* 18.3% (overall complications)		NA	6.4% *vs* 0.9%
Chao *et al* [137], 2016	Meta-analysis of 17 studies (retrospective)	China	2003 patients/2003 lesions (EMR: 1054; ESD: 949)	Sessile: carcinoids (11 studies) or carcinomas (5 studies); LST (1 study)	≥ 5 mm	Range, 15.0-65.9 *vs* 3.5-29.4 min	89.8% *vs* 92.0%	61.4% *vs* 86.5%	1.5% *vs* 5.9 %	3.3% *vs* 3.7%	NA	9.9% *vs* 1.0%
Fujiya *et al* [103], 2015	Meta-analysis of 8 studies (non-randomized, 6 cohort and 2 case-control)	Japan	1262 patients (EMR: 634; ESD: 628)/1763 lesions (EMR: 949; ESD: 814)	Morphological features of lesions in 7 studies were[2], in the EMR group: 0-I (269 cases) and 0-II (679 cases); in the ESD group: 0-I (125 cases) and 0-II (680 cases); 576 adenomas and 380 carcinomas	≥ 20 mm (5 studies), ≥ 10 mm (1 study), > 5 mm (1 study)	Range, 29.0-30.0 *vs* 65.9-108.0 min	46.7% *vs* 91.7%	42.3% *vs* 80.3%	0% *vs* 8.5%	3.5% *vs* 2.0%	5.8% *vs* 9.9%	12.2% *vs* 0.9%
Arezzo *et al* [138], 2016	Systematic review with	Japan, Korea, France	4678 patients/4678	Sessile (LST-NG and LST-G	≥ 20 mm (except in 3	29.1 *vs* 66.5 min	34.9% *vs* 89.9%	36.2% *vs* 79.6%	0.9% *vs* 4.9%	2.9% *vs* 1.9%	3.0% *vs* 7.8%	12.7% *vs* 0.7%

	meta-analysis of 11 studies (10 retrospective and 1 case-control)		lesions (EMR: 3161; ESD: 1517)	were also included in 3 studies): adenomas, carcinomas in situ, invasive cancers or carcinoids	studies)							
De Ceglie *et al* [107], 2016	Systematic review of 66 studies (3 RCTs; 22 prospective and 41 retrospective)	Germany, Taiwan, France, Japan, Greece, Great Britain, Czech Republic, Malaysia, Australia, Italy, China, United States, Brazil, Korea, Portugal, Serbia	13659 patients (EMR: 8660; ESD: 4999)/17950 lesions (EMR: 11.873; ESD: 6077)	Sessile or LST	LST-NG ≥ 20 mm and for LST-G ≥ 30 mm or ≥ 40 mm	NA	62.8% *vs* 90.5%	92.0% *vs* 82.1%	0.9% *vs* 4.8%		2.3% *vs* 2.0%	NA	10.4% (3.0% in *en bloc* and 12% in piecemeal) *vs* 1.2%

[1]Endoscopic mucosal resection *vs* Endoscopic submucosal dissection.

[2]According to Paris classification. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection; LST: Laterally spreading tumor; NG: Non-granular type; G: Granular type; RCT: Randomized controlled trial; NA: Not available.

OR = 0.06; 95%CI: 0.03–0.11; $P < 0.001$), and De Ceglie *et al*[107] (1.2% *vs* 10.4%; OR = 8.19; 95%CI: 6.2–10.9; $P < 0.001$). Only one meta-analysis[134] showed a similar recurrence rate between ESD and EMR (0% *vs* 9%).

Surgery rates: The data for the surgical rate for any reason was available only in three studies[103,134,138].

In the meta-analysis of Zhong *et al*[134], one patient underwent surgery as rescue therapy for non-manageable recurrence after EMR and none in the ESD group (0.7% *vs* 0%, P = not significant).

In the meta-analysis of Fujiya *et al*[103], the most frequent indication for additional surgery was, for both ESD and EMR groups, non-curative reasons rather than perforation (9.9% *vs* 5.8%; OR = 2.16; 95%CI: 1.16-4.03; $P < 0.001$). This resulted from the analysis of two studies.

In the study by Arezzo *et al*[138], the overall surgery requirement for complications was higher in the ESD group (7.8% *vs* 3.0%; OR = 2.40; 95%CI: 1.51–3.82; $P < 0.001$). In detail, the rates of surgery for complications (OR = 7.21; 95%CI: 2.19–23.76; $P < 0.001$), and surgery for non-curative reasons (OR = 1.55; 95%CI: 1.03–2.33; $P < 0.034$) were 3.0% and 6.9%, respectively, in the ESD group and 0.4% and 4.1% in the EMR group.

CONCLUSION

Conclusively, it is crucial to enhance the preoperative diagnostic workup because the prevailing technology concomitantly with operator skills is still exceedingly misleading, especially in deciding the most suitable endoscopic method for radical resection of non-pedunculated colorectal lesions at risk of underlying malignancy. Admittedly, the prevailing unsolved challenge concerns the requirement for a secure SMIC estimation method to properly stratify the chance of the post-procedural necessity for surgery following ESD and proficient in determining the at-risk subgroups of patients in whom ESD could obtain the most fitting approach.

Additionally, ESD necessitates being further improved considering the excessively time-consuming as well as the intraprocedural technical hindrances and related complications, even in expert hands.

Therefore, in this time frame, it is demanded a substantial ability to choose and perform EMR when it is proper and ESD only when obliged by the highly suspected endoscopic features of colorectal lesions.

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Endo-hepatology: An emerging field

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Abstract

Gastroenterologists have long been spearheading the care of patients with various forms of liver disease. The diagnosis and management of liver disease has traditionally been a combination of clinical, laboratory, and imaging findings coupled with percutaneous and intravascular procedures with endoscopy largely limited to screening for and therapy of esophageal and gastric varices. As the applications of diagnostic and therapeutic endoscopic ultrasound (EUS) have evolved, it has found a particular niche within hepatology now coined. Here we discuss several EUS-guided procedures such as liver biopsy, shear wave elastography, direct portal pressure measurement, paracentesis, as well as EUS-guided therapies for variceal hemorrhage.

Key Words: Endoscopic ultrasound; Therapeutic endoscopic ultrasound; Hepatology; Liver disease; Liver biopsy

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Core Tip: Endo-hepatology in an emerging field which utilizes diagnostic and therapeutic endoscopic ultrasound to help gastroenterologists diagnose and manage liver disease. Our paper will focus on liver biopsy, ultrasound and shear wave elastography, ascitic fluid sampling, portal pressure measurement, management of varices, and vascular interventions.

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INTRODUCTION

Gastroenterologists have long been spearheading the care of patients with various forms of liver disease. The diagnosis and management of liver disease has traditionally been a combination of clinical, laboratory, and imaging findings coupled with percutaneous and intravascular procedures with endoscopy largely limited to screening for and therapy of esophageal and gastric varices. As the applications of diagnostic and therapeutic endoscopic ultrasound (EUS) have evolved, it has found a particular niche within hepatology now coined endo-hepatology which puts new endoscopic tools in the gastroenterologist hands[1,2]. Liver disease in pre-cirrhotic and cirrhotic populations present different challenges. Pre-cirrhotic disease requires longitudinal management to evaluate fibrosis severity and strategies to prevent progression, whereas cirrhotic liver disease presents challenges in the management of portal hypertension. Additionally, biliary and hepatic malignancy can present challenges to diagnosis and therapy that may be obviated by new techniques. Our paper will describe the role of endo-hepatology in these increasingly prevalent conditions.

LIVER BIOPSY

Liver biopsy has long been considered the gold standard to differentiate between several types of liver disease, using histological findings to distinguish between autoimmune etiologies, non-alcoholic fatty liver disease and non-alcoholic steatohepatitis, *etc.* Traditional liver biopsy involves a 16 or 18 gauge needle and a percutaneous approach. These biopsies were at one point targeted using a percussion method, however, this has been largely replaced by ultrasound (US) or computed tomography (CT) guided methods[3]. Despite imaging guidance, percutaneous liver biopsy can still lead to complications such as pain, hemorrhage, tumor-seeding, intestinal perforation, peritonitis, hemothorax or pneumothorax, bacteremia, and even death. Transjugular liver biopsy emerged as a safer alternative, particularly in patients with massive ascites, obesity, or coagulopathy[4], though this approach still carries a relatively high complication rate near 7%, including pseudoaneurysm, hemorrhage, bile leak, pneumothorax, and ventricular arrhythmia[5]. Through esophageal, gastric, and duodenal views, EUS offers exceptional detail in evaluating the biliary tract, liver, pancreas, stomach, esophagus, and mediastinal structures. Unlike conventional US or CT, EUS allows the liver to be visualized or conceptualized in a three-dimensional view, allowing the liver to be viewed through the Couinaud classification which divides the liver into eight separate functional units. Due to proximity, direct echoendoscopic visualization, and utilization of doppler ultrasound, there is increased potential for diagnostic success and a low rate of adverse events (estimated approximately 2.5%)[6] with EUS-guided liver biopsy[7]. The technique involves a linear echoendoscope which can locate either the right or left hepatic lobe. Using a fine needle biopsy (FNB) needle with a vacuum syringe, the endoscopist has the ability to biopsy either or both lobes of the liver, and allows for several actuations with a single puncture of the liver capsule[8]. This approach can also offer a simultaneous endoscopic esophageal variceal screening, or endoscopic shear wave elastography (SWE) or portal pressure gradient (PPG) measurement[9].

NON-INVASIVE MEASUREMENT OF FIBROSIS

Imaging such as SWE has proven useful as a non-invasive tool for measuring liver fibrosis with a correlation to histologically measured liver fibrosis[10]. This correlation, though, is affected by variability between the right and left lobe of the liver as transcutaneous SWE is typically performed over the right lobe of the liver[11]. Newer EUS processors have the capability to carry out SWE both in the right and left lobe of the liver, allowing for the assessment of fibrosis during endoscopy. While more invasive than traditional transcutaneous SWE, in those already undergoing endoscopic evaluation or those with a body mass index > 35 which may require a special probe to

assure accuracy, EUS-SWE appears to be both feasible and reliable[9,12]. Two-dimensional ultrasound views during EUS-SWE or EUS alone can also allow for routine hepatocellular carcinoma screening. Doing so during an EUS allows for simultaneous FNB of small or suspicious lesions which may be found during EUS evaluation[8,13].

PORTAL PRESSURE MEASUREMENT

Portal hypertension is the driving force for complications in liver fibrosis and cirrhosis. Portal venous pressure (PVP) measurement, therefore, is a key to anticipating complications. The current technique is similar to transjugular liver biopsy, during which a catheter is inserted into the jugular vein and advanced into the hepatic vein. The portal vein is not directly accessible *via* this approach, but the pressure can be estimated using wedge hepatic venous pressure (WHVP). The intravascular catheter is able to directly measure the WHVP and the free hepatic venous pressure, the difference of which is the PPG, which reflects the degree of portal hypertension (PH) and PVP[14]. In 2004, a porcine model was used to demonstrate the ability to use EUS to directly access the portal vein and measure portal venous pressure (PVP). This has been recreated in humans in a pilot study using a linear echoendoscope, a 25 gauge access needle, and a compact manometer. The portal vein and hepatic vein are able to be accessed directly, and their pressures measured *via* the manometer. PVP was able to be measured and had a high degree of correlation with clinical and endoscopic parameters of PH including thrombocytopenia, ascites, portal hypertensive gastropathy, and gastroesophageal varices[14]. Despite the significant correlation of PVP to clinical outcomes, PPG remains as the current standard for measurement and is estimated *via* the WHVP rather than direct measurement of portal vein. With additional expertise and safety outcomes data, one may yet find a role for this technology and technique in patient's where traditional techniques will be ineffective, such as those with hepatic vein clots or those who have undergone prior vascular interventions.

COMPLICATIONS OF PORTAL HYPERTENSION: ASCITES

Ascites is another common manifestation of advanced liver disease, often thought to be from an imbalance in the resorption of fluid due to elevated portal and oncotic pressure. The etiology of ascites and evidence of spontaneous bacterial peritonitis requires sampling the fluid directly. This is frequently done with a combination of imaging and abdominal paracentesis. EUS offers another modality to access ascitic fluid with higher sensitivity than CT and transabdominal ultrasound[15,16]. The ability of EUS to sample retroperitoneal and intra-abdominal collections and masses can also be applied to ascitic fluid. EUS has been previously described for use in direct sampling of fluid collections that may not be amenable to percutaneous drainage due to small volume or loculated collections[17]. EUS-guided paracentesis (EUS-P) has been shown to be technically feasible, however, the significance of risk associated with EUS-P including infection, contamination, and seeding of malignancy remains unknown. This is highlighted by the limitation that EUS-P cannot be performed in a sterile fashion as it requires puncture through the bowel lumen[18].

COMPLICATIONS OF PORTAL HYPERTENSION: VARICES AND VARICEAL HEMORRHAGE

The initial management of both bleeding and non-bleeding esophageal and gastric varices has largely been endoscopic[19]. All cirrhotic patients should undergo screening for esophageal varices after their diagnosis. The grading of varices can be quite subjective and is endoscopist dependent, taking into account diameter, location, character, and tortuosity of the vessel. In several studies, EUS has been more effective than esophagogastroduodenoscopy (EGD) in the detection of gastric and paraesophageal varices. Many of these lesions can appear as folds or submucosal lesions, but EUS allows the endoscopist to view below the mucosal surface and utilize doppler to evaluate for blood flow. The use of doppler ultrasound increases the ability to detect varices, particularly in the duodenum, and collateral vasculature. Some EUS findings

can also be used to determine the risk of variceal hemorrhage by evaluating the cumulative cross-sectional area of all distal esophageal varices, with a 76-fold increase per year with each 1 cm^2 increase in cumulative area. The utility of EUS in minimizing interobserver variability is limited by correlation with EGD and the lack of a standardized grading system for varices seen during EUS. Kane *et al*[20] applied transnasal high-resolution endoluminal ultrasound (HRES) and was able to demonstrate correlation to EGD. Furthermore, application of transnasal HRES allows examination without sedation.

Injection sclerotherapy, variceal ligation (EVL), or cyanoacrylate glue injection is usually performed relatively blindly during treatment of acute hemorrhage. EUS can allow for visualization of the lumen of the varix[21]. EVL has been the treatment of choice for esophageal variceal hemorrhage and for secondary prevention. Usually several endoscopies are required for complete variceal containment, and the most common post-procedure complication is post-EVL induced bleeding with an incidence of roughly 2.8%. This can be treated with a course of proton pump inhibitors, and further endoscopic interventions such as sclerotherapy or transjugular intrahepatic portosystemic shunt (TIPS) placement[22].

Injection of cyanoacrylate glue has been shown to have improved hemostasis and lower rebleeding rates in the treatment of gastric varices when compared to EVL[23]. This method, however, is technically more challenging and complications can be severe, including pulmonary and cerebral emboli. EUS-guided cyanoacrylate injection allows for direct visualization of the culprit vessel and confirmation of hemostasis utilizing doppler ultrasound[24]. EUS-guided microcoil embolization has been evaluated as a method of hemostasis with comparable efficacy and a decreased risk of migration or distant emboli[25]. Recently, EUS-guided deployment of coils in conjunction with cyanoacrylate injection has been demonstrated to reduce the risk of glue embolization, and can be more effective than coil embolization alone[26].

When endoscopic therapy of variceal hemorrhage is unsuccessful, interventional vascular procedures such as TIPS or balloon-occluded retrograde transvenous obliteration have been employed[22]. Recent studies using a porcine model have shown that even these predominantly surgical or endovascular procedures can also theoretically be carried out using EUS. Using an access needle, the hepatic vein is accessed, and a catheter is advanced further into an accessible branch of the portal vein. Using a lumen-apposing metal stent, the hepatic vein and portal vein are fistulized[27]. While this study was small and simply a proof-of-concept, it illustrates the future applications of EUS in the world of hepatology.

CONCLUSION

EUS-guided interventions may appear more invasive than the traditional percutaneous or intravascular procedures. However, when advantages in recovery time, diagnostic yield, and complication rates are factored in, the EUS-guided procedures may be more efficient, thus more cost-effective. This is particularly apparent considering multiple interventions can be combined into a single endoscopic procedure[8,9]. Furthermore, endoscopic screening and surveillance are commonly implemented in management of advanced liver disease, decreasing the overall risk applied by addition of EUS evaluation. More data regarding feasibility and safety is needed-particularly in regards to EUS-guided paracentesis, portal pressure measurement, and portosystemic shunting-and while endo-hepatology remains in its infancy, interventional EUS is well on its way to becoming an integral part of routine liver disease management and care.

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MINIREVIEWS

Endoscopic ultrasound-guided biliary drainage: Are we there yet?

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) is the mainstay procedure of choice for management of obstructive biliary disease. While ERCP is widely performed with high success rates, the procedure is not feasible in every patient such as cases of non-accessible papilla. In the setting of unsuccessful ERCP, endoscopic ultrasound-guided biliary drainage (EUS-BD) has become a promising alternative to surgical bypass and percutaneous biliary drainage (PTBD). A variety of different forms of EUS-BD have been described, allowing for both intrahepatic and extrahepatic approaches. Recent studies have reported high success rates utilizing EUS-BD for both transpapillary and transluminal drainage, with fewer adverse events when compared to PTBD. Advancements in novel technologies designed specifically for EUS-BD have led to increased success rates as well as improved safety profile for the procedure. The techniques of EUS-BD are yet to be fully standardized and are currently performed by highly trained advanced endoscopists. The aim of our review is to highlight the different EUS-guided interventions for achieving biliary drainage and to both assess the progress that has been made in the field as well as consider what the future may hold.

Key Words: Endoscopic ultrasound-guided biliary drainage; Endoscopic ultrasound-guided rendezvous; Endoscopic ultrasound-guided choledochoduodenostomy; Endoscopic ultrasound-guided hepaticogastrostomy; Endoscopic ultrasound-guided gallbladder drainage; Endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiopancreatography

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Core Tip: Endoscopic ultrasound-guided biliary drainage (EUS-BD) has emerged as a promising procedure for the management of obstructive biliary disease following failed endoscopic retrograde cholangiography. A number of different techniques have been described, with both intrahepatic and extrahepatic approaches. Using EUS-BD, either transpapillary or transluminal biliary decompression can be attained. Increased experience in these techniques along with introduction of novel devices and stents has led to improved outcomes when performing EUS-BD.

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INTRODUCTION

For decades, endoscopic retrograde cholangiopancreatography (ERCP) has remained the gold standard procedure for management of biliary obstruction. The success rate of this procedure in achieving deep cannulation of the desired duct ranges from 89%-92% using conventional techniques[1-3]. Advanced techniques to achieve biliary or pancreatic access have shown to improve cannulation up to 97%[4]. Common causes of ERCP failure include distortion of the ampulla secondary to malignant infiltration or periampullary diverticulum. In addition, non-accessible papilla secondary to surgically altered gastrointestinal (GI) anatomy or gastric outlet obstruction (GOO) secondary to benign or malignant diseases can also result in failure[5]. Conventionally, percutaneous transhepatic biliary drainage (PTBD) was the rescue therapy in the setting of ERCP failure. While PTBD has a high success rate, drainage complications including tube occlusion or dislodgement and cholangitis continue to be a major problem along with significantly reduced quality of life[6,7].

The use of endoscopic ultrasound (EUS) for performing cholangiopancreatography was first reported by Wiersema *et al*[8] in 1996. In 2001, Giovannini *et al*[9] first described the use of EUS for biliary drainage (EUS-BD)[9]. Since that time, a number of studies have compared EUS-BD to PTBD, finding similarly high rates of technical success, but lower rates of procedure-related complications as well as need for re-intervention with EUS-BD[10-12]. Recent meta-analyses and systematic reviews have offered the same conclusion, recommending EUS-BD over PTBD in the setting of ERCP failure due to higher rates of clinical success, fewer adverse events, and better quality of life[13,14].

The aim of this review is to describe recent advancements in EUS-BD with up-to-date techniques for achieving biliary access and drainage in patients with benign and malignant biliary obstruction where standard ERCP cannot be performed (Table 1).

EUS-GUIDED RENDEZVOUS

EUS-guided rendezvous (EUS-RV) as a salvage technique after unsuccessful ERCP was first described by Mallery *et al*[15] in 2004. This technique is used when the papilla is accessible, but deep cannulation cannot be achieved during ERCP. EUS-RV can be performed using a transhepatic or extrahepatic approach. For the transhepatic approach, the linear echoendoscope is placed in the stomach and a dilated segment II or segment III biliary branch is punctured with a 19-gauge needle. Following cholangiogram, a long (450 cm) 0.025 inch or 0.035 inch guidewire is advanced downstream into the duodenum. The extrahepatic approach involves puncture of the common bile duct (CBD) from the duodenal bulb (D1) or second portion of the duodenum (D2) followed by guidewire manipulation past the ampulla into the small bowel. Biliary cannulation is then re-attempted using a standard duodenoscope along the EUS-placed guidewire or the distal end of the guidewire is grasped with a forceps or snare and withdrawn *via* the accessory channel in the scope followed by a conventional ERCP[16].

Table 1 Endoscopic ultrasound-guided biliary drainage procedures

	EUS-BD procedures
1	EUS-guided rendezvous
2	EUS-guided choledochoduodenostomy
3	EUS-guided hepaticogastrostomy
4	EUS-guided gallbladder drainage
5	EUS-directed transgastric ERCP

EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangiopancreatography; BD: Biliary drainage.

Different standardized algorithms have been proposed, often recommending initial approach from the D2 position if possible, followed by the D1 position and eventually transhepatic (*via* the stomach) if needed[16,17]. This recommendation is based on a number of factors including distance from puncture to ampulla and direction of needle position. A transhepatic approach requires a longer path to the papilla but requires less manipulation and steering of the guidewire compared to the extrahepatic approach. A study that compared extrahepatic *vs* transhepatic approach found similar success rates (100% *vs* 94.1%)in the two groups, but higher rates of post-procedure pain (5.5% *vs* 41.7%, $P = 0.017$), longer procedure times (25.7 min *vs* 34.4 min, $P = 0.0004$) and longer duration of hospitalization (2.52 d *vs* 0.17 d; $P = 0.0015$) in the transhepatic group[18].

One advantage of a transhepatic approach is the ability to perform EUS-guided antegrade therapy (EUS-AG) in patients following failed ERCP and inaccessible papilla. The technique can be performed in patients with surgically altered GI anatomy in which conventional EUS-RV is not feasible. Similar to the steps of EUS-RV, a guidewire is placed into the biliary system and advanced through the bile duct into the duodenum. This is followed by dilation of the fistulous tract if required. Subsequent biliary interventions such as stricture dilation, stone removal and transpapillary stent placement are then performed in an antegrade fashion without switching to a duodenoscope.

Iwashita *et al*[19] performed EUS-AG stenting in 20 patients with surgically altered GI anatomy who presented with malignant biliary obstructions (MBO)[19]. Technical and clinical success was achieved in 95% (19/20) of patients. The authors observed that approaching *via* the segment II intrahepatic allowed for a straighter approach course through the papilla. In a study using EUS-AG for management of biliary stones in patients with surgically altered GI anatomy, successful stone removal was performed in 72% (21/29) patients[20]. One major limitation of EUS-AG is the difficulty of reintervention if needed. In these cases, repeat EUS-AG or EUS-hepatico-gastrostomy may need be performed.

Guidewire manipulation through the ampulla into the duodenum proves to be a difficult step in EUS-RV and is a common cause of failure. Angled tip guidewires have allowed endoscopists more maneuverability when adjusting trajectory in the biliary tree. Shearing of the guidewire has been documented as a potential complication following intense manipulation[21]. Martínez *et al*[22] reported good procedural success (80.6%) using a 22-gauge needle and 0.018 inch guidewire in cases with benign pathology and non-dilated ducts, where use of a 19-gauge needle often proves difficult [22]. More recently a steerable access system (Beacon EUS Access System; Covidien/Medtronic, Inc, Dublin, Ireland) has been designed allowing better control of the direction of wire through the biliary system. In a study by Ryou *et al*[23] using this steerable access device for EUS-BD, guidewire advancement in the intended direction was successful in 100% cases without any reported cases of wire shearing [23].

EUS-RV has been used as an alternative to precut papillotomy for achieving biliary access following ERCP failure. A retrospective study comparing precut papillotomy to EUS-RV showed higher success rate in achieving biliary access in the EUS-RV group (98.3 *vs* 90.3%, $P = 0.038$) with similar degree of adverse events in both groups (3.4% in EUS *vs* 6.9% in precut)[24]. In a later study, Lee *et al*[25] compared two groups of patients failing standard ERCP. Following failed cannulation, patients in group one underwent precut papillotomy and/or EUS-BD, while patients in group two only had precut papillotomy available. It was observed that group one patients had a significantly lower ERCP failure rate compared to group two patients (1% *vs* 3.6%).

Additionally, patients who underwent EUS-BD had higher success rates overall when compared with patients undergoing precut papillotomy alone (95.1% *vs* 75.3%)[25]. Despite these findings, precut papillotomy is often used as a first line salvage therapy in patients with failed biliary cannulation due to high success rate with experienced endoscopists, and lack of widespread availability of EUS expertise and equipment[26].

One of the limitations for EUS-RV is difficultly in advancing the guidewire through a malignant stricture and past the ampulla for performing ERCP. Given the lower success rates of EUS-RV compared to other forms of EUS-BD in malignant biliary disease, EUS-RV is preferred for managing patients with benign conditions such as choledocholithiasis and post-cholecystectomy bile leak[27].

EUS-GUIDED CHOLEDOCHODUODENOSTOMY

EUS-guided choledochoduodenostomy (EUS-CDS) is a transluminal technique that results in formation of a fistula connecting the duodenum and the dilated CBD[28]. It is commonly used in patients with distal MBO following failed cannulation.

This technique involves using a linear echoendoscope to identify the CBD from the duodenal bulb. The bile duct is then punctured using a 19-gauge needle and the needle position is confirmed by aspiration of bile and injection of contrast to perform a cholangiogram. A guidewire is then advanced through the needle towards the main biliary confluence, following which the needle is removed and the tract dilated (balloon dilators, cystotomes, needle knives, or graduated dilation catheters). Following dilation of the fistulous tract, a stent is placed across the choledochoduodenostomy site into the extrahepatic bile duct[29]. The first report on EUS-CDS was published in 2001 with placement of a 10 Fr plastic stent between the duodenum and CBD[9]. Further case reports described success with this technique, noting specific benefits including the ability to access the bile duct in a safe and stable manner, away from an obstructive tumor causing distal MBO[30,31].

Plastic stents (PS) were initially used for biliary drainage in EUS-CDS; however, high rates of complications were noted with these stents[32]. In a 2011 review on stent selection for EUS-BD, the authors observed shorter patency along with increased risk of bile leak, migration and dislocation with PS when compared with self-expanding metal stents (SEMS)[33]. Hara *et al*[34,35] conducted two clinical studies, one using PS and one fully covered (FC)-SEMS, for EUS-CDS and found a higher stent occlusion rate associated with PS (53% patients) compared to FC-SEMS (11% patients)[34,35]. Similar results were observed in a 2016 study by Khashab *et al*[36], where significantly more adverse events were seen in patients undergoing plastic stenting (42.86%) compared to patients treated with metal stents (13.08%)[36]. Uncovered SEMS (UC-SEMS) are generally avoided as the initial stent in EUS-CDS as there is not a formed tract between the bile duct and the intestine, leading to a risk of bile leak.

A prospective study of 34 patients with unresectable MBO who underwent EUS-CDS with covered metal stent reported high technical (97%) and functional success (100%)[37]. However non-tumor related recurrent biliary obstruction (RBO) was seen in 29% patients secondary to stent migration (18%), sludge/food impaction (9%) and duodenal wall impaction (3%). The median cumulative time to RBO was 11.3 mo (95%CI: 7.4–NA). Despite achieving high success rates of EUS-CDS with FC-SEMS, stent migration following placement was a worrisome complication, likely attributed to their large size, tubular shape and rigid properties[38-40]. At times, endoscopists chose to first place an UC-SEMS to decrease the likelihood of stent migration, followed by FC-SEMS placement into the existing stent to prevent bile leakage[33].

The high rate of complications observed with plastic and tubular metal stents led to the use of a novel, fully covered lumen-apposing self-expanding metal stent (LAMS) for EUS-CDS. This stent was originally designed for drainage of pancreatic fluid collections. The AXIOS LAMS (AXIOS, Boston Scientific, Marlborough, MA, United States) has bilateral flanged ends which provide anchorage across non-adherent luminal structures, thereby decreasing the risk of stent displacement, bile leak and preventing tissue ingrowth[41,42]. Further advancements were made with the introduction of the electrocautery (EC)-enhanced delivery system which merged puncture and release of the stent in a single step[43]. This system removes the need for separate needle puncture, tract dilation and multiple guidewire exchanges which in turn may reduce risk of complications as well as procedure duration. The delivery system also allows the endoscopist to release the bilateral flanges independent of one another, preventing premature deployment of the proximal flange. The stent is available in different diameters and lengths (6 mm × 8 mm, 8 mm × 8 mm, 10 mm × 10

mm, 15 mm × 10 mm, and 20 mm × 10 mm) and is delivered through a 9 Fr or 10.8 Fr catheter. For purposes of EUS-CDS, LAMS with smaller diameters (6 mm, 8 mm, or 10 mm) are preferred, though the 6 mm and 8 mm diameter stents are not currently available in the United States (Figure 1). However, these stents are expensive when compared with plastic and tubular SEMS and may result in complications secondary to inadvertent deployment of the stent by an inexperienced user.

The first successful case of EUS-CDS using LAMS was described by Itoi and Binmoeller[44] in 2014. In 2018, a prospective multicenter study evaluated the long term outcomes of using LAMS for EUS-CDS in 19 patients with unresectable MBO [45]. Successful stent placement was performed in 100% patients and clinical success was achieved in 95%. During the follow up period (median 184 d), 95% of stents remained in good position without migration. RBO was noted in five patients (26%) due to food impaction (n = 2), kinking (n = 1), tumor ingrowth (n = 1) and stent dislodgement (n = 1), with four patients requiring reintervention. The risk of stent clogging was attributed to 6mm and 8mm diameter stents used in the study with the authors speculating that a larger stent diameter may reduce this complication. In 2019, a multi-center trial evaluated 67 patients undergoing EUS-CDS with 10 mm diameter EC-LAMS[46]. The technical success rate was 95.5% while early adverse event rate was 6.3%. Clinical success (> 50% decrease in bilirubin) was 100% (40/40) in patients who followed up at four weeks, though 17.4% (7/40) later developed RBO requiring reintervention. The high clinical success observed in this study was probably influenced by limited follow-up, with 27 patients having a follow-up duration of < 4 wk. These patients were not evaluated in terms of clinical success and need for biliary re-intervention.

A systematic review and meta-analysis of thirteen studies and 572 patients who underwent EUS-CDS with PS, SEMS or LAMS showed an overall technical and clinical success rate of 91.9% and an adverse event rate of 14.5%[47]. The most common adverse events were cholangitis, bleeding, bile leak and perforation. Though a trend was observed for improved safety with LAMS over other stents, it did not reach statistical significance. The safety and efficacy of EUS-CDS using EC-LAMS was further evaluated in a subgroup meta-analysis of five studies and 201 patients demonstrating a technical success of 93.8%, clinical success rate of 95.9% and post procedure adverse events rate of 5.6%[48]. The lower rates of adverse events in more recent studies can be attributed to recent advances in EUS technology and growing experience with EUS-BD.

Despite the high technical and clinical success associated with EUS-CDS for distal MBO, the technique was generally reserved for palliative management due to concerns about potential stent inference in patients undergoing curative resection. In 2019, Fabbri *et al*[49] reported five cases of resectable distal MBO where EUS-CDS was utilized as a bridge to surgery following failed ERCP[49]. All five patients underwent successful EUS-CDS, and each subsequently underwent successful pylorus-preserving pancreaticoduodenectomy. The transduodenal LAMS did not impede surgery thereby suggesting that EUS-CDS can be performed even in patients with resectable malignancy. Additionally, in patients with both duodenal and distal biliary obstruction, a one-step procedure with successful EUS-CDS and duodenal stenting has been described[50]. In this case series, a duodenal SEMS was placed during the same procedure as EUS-CDS without need the need to switch the echoendoscope with a duodenoscope or forward viewing endoscope.

EUS-CDS provides a viable alternative for biliary drainage (after unsuccessful ERCP) in patients presenting with distal MBO. However, this procedure cannot be performed in patients with a proximal obstruction. Additionally, GOO inhibiting endoscopic access to the duodenal bulb can be a limiting factor. In such cases, an intrahepatic approach is more often feasible.

EUS-GUIDED HEPATICOGASTROSTOMY

EUS-guided hepaticogastrostomy (EUS-HGS) is a feasible treatment option in patients when transpapillary or transduodenal forms of biliary drainage are not possible. This includes patients with GOO and surgically altered GI anatomy. The technique was first described in 2003 in a patient with a partial gastrectomy with Billroth II reconstruction, in which a transgastric plastic stent was successfully placed into a dilated left intrahepatic duct[51].

With the echoendoscope positioned in the stomach, a dilated left intrahepatic bile duct (segment III) is identified and punctured with a 19-gauge fine-needle aspiration

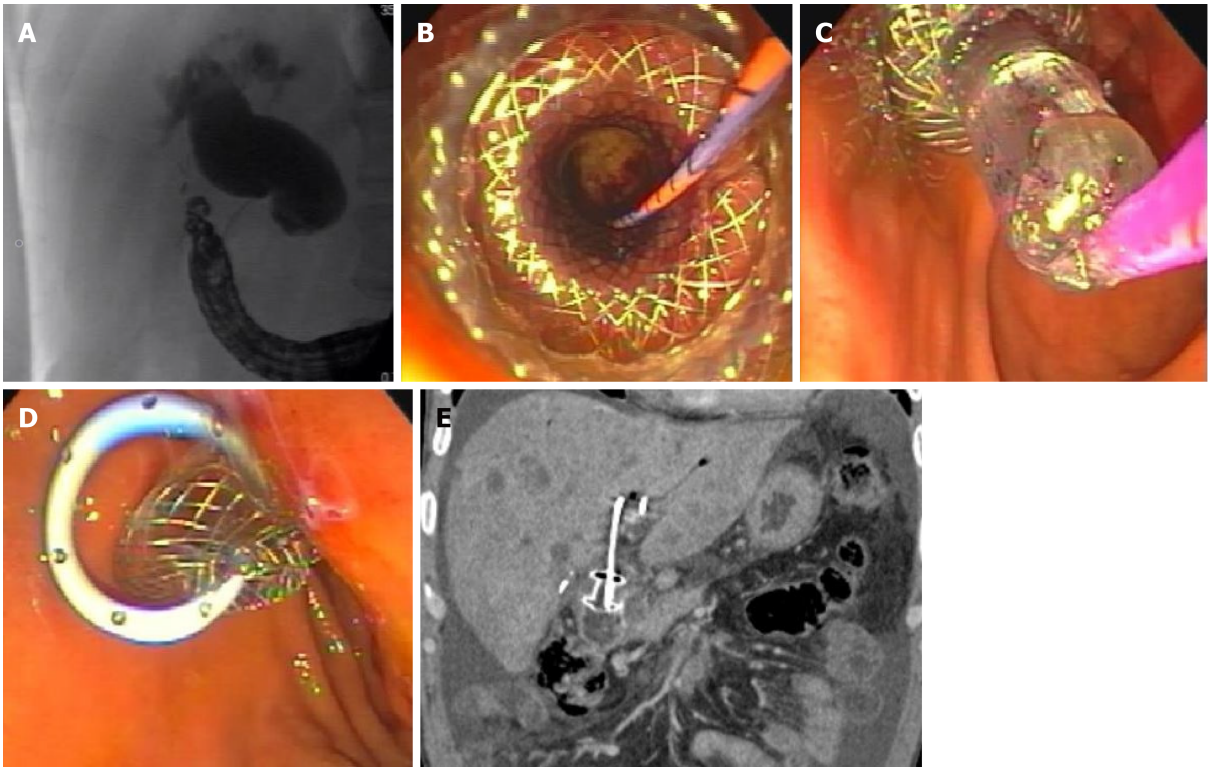

Figure 1 Endoscopic ultrasound-guided choledochoduodenostomy for distal malignant biliary obstruction using an electrocautery-enhanced lumen apposing metal stent. A: Fluoroscopic image showing a dilated bile duct with distal biliary stricture secondary to pancreas head mass; B: Endoscopic image following lumen-apposing self-expanding metal stent (LAMS) deployment in the common bile duct; C: Balloon dilation of LAMS using a wire-guided balloon; D: Endoscopic image with double pigtail stent through the LAMS in the duodenal bulb; E: Computed tomography coronal image showing choledochoduodenostomy with a double pigtail stent through the LAMS. The proximal end of the double pigtail plastic stent is in the left intrahepatic duct.

(FNA) needle. After confirmation of needle placement into the duct by aspiration of bile and cholangiogram, a guidewire is advanced downstream into the distal bile duct, followed by tract dilation and stent placement through the fistulous tract with the distal end of the stent in the intrahepatic bile duct and the proximal end in the stomach [52,53]. In 2017 Oh *et al*[54] set out to determine the ideal biliary access point for successful EUS-HGS[54]. In the study of 129 patients, technical success was achieved in 93% and functional success in 81.4%, while adverse event rate was 24.8%. From data analysis, authors concluded the intrahepatic bile duct diameter at point of puncture should be > 5 mm. Additionally, it was suggested a hepatic portion length (distance from mural wall to punctured bile duct) of 1 to £ 3 cm may facilitate successful EUS-HGS.

Despite the high technical success rates associated with this procedure, adverse events with EUS-HGS are not infrequent. These include stent migration with bile peritonitis, bleeding and pneumoperitoneum. Ogura and Higuchi[55] described increased risk of mediastinitis associated with puncture of the segment II radical from the esophagus[55]. Similar to EUS-RV, guidewire manipulation through the intrahepatic bile ducts is a difficult step of the procedure and can result in wire shearing. A "liver impaction technique" has been described in which, after the guidewire is pushed adequately into the peripheral bile duct, the FNA needle is pulled back into the hepatic parenchyma[56]. Authors noted that because the tip of the FNA needle is now within the hepatic parenchyma, shearing while manipulating the guidewire within the biliary system becomes less likely.

Numerous studies have demonstrated increased risk of bleeding with the use of non-coaxial electrocautery for tract dilation. In a prospective study by Park *et al*[57], post procedure adverse events with tract dilation using needle-knife were significantly higher when compared to graded dilation (33% *vs* 7%, $P = 0.02$)[57]. Similar results were seen by Honjo *et al*[58] when comparing dilation with ultra-tapered mechanical dilators *vs* electrocautery dilator[58] Though the procedure duration was shorter in the electrocautery group, the risk of bleeding was significantly higher. In a 2016 study by Khashab *et al*[36], coaxial and non-coaxial electrocautery for achieving tract dilation were separately analyzed, with increased risk of adverse events associated with non-coaxial electrocautery (OR 3.95, $P = 0.03$)[36].

Choice of stent for EUS-HGS plays an important role in procedural success and safety. As with EUS-CDS, PS have several disadvantages when compared to metal stents including increased risk of clogging (due to smaller diameter) as well as bile leak and bleeding (due to lack of tamponade effect)[33,36,53]. For these reasons, tubular metal stents are favored in EUS-HGS. However, stent migration following EUS-HGS is noted to be a major, and at times fatal, adverse event with the use of FC-SEMS[59,60]. One technique utilized by endoscopists to prevent stent migration is placement of a double pigtail plastic stent inside the metal stent, allowing the pigtails to function as anchors[61]. An intra-scope channel release technique has also been described to prevent this complication[62]. In this method the SEMS is released within the scope channel to minimize the stent length in the abdominal cavity. In a study directly comparing outcomes in patients undergoing EUS-HGS using either intra-scope (n = 21) or extra-scope (n = 20) channel release technique, it was observed that the intra-scope group had significantly shorter distance between the hepatic parenchyma and the stomach wall (0.66 ± 1.25 *vs* 2.52 ± 0.97, P < 0.05) following stent placement[63]. Adverse events, including stent migration, were only noted in the extra-scope channel group, and the authors concluded the intra-scope release technique was useful for prevention of stent migration. LAMS, while appropriate for use in EUS-CDS, are not suitable for transhepatic drainage.

The use of tubular FC-SEMS for EUS-HGS can result in segmental cholangitis or liver abscess secondary to obstruction of peripheral bile ducts. A prospective preliminary feasibility study by Umeda *et al*[64] in 2015 evaluated the outcomes of a newly designed 8 Fr single pigtail plastic stent for EUS-HGS[64]. The stent had a tapered distal tip, with four flanges and pigtail anchor to prevent proximal and distal stent migration. There were no apertures in the middle part of the stent, thereby decreasing risk of bile leak into the peritoneal cavity. Twenty-three cases were performed using this stent with high technical (100%) and clinical (100%) success reported. Adverse events were noted in 17.4% (comparable to conventional PS), and re-occlusion rate was 13.7% after a median follow-up of 5 mo.

In an effort to minimize the risk of bile leak following fistula dilation, Park *et al*[65] performed a randomized control trial to evaluate the feasibility and safety of a novel dedicated device for one-step EUS-BD[65]. Sixteen patients underwent EUS-BD using a dedicated stent introducer with a modified hybrid metal stent (DH group). The stent introducer (DEUS, Standard Sci Tech, Seoul, South Korea) had a 3 Fr catheter with a 4 Fr tapered metal tip for the puncture of the intestine and liver without the need for tract dilation. The outer sheath of the delivery catheter was 7 Fr. A modified hybrid metal stent with an UC proximal end and covered distal portion was preloaded into the catheter. A conventional 8.5 Fr biliary metal stent introducer with a fully covered metal stent was used in the remaining 16 patients (FC group). Though the procedure duration was significantly shorter in the DH group, the rate of adverse events between the two groups did not reach statistical significance.

In 2017 Cho *et al*[66] reported long term outcomes of a novel hybrid metal stent used to perform EUS-HGS in 21 patients[66]. This hybrid metal stent (Standard Sci Tech Inc., Seoul, South Korea) had a distal covered portion (3.5 cm in length) to prevent bile leak and a proximal UC portion (1.5 to 6.5 cm in length) to decrease the likelihood of cholangitis from intrahepatic biliary obstruction. The proximal and distal anchoring flaps on the covered portion prevented stent migration. The hybrid stents used in this study measured 8 mm or 10 mm in diameter and ranged from 5 cm to 10 cm in length. High technical (100%) and clinical (85.7%) success was reported, with an early adverse event rate of 19%. Stent migration was not observed in the follow-up period, though stent occlusion requiring reintervention occurred in 10 (47.6%) patients after a median of 53.5 d. A retrospective study of 110 patients who underwent EUS-HGS with a long, partially covered (30% UC, 70% covered) metal stent was published by Nakai *el al*[67] in 2020[67]. The authors reported high technical (100%) and functional (94%) success with no reported cases of stent migration. However, 33% of patients eventually suffered RBO requiring re-intervention due to the hyperplastic ingrowth of the UC flange. In this study a shorter stent was associated with shorter time until RBO, and the authors recommended a 10 cm or longer metal stent to prolong stent patency.

In 2015 Ogura *et al*[68] performed a retrospective study to examine potential predictors of stent patency[68]. EUS-HGS using a metal stent (of varying lengths) was performed in 51 patients, with each patient undergoing computed tomography imaging the following day to measure the stent length in the stomach. It was noted that patients with intraluminal stent length < 3 cm had a shorter stent patency compared to patients in whom the stent length was > 3 cm (mean 52 d in < 3 cm *vs* mean 195 d in > 3 cm). In an effort to prolong stent patency, some endoscopists have utilized a technique combining EUS-HGS with EUS-AG stent placement[69]. Imai *et al*

[70] performed a retrospective study comparing outcomes in patients with MBO treated with EUS-HGS alone (Group A, *n* = 42) versus combined EUS-HGS and EUS-AG (Group B, *n* = 37)[70]. Technical success was higher in Group A (97.6% *vs* 83.8%) while clinical success was equal in both groups (90.2% *vs* 90.3%). Though there were no significant differences noted in duration of stent patency and number of reinterventions between the two groups, group A patients had a higher rate of adverse events (26.1 *vs* 10.8%, *P* = 0.03). Of note, bile leak was noted in seven patients in group A, and only one patient in group B.

In addition to achieving biliary drainage in the setting of MBO, EUS-HGS can also be used to manage benign biliary diseases (such as choledocholithiasis, hepatolithiasis and biliary stricture) in patients with inaccessible papilla[71,72] (Figure 2). In 2018 James *et al*[73] performed a retrospective review of 20 patients with surgically altered GI anatomy who underwent EUS-hepaticoenterostomy (EUS-HE) for management for benign biliary disease[73]. Indications included CBD stones (*n* = 8), biliary stricture (*n* = 11) and bile leak (*n* = 1). Technical success was achieved in 100% patients, with 90% (18/20) then undergoing antegrade biliary therapy for stone clearance or treatment of biliary stricture. Patients underwent a mean of 2.7 procedures until resolution of their condition, with successful removal of the EUS-HE stent in 17/20 patients after a mean of 91 d.

A complete hilar biliary obstruction (HBO) presents a limitation for EUS-HGS, as drainage from the left intrahepatic duct does not necessarily relieve a right sided obstruction. In 2013 Park *et al*[74] described a technique of direct puncture of the right hepatic duct from the bulb of the duodenum with transluminal stent placement, forming a hepaticoduodenostomy[74]. Ogura *et al*[75] reported success using a novel "bridge" technique which involves placement of a stent across the HBO, thus connecting the right and left intrahepatic, followed by EUS-HGS[75]. Both techniques are challenging and only a small number of cases performed in referral centers have been reported to date[76]. In addition, EUS-HGS may be contraindicated in patients with large abdominal ascites (preventing fistula formation with increased risk of stent migration) and unresectable gastric cancer.

EUS-CDS *VS* EUS-HGS

EUS-CDS and EUS-HGS are both effective in management of biliary obstruction following ERCP failure. EUS-HGS however, may be associated with a slightly higher rate of adverse events, likely due to a number of factors including the precise puncture of smaller caliber intrahepatic bile ducts through the liver parenchyma as well as increased risk of pneumoperitoneum and bile leakage in the peritoneal cavity.

A retrospective study directly comparing EUS-CDS and EUS-HGS in 121 patients (60 CDS and 61 HGS) showed a high technical (93.3% CDS and 91.8% HGS) and clinical (85.5% CDS and 82.1% HGS) success with both techniques, with a similar rate of adverse events (13.3% CDS *vs* 19.67% HGS, *P* = 0.37) in both groups[36]. The stent patency duration between the two groups was not statistically significant (*P* = 0.228). Similar results were seen in a meta-analysis of 434 patients (208 HGS and 226 CDS) with comparable technical success (93.7% HGS and 94.1 CDS), clinical success (84.5% HGS and 88.5% CDS) and adverse events (OR = 0.97, 95%CI: 0.60-1.56) in both groups [77]. However, in a separate meta-analysis of 686 patients (283 CDS and 403 HGS) adverse events were noted to be significantly higher in the EUS-HGS group (29% HGS and 20% CDS, *P* = 0.01)[78].

In the end, the choice between EUS-CDS or EUS-HGS often comes down to a patient-by-patient basis, with a decision based on patient anatomy, site of obstructing lesion, operator expertise and location of biliary dilation. EUS-CDS is most suitable in patients with distal MBO. However, it is not feasible in patients with proximal MBO. EUS-HGS can be utilized in such patients, as well as those with surgically altered GI anatomy. Nevertheless, if intrahepatic ductal dilation is not present, EUS-HGS is not a practical option.

EUS-GUIDED GALLBLADDER DRAINAGE

EUS-guided gallbladder drainage (EUS-GBD) allows for direct internal decompression of the gallbladder in patients presenting with acute cholecystitis who are poor surgical candidates. The technique was first described by Baron and Topazian[79] in 2007. Since then, numerous studies have demonstrated success with this technique using

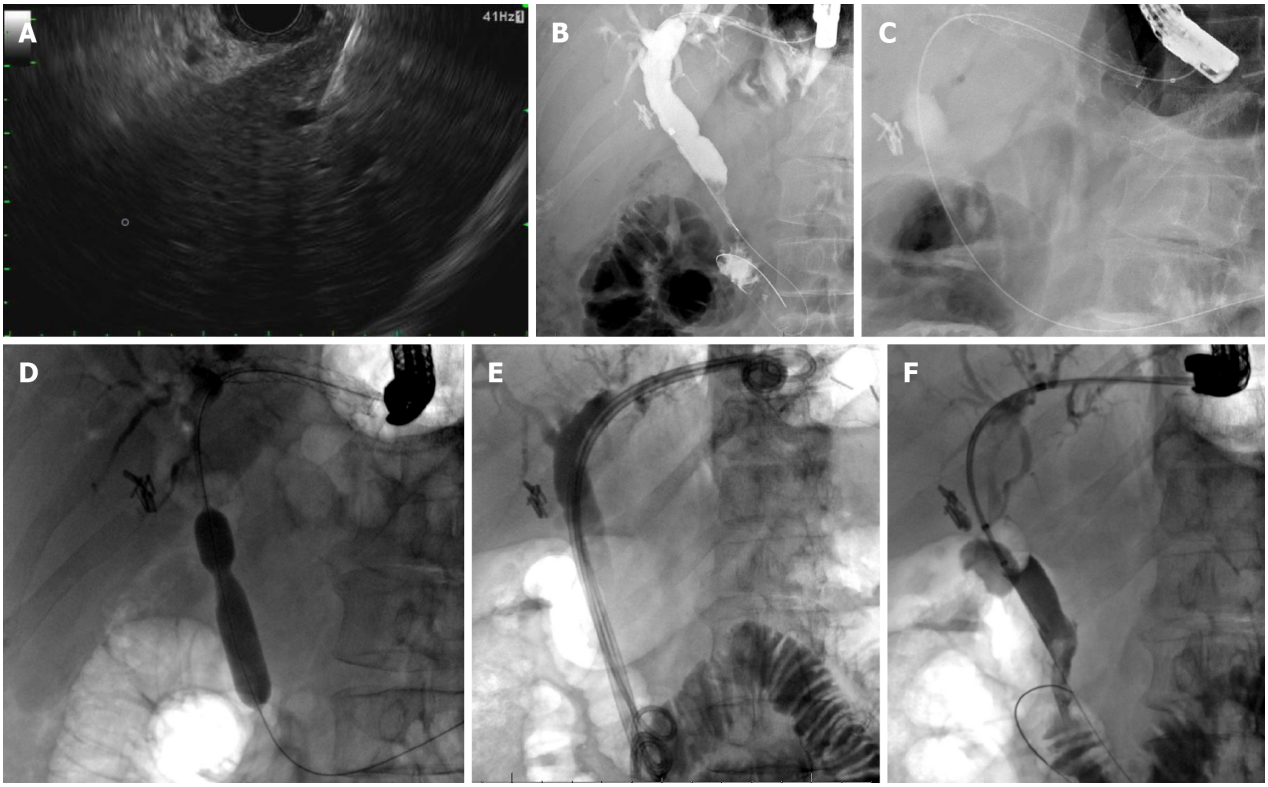

Figure 2 Endoscopic ultrasound-guided hepaticogastrostomy for benign distal biliary stricture in a patient with history of roux-en-Y gastric bypass surgery. A: Endoscopic ultrasound-guided puncture of a dilated B3 radical with a 19-gauge needle; B: Fluoroscopic image showing a dilated bile duct with distal biliary stricture; C: Fluoroscopic image showing placement of a fully covered hepaticogastrostomy metal stent; D: Antegrade balloon dilation of the distal bile duct stricture using a wire-guided balloon; E: Successful placement of four 7 Fr × 18 cm double pigtail biliary stents with the distal end past the ampulla in the small bowel and the proximal end in the stomach; F: Occlusion cholangiogram following removal of plastic hepaticogastrostomy stents showing resolution of distal bile duct stricture with free flow of contrast into the small bowel.

both transgastric and transduodenal approaches[80,81].

In 2013, Itoi *et al*[82] performed EUS-GBD using LAMS for management of obstructive jaundice secondary to distal MBO[82]. Following this, Imai *et al*[83] published a case series of 12 patients with unresectable distal MBO who underwent EUS-GBD following failed ERCP with high technical (100%) and functional (91.7%) success[83]. Adverse events were noted in 16.7% patients, with stent dysfunction occurring in 8%. A recent multicenter retrospective study of 28 patients undergoing EUS-GBD for distal MBO reported similar high technical (100%) and clinical (93%) success rates[84]. Delayed adverse events requiring reintervention occurred in 17.9% (5/28) patients. These included three patients with food impaction leading to acute cholecystitis and two patients with delayed bleeding. No perforation or stent migration was observed in this study.

In summary, EUS-GBD can be utilized in management of patients with distal MBO when standard ERCP and other forms of EUS-BD (EUS-CDS, EUS-HGS and EUS-RV) are not technically feasible. Cystic duct patency should always be evaluated prior to performing this procedure for biliary drainage. The biliary obstruction should be distal to the cystic duct takeoff to allow for proper biliary decompression[85] (Figure 3).

EUS-DIRECTED TRANSGASTRIC ERCP

EUS-directed transgastric ERCP (EDGE) is a valuable alternative to enteroscopy-assisted ERCP (e-ERCP) and laparoscopy-assisted ERCP (LA-ERCP) in patients with roux-en-Y gastric bypass (RYGB) anatomy requiring pancreatobiliary intervention. Under EUS guidance, the excluded stomach can be identified from the remnant gastric pouch or jejunum. Following puncture with a 19-gauge needle, a guidewire is advanced in the excluded stomach, followed by LAMS placement over the guidewire to create a gastrogastric or jejunogastric fistula. A duodenoscope is then passed through the LAMS and advanced to the major papilla to perform standard ERCP.

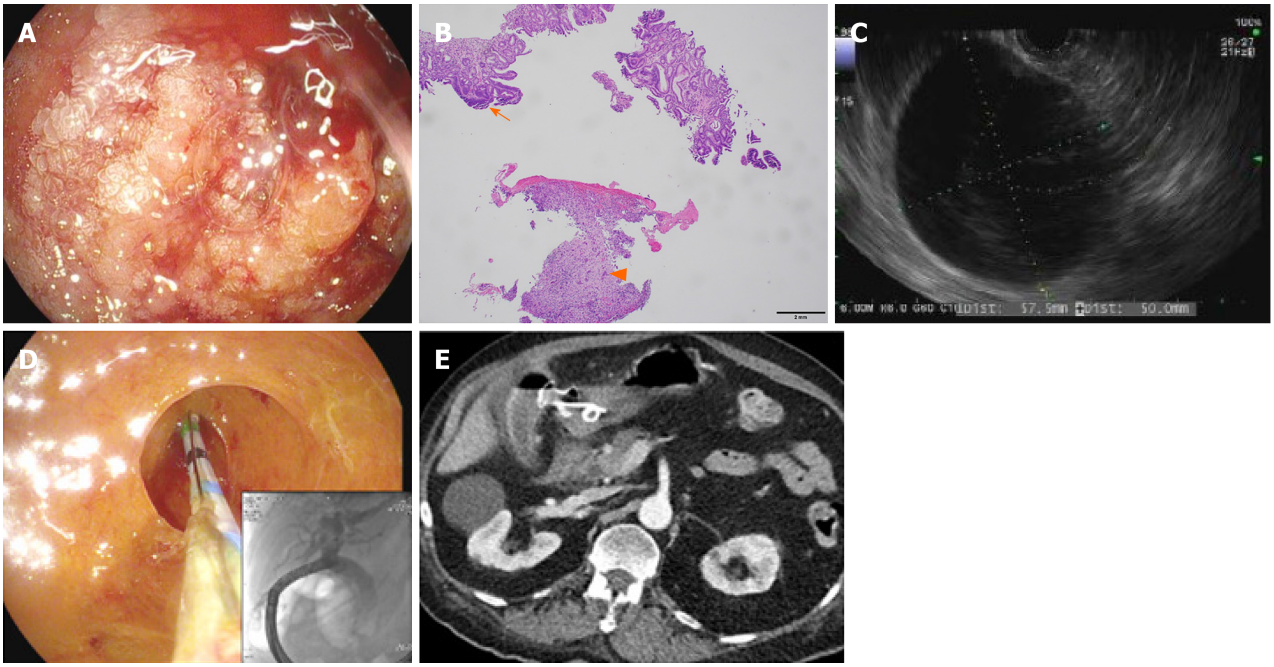

Figure 3 Endoscopic ultrasound-guided gallbladder drainage for distal malignant biliary obstruction secondary to duodenal adenocarcinoma using an electrocautery-enhanced lumen apposing metal stent. A: Duodenal adenocarcinoma involving the duodenal sweep causing luminal narrowing; B: Adenocarcinoma (arrow heads) arising in a background of adenoma (arrow) with focal high-grade dysplasia (H&E stain); C: Endoscopic ultrasound image displaying distended gallbladder; D: Cholecystoscopy [post lumen-apposing self-expanding metal stent (LAMS) placement] with contrast injection *via* cystic duct opening opacifying the biliary tree showing a patent cystic duct; E: Post-procedural computed tomography scan displaying double pigtail stent and LAMS in place between gastric antrum and gallbladder.

Intervention can be performed during the index procedure or in a subsequent session. Once access to the duodenum and papilla is no longer required, the LAMS can be removed, and fistula closed using argon plasma coagulation, endoscopic clips, or endoscopic sutures (Figure 4).

The EDGE procedure was first described by Kedia *el al*[86] in 2014[86]. In 2017, a multicenter study on 16 patients undergoing EDGE procedure reported a high technical (100%) and clinical (91%) success, with stent dislodgement occurring in 19% patients[87]. A recent multicenter retrospective study by Runge *et al*[88] reported long-term outcomes in 178 patients following EDGE procedure[88]. Technical success was achieved in 98% cases with adverse events occurring in 28 (15.7%) patients. The most common adverse events noted were LAMS misdeployment or migration (n = 13) and perforation (n = 6). Follow up endoscopy or upper GI imaging was completed in 90 patients (following stent removal) with nine patients (10%) showing persistent fistula. Fistula closure was successful in all five patients who then returned for follow up.

A 2018 study by Bukhari *et al*[89] compared outcomes of EDGE *vs* e-ERCP[89]. Technical success was higher in patients undergoing EDGE procedure (100% EDGE *vs* 60% e-ERCP) with a significantly shorter procedure time noted in this group (49.8 min EDGE *vs* 90.7 min e-ERCP, $P < 0.001$). Adverse events were similar in both groups. Outcomes of EDGE and LA-ERCP were compared in a 2019 study by Kedia *et al*[90] with similar success rates (96.5% EDGE and 97.7% LA-ERCP) and adverse events (24% EDGE and 19% LA-ERCP) in both groups[90]. However, shorter procedure times ($P < 0.00001$) and lengths of hospital stay ($P < 0.00008$) were noted in the EDGE group.

LAMS dislodgement during ERCP is a major adverse event which can result in perforation if the fistula tract has not yet matured. To avoid this, some endoscopists recommend performing EDGE in two steps, allowing fistula maturation following LAMS placement prior to performing ERCP[89]. Alternatively, a single-stage EDGE can be performed by securing LAMS with an endoscopic stitch or over-the-scope clip [91]. Persistent fistula between the gastric remnant and excluded stomach and subsequent weight gain is a worrisome complication of the EDGE procedure. However, most major studies have not shown any significant weight gain associated with the procedure[88-90]. Given the reported safety profile and high success rate of the EDGE procedure, it can be used as a first line therapy in RYGB patients requiring biliary interventions.

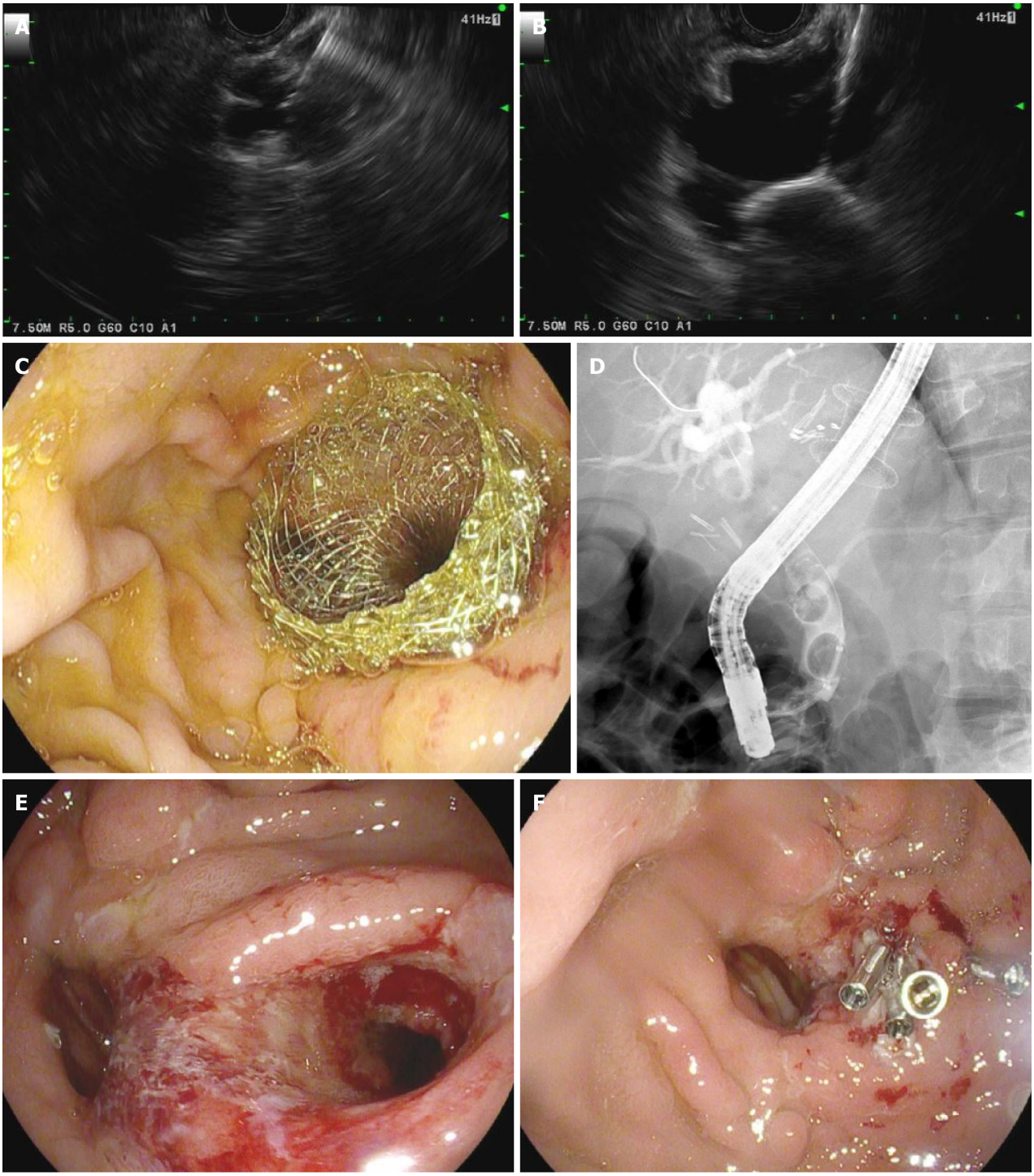

Figure 4 Endoscopic ultrasound-directed transgastric endoscopic retrograde cholangiography for choledocholithiasis in a patient with history of roux-en-Y gastric bypass surgery. A: Endoscopic ultrasound-guided puncture of excluded stomach using a 19-gauge needle; B: Endoscopic ultrasound showing deployment of proximal flange of lumen-apposing self-expanding metal stent (LAMS) in the excluded stomach; C: Endoscopic image showing distal flange of LAMS in the gastric pouch; D: Fluoroscopic image of endoscopic retrograde cholangiopancreatography through LAMS showing multiple stones in the common bile duct; E: Gastrogastric fistula seen following LAMS removal; F: Successful closure of gastrogastric fistula using argon plasma coagulation and clips.

CONCLUSION

Over the past two decades, EUS-BD has continued to evolve and is more frequently utilized in managing patients with benign and malignant biliary diseases at tertiary care centers with EUS expertise (Figure 5). The procedure has a high success rate and fewer complications than other forms of biliary drainage including PTBD and surgical bypass, making it a preferred alternative following failed ERCP. However, a significant learning curve is associated with this procedure, with literature suggesting experienced endoscopists requiring over 30 cases to become efficient and nearly 100

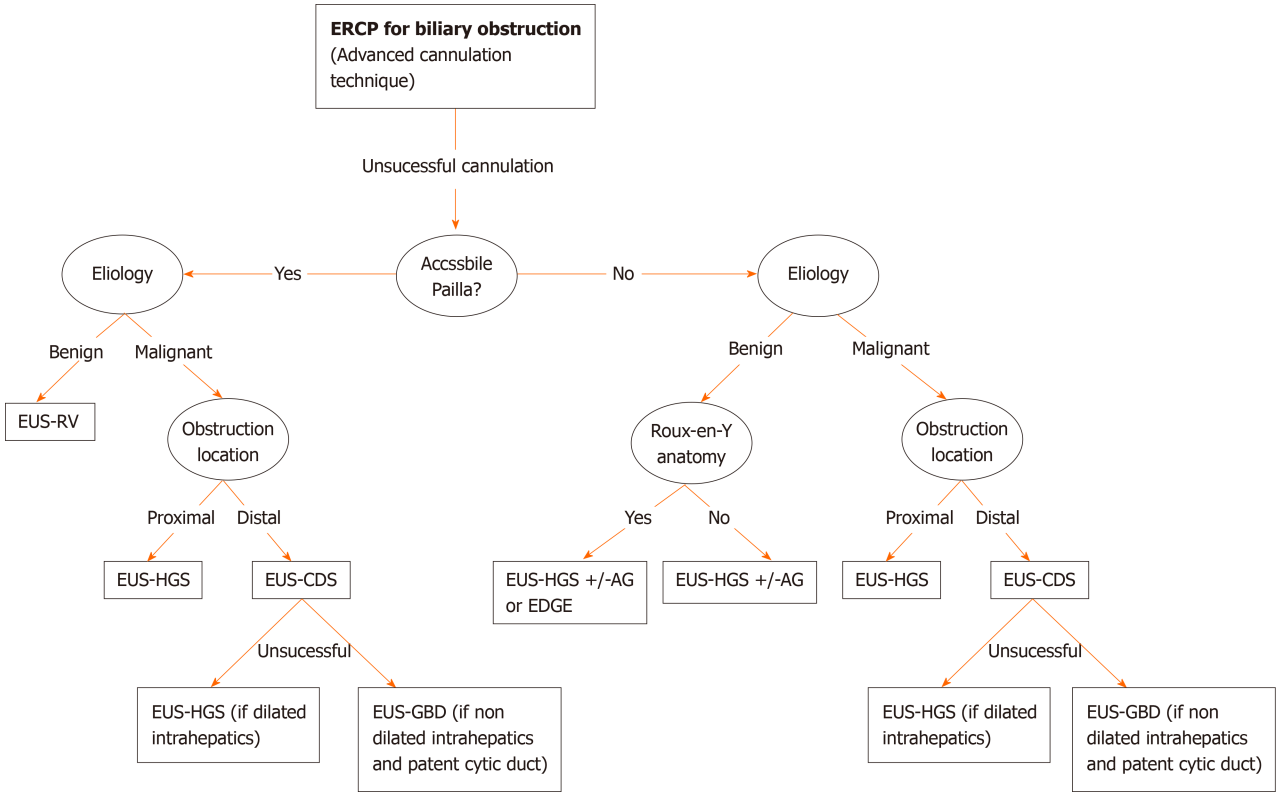

Figure 5 Proposed algorithm for endoscopic ultrasound-guided biliary drainage for biliary obstruction following failed endoscopic retrograde cholangiopancreatography. EUS: Endoscopic ultrasound; HGS: Hepaticogastrostomy; CDS: Choledochoduodenostomy; ERCP: Endoscopic retrograde cholangiopancreatography; EDGE: EUS-directed transgastric ERCP; GBD: Gallbladder drainage; RV: Rendezvous.

cases before mastering these techniques[92]. In addition, there is insufficient evidence on the route of choice, and patients with biliary obstruction should be evaluated on a case-by-case basis by an experienced therapeutic endoscopist backed by a multidisciplinary team. The development of novel LAMS has led to improved outcomes in patients undergoing EUS-CDS. Further innovations in the development of EUS-BD specific tools coupled with standardization of techniques will likely lead to improved safety. Future prospective clinical trials are needed to better evaluate outcomes and further advance this rapidly evolving field of interventional EUS.

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ORIGINAL ARTICLE

Retrospective Study

Thoracoscopic esophagectomy is related to better outcomes in early adenocarcinoma of esophagogastric junction tumors

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Institutional review board statement: This is a retrospective review performed at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo and Instituto do Câncer do Estado de São Paulo (ICESP). As this is a retrospective analysis, the Ethics committee of both institutions exempted the need for approval.

Informed consent statement:

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Abstract

BACKGROUND

Thoracoscopic esophagectomy is related to an extended lymphadenectomy, and a high number of retrieved lymph nodes, compared to the transhiatal approach; however, its association with an improvement in overall survival (OS) is debatable.

AIM

To compare thoracoscopic esophagectomy with transhiatal esophagectomy in patients with adenocarcinoma of the esophagogastric junction (AEGJ) in terms of survival, number of lymph nodes, and complications.

METHODS

In total, 147 patients with AEGJ were selected retrospectively from 2002 to 2019, and divided into Group A for thoracoscopic esophagectomy, and group B for transhiatal esophagectomy. OS, disease-free survival, postoperative complications, and number of nodes, were similarly evaluated.

RESULTS

One hundred and thirty (88%) were male; the mean age was 64 years. Group A had a mean age of 61.1 years and group B 65.7 years (P = 0.009). Concerning the extent of lymphadenectomy, group A showed a higher number of retrieved lymph nodes (mean of 31.89 ± 8.2 *vs* 20.73 ± 7; P < 0.001), with more perioperative complications, such as hoarseness, surgical site infections, and respiratory complications. Although both groups had similar OS rates, subgroup analysis showed better survival of transthoracic esophagectomy in patients with earlier diseases.

Informed written consent was obtained from the patient for publication of this report and any accompanying images.

Conflict-of-interest statement: All authors deny any conflict of interest.

Data sharing statement: Consent was not obtained but the presented data are anonymized and risk of identification is low.

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CONCLUSION

Both methods are safe, having similar morbidity and mortality rates. Transthoracic thoracoscopic esophagectomy allows a more extensive resection of the lymph nodes and may have better oncological outcomes during earlier stages of the disease. Prospective studies are warranted to better evaluate these findings.

Key Words: Adenocarcinoma; Esophagogastric junction; Transhiatal; Thoracoscopic; Lymph nodes; Surgery

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Core Tip: The type of access during esophagectomy to adenocarcinoma of esophagogastric junction tumor is on debate. Thoracoscopic esophagectomy produces higher numbers of retrieved lymph nodes than transhiatal esophagectomy but is associated with more perioperative complications. The relationship between lymphadenectomy's extension and survival outcomes is debatable. We compared both access and found better survival in early staging of patients treated by thoracoscopic esophagectomy, probably due to the extension of lymphadenectomy and acceptable complication rate. These findings reveal a new place of thoracoscopic esophagectomy for adenocarcinoma of the esophagogastric junction tumor in the multimodal era.

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INTRODUCTION

Esophageal cancer is one of the most lethal neoplasms worldwide (with about 17000 new cases per year), and the sixth leading cause of cancer deaths (286000 deaths per year)[1]. The most frequent histologic type of esophageal neoplasm is squamous cell carcinoma, responsible for 76% of cases, followed by adenocarcinoma[2] in Eastern countries. In our institution, adenocarcinoma increased from 15% to 32.5% over the last thirteen years[3]. In the same way, the prevalence of adenocarcinoma of the esophagogastric junction (AEGJ) is rising in Western countries, mostly due to the higher prevalence of risk factors such as obesity[4].

The topographic distribution of metastatic lymph nodes of AEGJ varies according to the Siewert classification. In Siewert type I, the main lymphatic drainages are predominantly in the middle and lower mediastinum; in type II, in the lower mediastinum, thoracoabdominal transition, and abdominal part; and in type III, almost entirely abdominal[5]. Regarding surgical treatment, Siewert type II leads the indication for the transhiatal approach, and Siewert type I leads for the transthoracic approach[6,7]. Despite controversy over access to esophagectomy, transthoracic access is preferred by several Western surgeons[8-10], partly because most advocate an infracarinal lymphadenectomy[11]. However, the addition of minimally invasive techniques, associated with a lower number of postoperative complications and morbidity rates, makes transthoracic esophagectomy by thoracoscopy one of the main options. Yet, extensive radical resection has not shown better survival than transhiatal en bloc esophagectomy with extended lymphadenectomy[12]. Some studies find that the extremely invasive procedure leads to an increase in morbidity and mortality[13,14], which might interfere with overall survival (OS).

This study aimed to analyze the results of AEGJ surgical treatment, comparing transhiatal esophagectomy and transthoracic esophagectomy access by thoracoscopy, including outcomes such as complications and mortality rates, and extension of lymphadenectomy as represented by the number of resected lymph nodes.

MATERIALS AND METHODS

This is a retrospective study following the STROBE Statement Checklist analysing patients with a histological diagnosis of AEGJ, Siewert I and II types, who underwent surgical treatment [transthoracic esophagectomy by thoracoscopy (group A) (Figure 1A) and transhiatal esophagectomy (group B) (Figure 1B)] between 2002 and 2019 at Hospital das Clínicas da Faculdade de Medicina da Universidade de São Paulo and Instituto do Câncer do Estado de São Paulo. As this is a retrospective analysis, the Ethics committee of both institutions exempted the need for approval.

The following epidemiological data were analyzed and compared between group A and B: age, gender, body mass index, preoperative functional assessment by the Zubrod scale (Eastern Cooperative Oncology Group), and a relevant personal medical history (diabetes, cardiovascular disease, *etc.*).

Surgical treatment

Transhiatal esophagectomy: This procedure involves a dissection of the combined cervical and abdominal esophagus without opening the thorax. Improved by Pinotti [15], with transection of the diaphragm, it allowed dissection under direct view of almost the entire mediastinum, thereby avoiding the inconvenience of blunt dissection of the esophagus.

After opening the diaphragm, the infracarinal lymphadenectomy is performed around the bilateral pleural, added to resection of lymph nodes around the hepatic artery, left gastric artery and vein, and the celiac trunk. In the abdominal section, the stomach is released in the great curvature, preserving the arch from the gastroepiploic vessels. The stomach is transposed into the cervical region through the posterior mediastinum, with cervical gastroplasty performed (preparation of the isoperistaltic gastric tube) with linear staplers and oversuturing.

Transthoracic thoracoscopic esophagectomy: After selective intubation of the left bronchus, the patient is placed in a prone position, along with five trocars. The first one at 12 mm is introduced at the inferior limit of the right scapula. The other four trocars are positioned under direct visualization (after positive intrathoracic insufflation of 8 mmHg of CO_2).

Three other trocars (two 10 mm and one 5 mm) are arranged with the first in a semicircular line from the medial border of the scapula to the posterior right costal border. Finally, the fifth trocar is positioned at the midpoint of this line, next to the spine.

Dissection of the esophagus is performed from the lower to upper mediastinum. Extensive lymphadenectomy takes place: periesophageal, periaortic, supradiaphragmatic, and pericardial lymph nodes are dissected. The right and left infracarinal lymph nodes are resected, which exposes the right and left bronchi to their origin in the carina.

In order to facilitate esophageal mobilization and the lymphadenectomy, the azygos vein is ligated and transected (preferentially with a laparoscopic stapler).

After dissection, the right pleural space is drained, and the trocars are withdrawn. The patient is placed supine in order to proceed with the abdominal part (which occurs similarly to that described in the open transhiatal esophagectomy).

Outcomes

The main outcomes of this study include resected lymph nodes, complications and deaths. Once the surgical specimen is removed, the lymph nodes are immediately dissected by the surgeon and separated based on lymph node stations. This material is sent for anatomopathological study (N), together with the surgical specimen, each in formaldehyde. The resected lymph nodes (LDs) for patients in groups A and B were compared. The lymph nodes affected (LA) and the status of the dissected and affected (LD/LA) in each group were evaluated. Postoperative complications analyzed include cervical fistulae, chylothorax, respiratory disorders (pneumonia, atelectasis, pleural effusions, and respiratory failure), hoarseness (paralysis or paresis of vocal cords), and infection (mediastinal collections and abscesses).

Statistical analysis

Data were reported as number (%) or mean ± SD. Categorical variables were compared using Pearson's chi-squared test or Fisher's exact test, and continuous variables were compared using Student's *t*-test. Survival outcomes were compared using the Kaplan-Meier method and the log-rank test. The Cox proportional hazards model was used to identify relevant prognostic factors, with significant covariables from the univariate

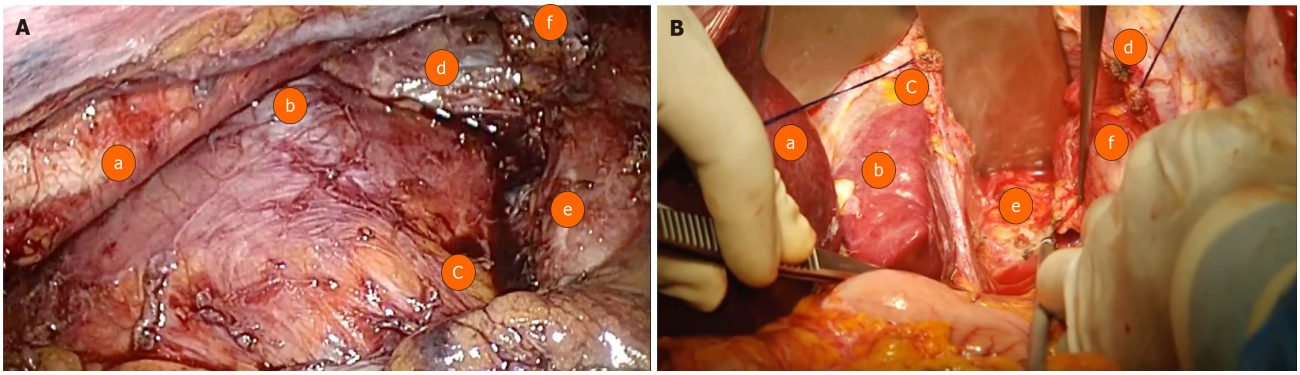

Figure 1 Esophagectomy approaches for patients with esophagogastric junction adenocarcinoma. A: Final mediastinal aspect after esophagectomy with lymphadenectomy by thoracoscopic transthoracic esophagectomy technique for patients with esophagogastric junction adenocarcinoma (a: Thoracic aorta; b: Left pulmonary vein; c: Right pulmonary vein; d: Left bronchi's; e: Right bronchus; and f: Azygous vein); B: Final mediastinal aspect after esophagectomy with lymphadenectomy by transhiatal esophagectomy technique for patients with esophagogastric junction adenocarcinoma (a: Left hepatic lobe; b: Caudate hepatic lobe; c: Right diaphragmatic pilar; d: Left diaphragmatic pilar; e: Thoracic aorta; and f: Distal esophagus).

analyses selected for the multivariate model. The results were reported as hazard ratios and 95%CIs. Differences were considered statistically significant at *P*-values of < 0.05, and all analyses were performed using IBM SPSS software (version 20, IBM Corp., Armonk, NY, United States).

RESULTS

Fifty-four patients underwent transthoracic esophagectomy by thoracoscopy (group A) and 93 transhiatal approach (group B). Forty-seven patients from group A (87.0%) and forty-three patients from group B (46.2%) received neoadjuvant treatment (chemotherapy associated with radiotherapy as needed).

Epidemiological data are shown in Table 1. Age was higher in patients undergoing transhiatal esophagectomy ($P = 0.009$); however, the other parameters analyzed were similar.

Complications and mortality

The absolute number of respiratory complications was higher in patients undergoing thoracoscopy esophagectomy, although no significant difference was observed between groups A and B. The most frequent respiratory complications involved segmental atelectasis. One patient experienced a residual pneumothorax, probably related to low flow of the peripheral air fistula.

Temporary paralysis of vocal cords, translated by hoarseness and surgical site infections, were more frequent in group A (both with $P = 0.017$).

Most infectious complications were related to atelectasis, complicated by bronchopneumonia (with diagnosis made through radiological findings, laboratory tests, and clinical evaluation).

Mortality within days was similar between the two groups. In group A, one death was reported due to cervical fistula with drainage to the mediastinum, while another was due to acute myocardial infarction. In group B, two deaths were related to cardiogenic shock. One patient died of massive bronchoaspiration, and one due to a fistula to the mediastinum.

Table 2 shows the main complications and mortality observed for the total number of patients in both groups.

Resected lymph nodes

In group A, 15 to 73 lymph nodes were resected (mean 31.89 + 8.2) and 1 to 25 Lymph nodes were affected (mean 3.96 + 1.7). In Group B, 14 to 48 Lymph nodes were resected (mean 20.73 + 7); 1 to 14 Lymph nodes were affected (mean 4.25 + 1).

The number of resected lymph nodes in group A was higher ($P < 0.001$). There was no difference in the number of lymph nodes affected ($P = 0.721$) or the DL/AL ratio in both groups ($P = 0.666$). The data regarding resected lymph nodes are summarized in Table 3.

Table 1 Epidemiological characteristics of the total number of patients with adenocarcinoma of the esophagogastric junction by type of operation

Characteristics		Group		Total	*P* value
		Thoracoscopygroup A	Transhiatalgroup B		
		n = 54, *n* (%)	*n* = 93, *n* (%)	*n* = 147, *n* (%)	
Gender	Female	6 (11.1)	11 (11.8)	17 (11.6)	0.896[1]
	Male	48 (88.9)	82 (88.2)	130 (88.4)	
Age (yr)	mean ± SD	61.11 ± 9.03	65.72 ± 10.73	64.03 ± 10.35	0.009[2]
	Mean (vmin-vmax)	62.50 (37-84)	65.00 (36-94)	64.00 (36-94)	
BMI class	BMI < 25 kg/m^2	46 (85.2)	78 (83.9)	124 (84.4)	0.833[1]
	BMI > 25 kg/m^2	8 (14.8)	15 (16.1)	23 (15.6)	
Pre-surgical ECOG§	Score 0	50 (92.6)	79 (84.9)	129 (87.8)	0.173[1]
	Score 1	4 (7.4)	14 (15.1)	18 (12.2)	
Diabetes	No	39 (72.2)	67 (72.0)	106 (72.1)	0.981[1]
	Yes	15 (27.8)	26 (28.0)	41 (27.9)	
Cardiovascular diseases	No	21 (38.9)	34 (36.6)	55 (37.4)	0.778[1]
	Yes	33 (61.1)	59 (63.4)	92 (62.6)	

[1]Pearson's chi-square test.
[2]Student's *t*-test.
§ Score 0: Totally active and restricted activities; and Score 1: Restricted physical activities, but walking e apt to perform light work activities. vmin: Minimum value; vmax: Maximum value.

Long-term results

With regard to OS and disease-free survival (DFS), there is no statistically significant difference between groups (Table 4). However, when results are analyzed by clinical stage, longer survival is observed in patients with earlier disease (up to stage 2B), undergoing thoracoscopic esophagectomy (P = 0.001, Figure 2 and Table 4).

Other factors associated with OS in the univariate analysis include transhiatal approach, grade 3, metastatic lymph node, pT3/4, and lymphatic invasion in the tumor specimen. The multivariable analysis demonstrated better results related to transhiatal access in early staging tumors, hazard ratio 1.73 (95%CI: 1.00-2.99, P = 0.049). Factors associated to DFS were: transhiatal approach, metastatic lymph node, pT3/4, and lymphatic invasion in the tumor specimen (Table 4).

DISCUSSION

AEGJ is one of the neoplasms with the highest global rate of increased incidence through the last years, associated with risk factors such as obesity and gastroesophageal reflux disease[16].

In Brazil and many Western countries, it is still a disease with a poor prognosis, mainly because about 65% are T3 or T4 at the time of diagnosis. Recently, Tustumi *et al*[3] published a cross-sectional study performed in our center, in which more than 550 patients with esophageal cancer had an OS rate of 20.2% for AEGJ (types I, II, and III). The percentage of curative-intent surgery in AEGJ was 30.4%, with a mean survival rate of 58% after five years follow-up.

Several factors associated with treatment contributed to improved survival of patients with AEGJ in recent years, among them, neoadjuvant treatment stands out[7, 17]. Based on the most recent data, neoadjuvant chemotherapy and radiotherapy (similar to the CROSS trial) were performed for esophageal tumors and for both pre- and postoperative chemotherapy in patients with predominantly gastric tumors.

Regarding surgical approach, transhiatal esophagectomy was initially performed by Akiyama *et al*[18] in Japan in 1975; Orringer *et al*[19] in the United States in 1978; and Pinotti[15] in Brazil in 1976, which was the preferred approach for AEGJ. Several

Table 2 Postoperative complications and mortality rates of the total number of patients with adenocarcinoma of the esophagogastric junction and by type of esophagectomy

		Group		Total	*P* value
		Thoracoscopygroup A	Transhiatalgroup B		
		n = 54, *n* (%)	*n* = 93, *n* (%)	*n* = 147 , *n* (%)	
Complications	No	27 (50.0)	60 (64.5)	87 (59.2)	0.084[1]
	Yes	27 (50.0)	33 (35.5)	60 (40.8)	
Fistulae	No	48 (88.9)	80 (86.0)	128 (87.1)	0.617[1]
	Yes	6 (11.1)	13 (14.0)	19 (12.9)	
Chylothorax	No	53 (98.1)	93 (100)	146 (99.3)	0.367[2]
	Yes	1 (1.9)	0	1 (0.7)	
Respiratory disorders	No	46 (85.2)	85 (91.4)	131 (89.1)	0.244[1]
	Yes	8 (14.8)	8 (8.6)	16 (10.9)	
Hoarseness	No	50 (92.6)	93 (100)	143 (97.3)	0.017[2]
	Yes	4 (7.4)	0	4 (2.7)	
Infections	No	50 (92.6)	91 (97.9)	143 (97.3)	0.017[2]
	Yes	4 (7.4)	2 (2.1)	4 (2.7)	
Mortality		2 (3.7)	4 (4.3)	6 (4.08%)	0.342[2]

[1]Chi-square test.
[2]Fisher exact test.

Table 3 Number and characteristics of resected lymph nodes of patients with adenocarcinoma of the esophagogastric junction submitted to surgical treatment by transthoracic and transhiatal transthoracic esophagectomy

		Group		Total	*P* value
		Thoracoscopygroup A	Transhiatalgroup B		
		n = 54, *n* (%)	*n* = 93, *n* (%)	*n* = 147, *n* (%)	
Dissected lymph nodes	mean ± SD	31.89 ± 17.65	20.73 ± 12.70	24.83 ± 15.62	< 0.001[1]
Metastatic lymph nodes	Median (vmin-vmax)	30 (3-73)	19 (2-85)	22 (2-85)	
	Median (vmin-vmax)	2 (0-25)	1 (0-34)	1 (0-34)	
AL/DL (%)	mean ± SD	15.59 (21.44)	20.56 (28.12)	18.73 (25.90)	0.696[1]
	Median (vmin-vmax)	5.86 (0-92.31)	5.88 (0-97.14)	5.88 (0-97.14)	

[1]Mann-Whitney test. vmin: Minimum; vmax: Maximum; AL/DL: Affected lymph nodes/dissected lymph nodes.

studies suggest fewer pulmonary complications than the transthoracic approach, despite a limited surgical view and difficult mediastinal lymph node resection; it became the preferred access route in AEGJ in Siewert types I and II at our institution for over twenty-five years. After the introduction of minimally invasive surgery with thoracoscopic access and standardization of the thoracic lymphadenectomy, and reasonable morbidity results[17], we modified our approach in types I and II AEGJ to transthoracic by thoracoscopy.

It is well-known that post-operative complications after esophagectomy are associated with a worse prognosis[20]. In particular, a higher incidence of respiratory infections (pneumonia and tracheobronchitis) is described in patients undergoing thoracoscopy, due to the fact that there is selective intubation and a longer duration of mechanical ventilation. We also observed this in our series, with respiratory complications occurring in 10.9% of patients in group A.

Table 4 Univariate and multivariate analysis for disease-free survival and overall survival

Disease-free survival	Univariate analysis			Multivariate analysis		
Variables	**HR**	**95%CI**	***P* value**	**HR**	**95%CI**	***P* value**
Male (*vs* female)	0.99	0.47–2.08	0.975			
Age (< 62 yr *vs* > 62 yr)	0.87	0.56–3.14	0.873			
Siewert 1 *vs* 2	1.11	0.14–8.89	0.921			
TH *vs* TT (1, 2A)	1.71	1.01–2.90	0.046	1.73	1.00–2.99	0.049
Post-operative complications	1.22	0.56-2.06	0.961			
G3 (*vs* G1/G2)	1.14	0.61–2.13	0.690			
LN+/LN-	2.61	1.71-3.56	0.001	1.77	0.99-3.24	0.101
pT3/pT4 status (*vs* pT0/T1/pT2)	2.21	1.86–7.31	0.003	1.56	0.97-3.89	0.102
pN+ (*vs* pN0)	2.54	1.57-5.78	0.05	1.43	0.88-3.32	0.103
Pathological exam						
Lymphatic	0.78	0.39-1.29	0.783			
Venous	1.67	0.35-2.72	0.246			
Neural	0.78	0.67-1.89	0.183			
Overall survival	Univariate analysis		Multivariate analysis			
Variables	HR	95%CI	*P* value	HR	95%CI	*P* value
Age (< 62 yr *vs* > 62 yr)	0.98	0.89-5.13	0.821			
Siewert 1 *vs* 2	1.31	0.16-10.68	0.799			
TH *vs* TT (1, 2A)	2.01	1.19-3.39	0.009	1.79	1.03-3.09	0.038
Post-operative complications	1.03	0.60-1.74	0.927			
G3 (*vs* G1/G2)	2.37	1.36-4.16	0.003	2.54	1.33-4.82	0.005
LN+/LN-	1.72	1.00-3.48	0.050	1.21	0.87-3.46	0.732
pT3/pT4 status (*vs* pT0/T1/pT2)	5.95	1.81-19.61	0.003	9.96	2.43-40.74	0.001
pN+ (*vs* pN0)	1.68	1.38-3.90	0.002	1.18	0.86-4.99	0.735
Pathological exam						
Lymphatic	0.47	0.23-1.78	0.109			
Venous	0.49	0.20-1.06	0.076			
Neural	1.80	0.96-3.35	0.065			

Another complication with an exclusive incidence in group A was hoarseness, probably secondary to mediastinal lymphadenectomy-with consequent manipulation of recurrent laryngeal nerves. In all, four cases were reported in our series. Of these, none evolved with severe speech dysfunction or bronchoaspiration, or the need for a tracheostomy.

The main surgical complication of both surgeries was anastomotic fistula. In this study, it was observed in 12.9% of cases, with no statistical difference between groups. Its prevalence ranges from 15.8% to 30%; although it is accompanied by low morbidity, as anastomosis is located in the neck, with a lower risk of mediastinal infection. When drainage is preferential to the neck incision, it can be managed by endoscopic treatment (3-5 endoscopic dilation sessions)[21].

Regarding surgery-related mortality rate, this study reported 3.7% in the thoracoscopy group and 4.3% in the transhiatal group, with 4.0% overall mortality, showing acceptable results compared to rates up to 15.4% as reported in a systematic review[22].

The number of lymph nodes resected by thoracoscopy was higher (31.89 lymph nodes on average) than transhiatal (20.73 lymph nodes on average), with a significant statistical difference ($P < 0.001$). However, the number of affected nodes were similar.

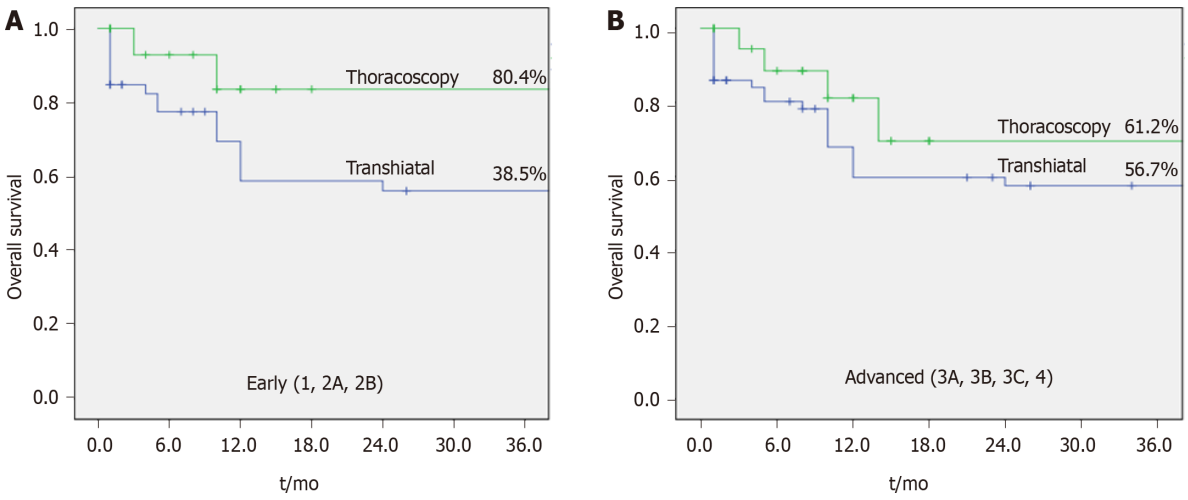

Figure 2 Overall survival of patients with adenocarcinoma of the esophagogastric junction who underwent esophagectomy. A: Early (P = 0.002); B: Advanced cases (P = 0.32).

With regard to long-term results, what was previously known is that both the transhiatal and transthoracic techniques resulted in similar oncological outcomes, with a tendency for greater perioperative morbidity with the transthoracic pathway[22-24], which is similar to our results.

However, when we analyzed OS and DFS for each clinical stage in isolation, we observed a trend of encouraging results in group A in the earlier stages (up to 2B).

Despite the close follow-up, this study has limitations such as the retrospective design and thus, patients were not randomly selected. There were some disparities in the neoadjuvant treatment between groups (87% in thoracoscopic *vs* 46% in transhiatal) which may be considered a limitation. However, the study aimed to assess overall survival on AEGJ tumors considering a cohort of patients in a "real-world" setting. The neoadjuvant therapy was indicated just in patients > 3A staged. Therefore, neoadjuvant treatment did not interfere in the early stage subgroup analysis. Regarding advanced stages, we believe that the possible limitation related to the difference between groups receiving neoadjuvant chemotherapy was minimized by the multivariate analysis.

CONCLUSION

Both esophagectomy approaches have low morbidity and mortality, given the magnitude of the procedures. Hoarseness and infectious complications were more significant in transthoracic esophagectomy by thoracoscopy. However, it allowed the resection of a more significant number of lymph nodes. In addition, this method is apparently associated with higher OS and DFS at earlier stages and may be a better approach. Further studies are required to confirm our findings.

ARTICLE HIGHLIGHTS

Research background

Extension of lymphadenectomy during esophagectomy is on debate for adenocarcinoma of the esophagogastric junction. Thoracoscopic transthoracic access is consider superior regarding retrieved lymphonodes comparing to transhiatal esophagectomy, but overall survival is questionable.

Research motivation

To understand the relationship between extension of lymphadenectomy and survival according to type of surgical approach.

Research objectives
To compare outcomes after thoracoscopic esophagectomy and transhiatal approach for adenocarcinoma of the esophagogastric junction.

Research methods
Retrospective review of medical records of patients were assessed. A total of 147 patients with adenocarcinoma of the esophagogastric junction were selected from 2002 to 2019, and divided into group A (thoracoscopic esophagectomy), and group B (transhiatal esophagectomy). Overall survival (OS), disease-free survival, post-operative complications, and number of nodes, were similarly evaluated.

Research results
Concerning the extent of lymphadenectomy, group A showed a higher number of retrieved lymph nodes (mean of 31.89 ± 8.2 *vs* 20.73 ± 7; $P < 0.001$), with more perioperative complications, such as hoarseness, surgical site infections, and respiratory complications. Although both groups had similar OS rates, subgroup analysis showed better survival of transthoracic esophagectomy in patients with earlier diseases.

Research conclusions
Both methods are safe, having similar morbidity and mortality rates. Transthoracic thoracoscopic esophagectomy allows a more extensive resection of the lymph nodes and may have better oncological outcomes during earlier stages of the disease.

Research perspectives
Prospective randomized trials addressing topics as long-term survival, the role of neoadjuvant therapies and costs.

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ORIGINAL ARTICLE

Prospective Study

Prospective evaluation of the hemorrhoid energy treatment for the management of bleeding internal hemorrhoids

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Author contributions: Kothari TH designed and conceptualized the study; Bittner K collected the data; Kothari TH, Bittner K, Kaul V and Kothari S contributed planning/conducting the study (literature review), interpretation of data, drafting/editing the manuscript, and approved the final draft.

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Abstract

BACKGROUND

The hemorrhoid energy treatment (HET) system is a non-surgical bipolar electro-therapy device, which has previously demonstrated efficacy in the management of bleeding Grade I and II internal hemorrhoids; however, data is limited.

AIM

To prospectively assess the safety and efficacy of the HET device.

METHODS

This was an IRB-approved prospective study of 73 patients with Grade I or II internal hemorrhoids who underwent HET from March 2016 to June 2019. Patient factors and procedural data were obtained. A post-procedure questionnaire was administered by telephone to all patients at 1-wk and 3-mo following HET to assess for improvement and/or resolution of rectal bleeding and adherence to a stool softener regimen. A chart review was performed to observe recurrent symptoms and durability of response. Statistical analyses were performed using SPSS software (IBM; SPSS Version 25.0).

RESULTS

Seventy-three patients underwent HET during the study period. Mean post-HET follow-up was 1.89 years. Complete resolution of bleeding was reported in 65% at 1 wk (n = 48), with improvement in bleeding in 97.2% (n = 71) of patients. At 3-mo, resolution and/or improvement in bleeding was reported in 90% (n = 64) of patients. No procedure-related pain or adverse events were reported.

CONCLUSION

HET is well tolerated, safe and highly effective in the majority of our patients presenting with Grade I and II symptomatic internal hemorrhoids.

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Core Tip: Bleeding internal hemorrhoids are a very common problem. More than 50% of population 50 years or older have issues with constipation leading to painless bleeding. Tremendous amount of money is spent in urgent care and emergency department visits for painless bleeding. Not many treatment modalities are available for internal hemorrhoids. Hemorrhoid energy treatment is a bipolar equipment for treatment of internal hemorrhoids grade I and II. Our study has reflected the benefits of this device through our prospective trial.

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INTRODUCTION

Internal hemorrhoids (IH) are a very common cause of lower gastrointestinal bleeding (LGIB) with an estimated prevalence in the United States of 4.4%, accounting for an estimated 3.3 million ambulatory care visits annually[1]. Approximately 40% of patients with hemorrhoids are asymptomatic; however, those presenting with symptoms most often report painless bleeding[2]. Conventionally, Grade I and II bleeding IH have been managed with noninvasive therapies that combine dietary and lifestyle modifications, including increased oral fluid intake, reduction of fat consumption, avoidance of straining during bowel movements, and increased fiber intake[3].

For symptomatic patients, several non-surgical outpatient office-based treatments are currently available including rubber band ligation, infrared coagulation, sclerotherapy, bipolar diathermy, laser photocoagulation, and sclerotherapy[4]. The goal of non-surgical treatment is to decrease vascularity, reduce redundant tissue, and increase hemorrhoidal rectal wall fixation to minimize prolapse[3]. Though success has been demonstrated with the above-mentioned techniques, anorectal pain, recurrent bleeding, and recurrence of hemorrhoids are well-reported adverse events[5,6].

A novel non-surgical bipolar electrotherapy device, the hemorrhoid energy treatment (HET) System, has previously demonstrated efficacy in the management of bleeding Grade I and II IH[7,8]. We present a prospective study to date evaluating the efficacy and safety of HET.

MATERIALS AND METHODS

This was an IRB-approved prospective cohort study (Research Subjects Review Board, University of Rochester, Study #780) conducted at our tertiary care referral center from 03/2016 to 06/2019. Adult patients (≥ 18 years old) with Grade I or Grade II IH scheduled for outpatient treatment with the HET system during the study period were eligible for inclusion. Written informed consent was obtained prior to study enrollment. All enrolled patients were contacted at 1-week post-procedure to assess improvement in rectal bleeding and self-reported compliance with stool softener use. At 3-mo post-procedure, the same survey was administered by telephone to evaluate if resolution or improvement in rectal bleeding had changed, and if compliance with stool softener use continued. All follow-up questionnaires were administered by telephone by one of the authors (Bittner K) utilizing a standardized script for each call. A concurrent chart review was performed to collect patient demographics, procedural and clinical data. All pre- and post-HET office visits with documented occurrences of

bleeding attributed to IH were recorded. Statistical analyses were performed with SPSS software (IBM, SPSS Version 25.0; Armonk, NY, United States).

HET Techniques

The HET Bipolar System (Medtronic, United States) is a modified anoscope, which incorporates bipolar forceps and incudes a separate tissue temperature monitor console (Figure 1). HET was utilized with a commercially available electrosurgical generator (ERBE; Marietta, GA, United States)[9]. Ablation of IH can be achieved with the use of one of three techniques. All HET procedures were performed by two advanced endoscopists (TK, VK), with an average procedure time of less than 15 min.

Medtronic anoscopy technique: This technique includes insertion of the bipolar forceps under LED light provided at the top of the forceps and performing the procedure under direct vision. The superior hemorrhoidal plexus area, approximately 1 cm above the proximal extent of the IH, was grasped with the bipolar forceps. After confirming that the tissue grasped is sufficient (by means of same level approximation of three red lines on bipolar forceps handle), bipolar current was applied with using the recommended electrosurgical generator coagulation settings (effect 1, 5 watts; Figure 2A).

Standard technique: Our *"standard technique"* included the use of gastroscope inside the bipolar forceps to perform the IH ablation under endoscopic vision (Figure 2B). The concept is to target the superior hemorrhoidal plexus. This method was utilized for the majority of patients in our study (n = 70/73).

Modified technique: At our center, we developed a technique called the *"modified HET technique"* that utilizes use of pediatric biopsy forceps for tissue grasping in addition to the use of the standard endoscope to guide the bipolar forceps. This modified technique facilitates the capture of target rectal tissue when flat and difficult to grasp with the bipolar forceps alone. The pediatric biopsy forceps are used to gently pull the tissue immediately proximal to the IH, which allows the superior hemorrhoidal plexus area to enter the forceps better for optimal treatment (Figure 3).

RESULTS

A total of 73 patients were enrolled during the study period (March 2016 through June 2019). The majority of patients were female (53.4%), with mean age of 50.3 years (Table 1). Mean follow-up duration (post-HET) was 1.89 years. Thirty-six patients (49.3%) presented with Grade I and twenty-six (35.6%) with Grade II IH. Grade of IH was not available for 10/73 (13.7%) patients. In one patient, a Grade III hemorrhoid confirmed on colonoscopy immediately prior to treatment. Approximately half of patients (45.2%) failed conservative therapy prior to HET (defined as: stool softeners, fiber supplements and/or hydrocortisone suppositories). Most patients (90.4%) reported persistent painless rectal bleeding at the office visit immediately prior to referral for HET.

HET was performed with flexible sigmoidoscopy in all cases, using a standard gastroscope. Our *"standard HET technique"* was utilized in 70/73 patients. Three patients were treated with the *"modified HET technique"*. All patients were contacted by telephone at 1-wk and 3-mo post-procedure (Tables 2 and 3) to complete a questionnaire regarding resolution and/or improvement of bleeding symptoms, and compliance with stool softener use. All patients successfully completed the 1-wk questionnaire; however, 2 patients were unable to be contacted at 3-mo (response rate = 100% and 97.3%, respectively). At 1-wk post-procedure, complete resolution of bleeding was reported in 66% of patients (n = 48/73), with improvement in bleeding reported in 97.2% (n = 71/73) patients. Polyethylene glycol and/or other stool softeners were prescribed post-procedure to prevent constipation; however, at 3-mo post-HET, only 55% of patients reported continued use.

A concurrent chart review was performed to assess for recurrence or persistence of symptoms and durability of response. At 3-mo post-procedure, complete resolution of bleeding was reported in 62% of patients (n = 44/71), with improvement in bleeding reported in 90.1% (n = 64/71) patients. Six patients required a repeat HET (mean of 7.6 mo following initial treatment) for persistent rectal bleeding, with complete resolution reported after the 2nd treatment in 3/6 of these patients. Three patients continued to report persistent rectal bleeding despite repeat HET.

Table 1 Patient characteristics

Patient characteristics	*n* = 73
Age at HET (yr), mean	50.3
Female, *n* (%)	39 (53.4)
Race, *n* (%)	
Caucasian	58 (79.5)
African-American	14 (19.2)
Asian	1 (1.4)
Grade of hemorrhoids at time of HET, *n* (%)	
Grade I	36 (49.3)
Grade II	26 (35.6)
Grade III	1 (1.4)
Not reported	10 (13.7)

HET: Hemorrhoid energy treatment.

Table 2 Responses to telephonic questionnaire

Responses to telephonic questionnaire, 1 wk post-procedure (*n* = 73)					
Bleeding resolved		**Bleeding improved**		**Use of stool softeners (post-HET)**	
Yes, *n* (%)	**No, *n* (%)**	**Yes, *n* (%)**	**No, *n* (%)**	**Yes, *n* (%)**	**No, *n* (%)**
48 (65.8)	25 (34.2)	23 (92.0)	2 (8.0)	36 (49.3)	37 (50.7)

HET: Hemorrhoid energy treatment.

Table 3 Responses to telephonic questionnaire

Responses to telephonic questionnaire, 3 mo post-procedure (*n* = 71)					
Bleeding resolved[1]		**Bleeding**[1] **improved**		**Use of stool softeners (post-HET)**	
Yes, *n* (%)	**No, *n* (%)**	**Yes, *n* (%)**	**No, *n* (%)**	**Yes, *n* (%)**	**No, *n* (%)**
44 (62.0)	27 (38.0)	20 (74.1)	7 (25.9)	39 (54.9)	32 (45.1)

[1]A total of 64/71 (90.1%) patients reported complete resolution or improvement of bleeding post-hemorrhoid energy treatment.
HET: Hemorrhoid energy treatment.

There were no instances of pain or rectal discomfort during or immediately following the HET procedure. One patient reported self-limited post-procedure bleeding. No other adverse events were noted from the procedure.

DISCUSSION

IH are common and can be symptomatic with rectal bleeding in many patients. They are often difficult to treat and can lead to significant morbidity, affect quality of life of the patient and put a significant burden on healthcare. Several non-surgical treatment modalities are available for treatment of Grade I and II bleeding IH. Current treatment guidelines recommend outpatient office-based procedures such as rubber-band ligation (RBL), sclerotherapy or infrared coagulation for patients who remain symptomatic after lifestyle modifications have failed[10].

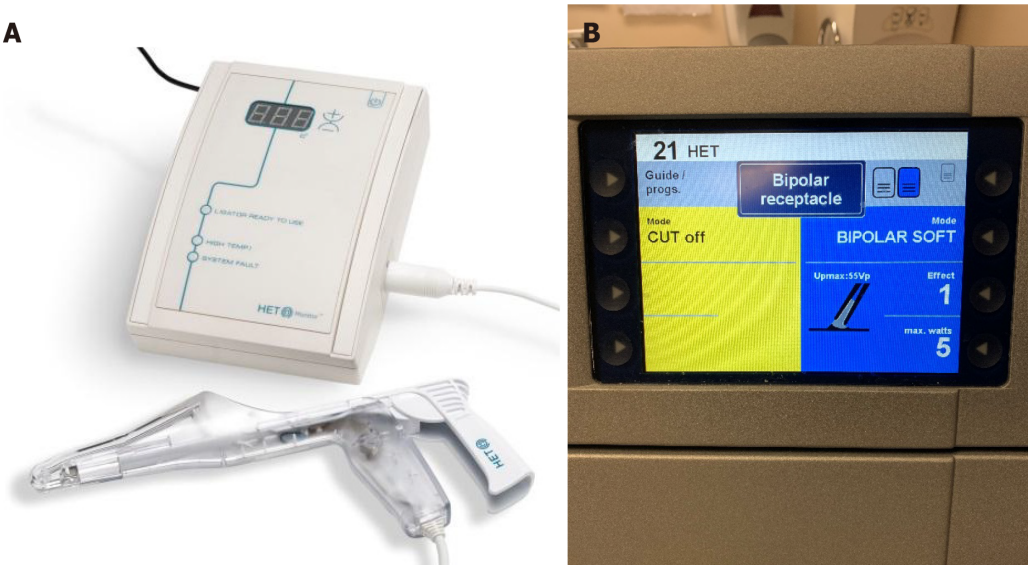

Figure 1 The hemorrhoid energy treatment bipolar system. A: Hemorrhoid energy treatment (HET) system with bipolar forceps and tissue temperature monitor. Permission for use of image granted by HET System, LLC; B: Electro-surgical generator with HET settings.

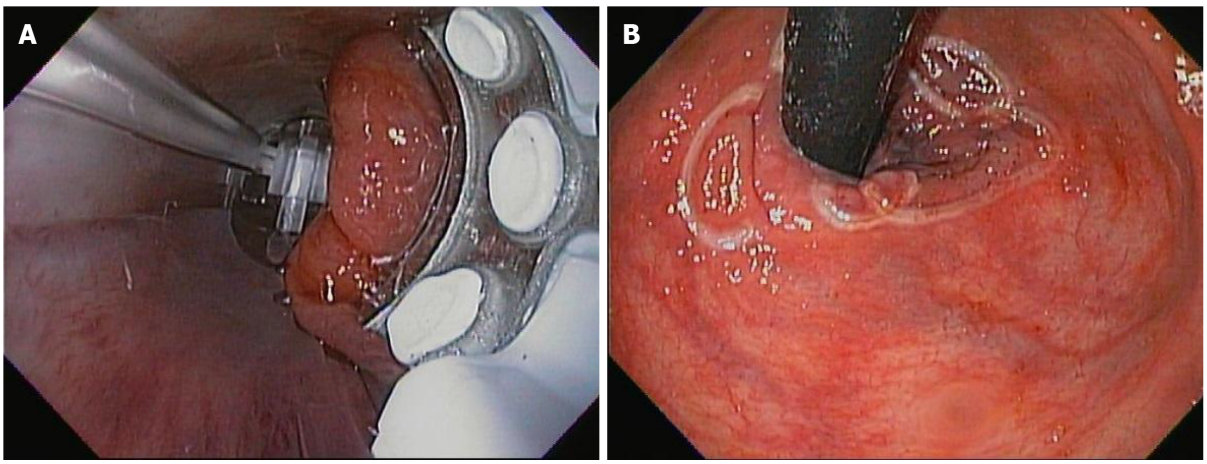

Figure 2 Antegrade view of internal hemorrhoids and retroflexed view of the anal verge. A: Antegrade view of internal hemorrhoids with a standard gastroscope; B: Retroflexed view of the anal verge post hemorrhoid energy treatment suggestive of treatment of multiple internal hemorrhoidal columns.

Rubber band ligation is the most frequently used procedure for hemorrhoid treatment. In a meta-analysis of 18 randomized controlled trials, RBL was noted to have a lower need for repeat treatments compared to sclerotherapy and infrared coagulation, although did cause significantly more pain reported in 25%-50% of patients[11-13].

Sclerotherapy is one of the oldest non-surgical therapy and involves injecting a sclerosant into the submucosa at the base of the hemorrhoid. Due to the nature of the procedure, there have been adverse events reported such as rectal fistulas and life-threatening retroperitoneal sepsis[14]. In a meta-analysis of randomized controlled studies comparing RBL, sclerotherapy and surgery, sclerotherapy was less effective than rubber band ligation and surgery. Infrared coagulation is less effective than banding or sclerotherapy and requires repeat treatment sessions[11].

HET is a novel non-surgical treatment for IH and has been reported to be both safe and effective in prior studies[7-9]. These studies have had limitations due to the retrospective nature of the study and small sample size. Piskun and Tucker[9] performed a direct comparison of the HET system with infrared coagulation in a live porcine model with favorable outcomes. The HET device combined target tissue compression with precise application of much lower temperature (55 °C) *vs* that of the infrared coagulation probe (149 ± 11.1 °C), minimizing heat-related collateral damage to tissues adjacent to the treatment areas. The authors concluded that the treatment with the HET System would cause less procedural pain and less post-procedural

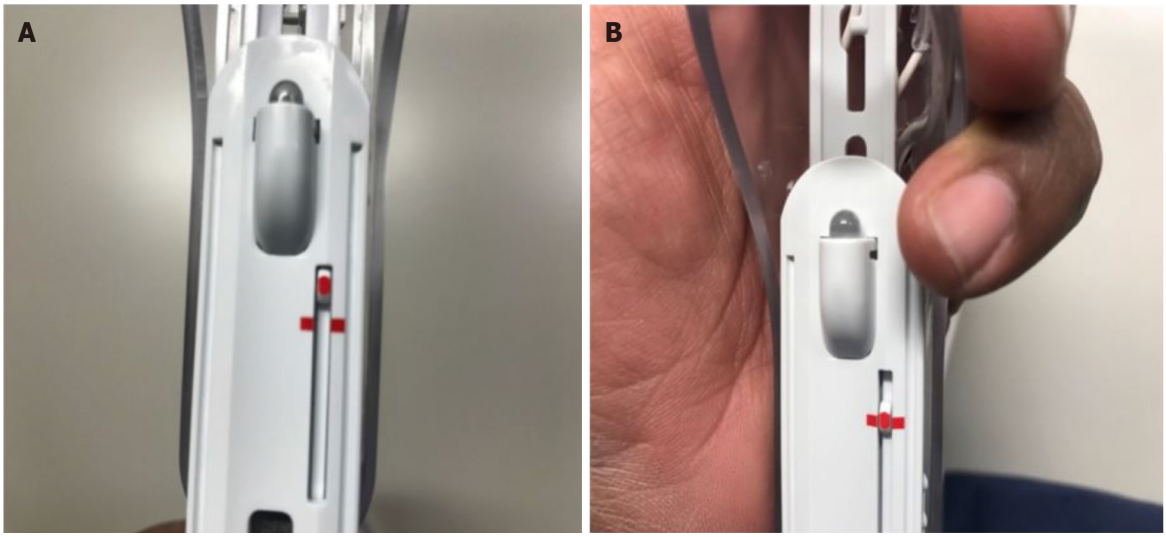

Figure 3 The pediatric biopsy forceps. A and B: Sufficient entrapment of the mucosa above the internal hemorrhoids is indicated with alignment of all three red lines.

adverse events *vs* existing non-surgical modalities for treatment of IH[9]. In 2013, Kantsevoy and Bitner[8] conducted a retrospective study of examining the use of HET for the indication of actively bleeding IH. All patients in this cohort (n = 23) tolerated the treatment without any pain or discomfort. No adverse events were reported in the study[8]. In 2016, Crawshaw *et al*[7] reported the safety and efficacy of HET technology in a prospective case series of 20 patients with bleeding improvement seen in > 80% of the patients.

Our study demonstrates the safety and efficacy of the HET platform in the treatment of Grade I and Grade II IH. Nearly half of patients had failed guideline-based conservative therapy prior to referral for HET. The majority of our cohort reported no immediate post-procedural pain or bleeding. Complete resolution and/or improvement in bleeding symptoms were reported in 97.2% and 90.1 % of patients at 1-week and 3-months post-procedure, respectively.

The main limitations of this study were relatively small sample size (n = 73), lack of comparison or control arm, and is our single-center's experience with HET use. The potential for lack of generalizability may exist due to the level of expertise of the endoscopists performing the HET procedure at our institution.

CONCLUSION

Our study represents one of the largest prospective studies reporting safety and efficacy for the use of HET system in patients with symptomatic Grade I and II IH. Further multi-center prospective studies are needed to validate the efficacy and safety of the device. In addition, these studies should also assess if the use of stool softeners for a brief period post-HET prevents recurrence of rectal bleeding.

ARTICLE HIGHLIGHTS

Research background

Painless rectal bleeding (*i.e.*, Grade I and Grade II Internal hemorrhoids) can be effectively treated with hemorrhoid energy treatment (HET). Our study has demonstrated that the procedure is safe, well tolerated and clinically effective for most patients.

Research motivation

There has been limited treatment for internal hemorrhoids, hence this manuscript is intended to add real-world clinical data to the literature.

Research objectives
To educate readers with clinical data regarding treatment of bleeding internal hemorrhoids with the help of HET system.

Research methods
This research study was a prospective cohort design.

Research results
The majority of patients reported complete resolution and/or improvement in bleeding resulting from internal hemorrhoids at 3-mo post-procedure.

Research conclusions
HET system can make a significant impact in treatment of bleeding internal hemorrhoids.

Research perspectives
Further research should be performed to expand upon our findings.

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SYSTEMATIC REVIEWS

Effect of pancreatic endotherapy on quality of life in chronic pancreatitis patients: A systematic review

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Abstract

BACKGROUND

Pancreatic endotherapy provides treatment options for the management of chronic pancreatitis-related structural complications such as pancreatic duct stones, strictures, and pancreatic fluid collections. Most studies detailing endotherapy, however, have focused on technical success outcomes such as stone clearance or stricture resolution.

AIM

To review the effect of pancreatic endotherapy on patient-centered outcomes.

METHODS

Systematic review of studies examining pancreatic endotherapy.

RESULTS

A total of 13 studies including 3 randomized clinical trials were included. The majority of studies found an improvement in quality of life with pancreatic endotherapy.

CONCLUSION

While pancreatic endotherapy does appear to improve quality of life, there are clear gaps in knowledge regarding many pancreatic endotherapy modalities. Furthermore, qualitative analysis is lacking in these studies and further work is needed to elucidate the patient experience with pancreatic endotherapy.

Key Words: Chronic pancreatitis; Pancreatic endotherapy; Endoscopic retrograde cholangiopancreatography; Quality of life

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Core Tip: Chronic pancreatitis remains difficult to treat and pancreatic endotherapy offers one option for the management of chronic pancreatitis-related complications. Pancreatic duct decompression *via* pancreatic duct stone lithotripsy and stenting appears to improve the quality of life of these patients in the short-term. More studies, however, are needed to examine the effect of endotherapy modalities such as endoscopic transmural drainage of pancreatic fluid collections, celiac plexus blocks and more recent innovations on quality of life in these patients.

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INTRODUCTION

Pain, the hallmark feature of chronic pancreatitis (CP), remains difficult to manage effectively and can significantly worsen patients' quality of life[1-3]. A variety of factors likely play a role in the mechanism of pain, which can include ductal hypertension, inflammation, or neuropathic pain from varying degrees of sensitization of the nervous system[1,4]. Targeted treatment based on the etiology of the pain therefore is challenging and initial treatment will typically consist of medical management.

Pancreatic endotherapy (PET) offers a treatment option for patients with CP-related structural complications such as pancreatic duct (PD) stones, strictures, stones, or pancreatic fluid collections such as pseudocysts. Patients must typically fail medical management before PET is considered with persistent pain being the most common indication. The last decade has ushered in a wave of new PET modalities that have advanced the field beyond standard endoscopic retrograde pancreatography. For PD stones, per-oral pancreatoscopy (POP)-guided lithotripsy using electrohydraulic lithotripsy or laser lithotripsy have dramatically increased the rates of successful PD stone clearance[5,6]. For pancreatic duct strictures, the use of fully covered metal stents, wire-guided cystotomes, and POP-guided laser dissection have greatly expanded the armament of the endoscopist for these refractory stenoses[7-11]. Lastly, the development of lumen-apposing metal stents has revolutionized the drainage of pancreatic fluid collections by facilitating endoscopic transmural drainage in a single step[12,13].

Despite these advances in PET, published studies have largely focused on technical success outcomes such as stricture resolution or stone clearance[5,6,14-16]. Furthermore, the few randomized studies have centered on pain improvement as the primary outcome, which while important, does not capture the holistic impact of PET on patients. As patients and physicians will have different priorities, expectations, and preferences regarding treatment choices, it is critically important to incorporate patient-centered outcomes such as quality of life in the evaluation of these modalities [17]. Therefore, the aim of this review is to detail the effect of PET on quality of life in patients with CP.

MATERIALS AND METHODS

Literature search strategy

We searched PubMed for relevant English-language articles published by January 5, 2021 with no restriction on earliest publication date. The search terms included quality of life and each of the following: endoscopic therapy, endoscopic retrograde cholangiopancreatography (ERCP), celiac plexus block, pancreatic duct stone, pancreatic duct stricture, pancreatic duct stent, pancreatic fluid collection, pseudocyst, pancreatoscopy, lithotripsy, and endoscopic ultrasound.

Inclusion and exclusion criteria

The relevance of the studies was determined using the hierarchical approach as recommended by the PRISMA statement. We assessed the studies by examining the title, abstract, and/or full text of the studies. We also examined the references of included studies to identify any additional studies. Inclusion criteria included the following: (1) Studies involving PET that included quality of life as an outcome; (2) Publication in the English language; (3) Availability of the full text; and (4) Publication date by January 5th, 2021. Exclusion criteria included the following: (1) Non-original studies including reviews, editorials, commentaries, and study protocols; (2) Insufficient data; and (3) Duplicate studies (*i.e.*, conference abstract and full-text manuscript).

RESULTS

The literature search flow diagram is presented in Figure 1. The initial PubMed database search yielded a total of 10, 242 articles. Upon title and abstract review, the full text of 123 articles were reviewed. Upon excluding 110 of these studies, which were found to be irrelevant, a total of 13 studies, including 3 randomized clinical trials and 10 observational studies were included (Table 1).

Comparison of surgery with endoscopy for pancreatic duct drainage

The major randomized trials comparing endoscopy with surgery focus on pancreatic duct drainage to relieve ductal hypertension. In the landmark trial comparing endoscopic treatment [ERCP with stricture dilation for PD strictures ± extracorporeal shock-wave lithotripsy (ESWL) for concomitant PD stones] with a side-to-side pancreaticojejunostomy, at 2 year follow-up patients who received endotherapy (n = 19) had an improvement in both physical health (31 ± 8 to 38 ± 9) and mental health (33 ± 8 to 40 ± 9) on the 36-Item Short Form Health Survey (SF-36) questionnaire[18]. While this was less than the improvement in quality of life seen in the surgery arm, in the follow-up study examining long-term (mean follow-up of 79 mo) outcomes of both arms, the improvement in both physical and mental quality of life persisted, but there was no longer any difference between the two arms[19]. More recently, the ESCAPE trial from the Dutch pancreatitis study group randomized patients with painful CP and a dilated PD to either early pancreatic drainage surgery (n = 44) or endotherapy (ERCP ± ESWL) first (n = 44)[20]. At 18 mo follow-up, patients in the endotherapy arm did experience an improvement in both physical (31 ± 8 to 36 ± 9) and mental (36 ± 11 to 41 ± 11) health on the SF-36 with no difference seen in quality of life between the two treatment groups. Lastly, in a retrospective study comparing surgery with endotherapy, the European Organization for Research and Treatment of Cancer (EORTC) quality of life instrument and the pancreatic cancer module (PAN26) instrument were utilized with the primary finding that patients treated with surgery had less nausea and vomiting [21].

Pancreatic duct stone therapy

Internationally, the combination of ESWL with ERCP represents the most common form of treatment for symptomatic PD stones. Starting with a prospective study by Brand *et al*[22] in 2000, ESWL followed by ERCP was associated with an improvement in pain, weight loss, fevers/chills, jaundice, and global quality of life on the EORTC instrument. Within an Indian patient population, Tandan *et al*[23] presented a large study (n = 636) of this treatment modality, finding that using a scale of 1-10 (10 representing the best quality of life), quality of life improvement was seen in 92.8% of patients at 2-5 year follow-up and in 92.6% of patients at > 5 year follow-up. In a large Chinese patient cohort using the SF-36, a significant improvement was seen in overall quality of life and physical health, but not in mental health[24,25]. Seven *et al*[26] presented data on this PET combination in a United States cohort, utilizing a 1-10 quality of life score (10 being the best quality of life), finding a significant improvement in quality of life (3.7 ± 2.4 to 7.3 ± 2.7) after completion of therapy. Similarly, in a study from Germany, Milovic *et al*[27] reported a significant improvement in quality of life after ESWL and ERCP on a 5-point quality of life scale (2.5 to 4).

In the only study examining pancreatoscopy-guided lithotripsy that included quality of life as a study outcome, Gerges *et al*[28] utilized both electrohydraulic and laser lithotripsy in 20 patients. They found that post-therapy, 89% of patients had no or only mild disability in daily activities and 47% of patients described their health as

Table 1 Key characteristics of included articles

Ref.	Study design	Endoscopic modality	*n*	Quality of life measurement	Quality of life findings
Cahen *et al*[18,19]	Randomized clinical trial	ERCP ± ESWL	19	SF-36	Physical health: 31 ± 8 to 38 ± 9 (2 yr) and 43 ± 11 (7 yr); Mental health: 33 ± 8 to 40 ± 9 (2 yr) and 46 ± 9 (7 yr)
Issa *et al* [20]	Randomized clinical trial	ERCP ± ESWL	44	SF-36	Physical health: 31 ± 8 to 36 ± 9; Mental health: 36 ± 11 to 41 ± 11
Stevens *et al*[31]	Randomized study	Celiac plexus block	40	SF-12	Change in physical score: -0.2 ± 7.5 (triamcinolone + bupivacaine), 1.7 ± 8.8 (bupivacaine); Change in mental score: 1.3 ± 10.0 (triamcinolone + bupivacaine), -2.1 ± 12.9 (bupivacaine)
Brand *et al*[22]	Prospective study	ERCP + ESWL	48	EORTC	Pain: 37.8 (range 0-81.5) to 18.8 (range 0-83.3); Weight loss: 66.7 (range 0-100) to 0 (range 0-100); Global quality of life: 41.7 (range 16.7-100) to 58.3 (range 8.3-100)
Hu *et al* [24]	Prospective study	ERCP + ESWL	214	SF-36	Physical health: 56.9 ± 18.7 to 59.2 ± 14.8 (no significant difference); Patients with pseudocysts: 95 (range 35-100) to 100 (range 75-100); Mental health: 52.2 ± 21.5 to 58.5 ± 16.4; Patients with pseudocysts: 68 (range 36-100) to 76 (range 28-100)
Milovic *et al*[27]	Prospective study	ERCP + ESWL	32	1-5 scale	4 (range 2-5) to 2.5 (range 1-4)
Basiński *et al*[32]	Prospective study	Celiac plexus block	92	EORTC	Quality of life significantly improved with greatest improvement seen in those with high religiosity
Rutter *et al*[21]	Retrospective study	ERCP	150	EORTC	Patients treated with surgery had less nausea/vomiting compared to those treated with endoscopy
Tandan *et al*[23]	Retrospective study	ERCP + ESWL	636	1-10 scale	252 (92.6%) patients had improved quality of life
Seven *et al*[26]	Retrospective study	ERCP + ESWL	120	1-10 scale	3.7 ± 2.4 to 7.3 ± 2.7
Gerges *et al*[28]	Retrospective study	Pancreatoscopy-guided lithotripsy	20	Generic quality of life instrument	89% had no or only mild disability in daily activities, 47% had "excellent" or "very good" general health
Vitale *et al*[29]	Retrospective study	Minor papilla stenting	32	Generic quality of life survey	100% stated improved quality of life, 100% stated satisfaction with treatment

ERCP: Endoscopic retrograde cholangiopancreatography; ESWL: Extracorporeal shock-wave lithotripsy; SF: Short Form Health Survey; EORTC: European Organisation for Research and Treatment of Cancer.

"excellent" or "very good."

Minor papilla endotherapy

Minor papilla endotherapy typically involves performing a minor papilla sphincterotomy and/or stenting. Depending on the presence of strictures or stones, endotherapy can also include dilation or stone lithotripsy. A single-center study examining 32 patients with CP and pancreas divisum-related strictures assessed quality of life through telephone surveys asking about their overall quality of life and their level of satisfaction post-treatment[29]. All subjects treated *via* endotherapy reported improved quality of life and satisfaction in their treatment.

Pancreatic fluid collection drainage

There were no studies examining transmural drainage of CP-associated pancreatic fluid collections that included quality of life as an outcome. In regards to patients with acute necrotizing pancreatitis, however, Smith *et al*[30] performed a single-center cross-sectional study examining patients treated with endoscopic ultrasound-guided transmural drainage of walled-off necrosis. Using the SF-36, the authors found that at 2 year follow-up, patients treated with transmural drainage had equivalent scores to a healthy control population in nearly all domains with the exception of the physical role and general health domains, where they had significantly lower scores (physical role: 58.5 ± 40.9 *vs* 81.0 ± 34.0, general health: 56.9 ± 25.8 *vs* 72.0 ± 20.3) Notably, these subjects had significantly higher quality of life scores in domains such as pain and vitality compared to patients with irritable bowel syndrome.

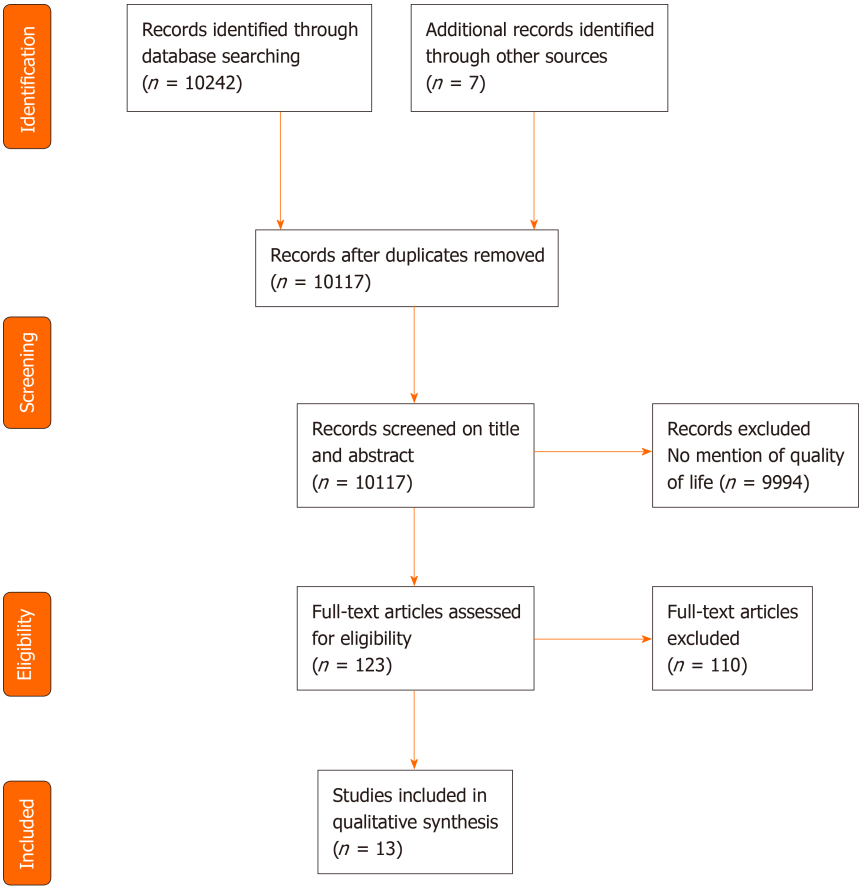

Figure 1 PRISMA flow diagram of article selection.

Celiac plexus block

In a single-center randomized study comparing celiac plexus block (using bupivacaine) with and without triamcinolone for patients with painful CP, pre and post-therapy quality of life was assessed using the SF-12[31]. The study was stopped prematurely at interim analysis due to no difference between the two treatment arms in improving pain and no significant differences in physical and mental quality of life were seen between the 2 arms. The triamcinolone arm saw a change of -0.2 ± 7.5 for physical health and a change of 1.3 ± 10.0 in mental health while the control arm saw a change of 1.7 ± 8.8 in physical health and a change of -2.1 ± 12.9 in mental health. In a study from Poland, Basiński *et al*[32] utilized the EORTC quality of life questionnaire, finding improvement in quality of life at 1- and 4-wk follow-up. Stratifying patients on their level of religiosity, the greatest improvement in quality of life was seen in those with high religiosity at both time points.

DISCUSSION

In this systematic review, while we demonstrate that PET does appear to improve quality of life in patients with CP, the most striking finding is the overall lack of evidence in many of these PET modalities. The majority of evidence comes from endoscopic treatment of pancreatic ductal obstruction secondary to PD stones and strictures with the 2 Landmark trials by Cahen *et al*[18] and Issa *et al*[20] comparing surgical with endoscopic drainage. There remain clear gaps in knowledge regarding how endoscopic therapies such as celiac plexus block, pancreatoscopy-guided therapies, endoscopic transmural drainage of pancreatic fluid collections and minor papilla endotherapy affect quality of life in the CP population. This highlights the continued emphasis of endoscopic studies on technical success outcomes rather than patient-centered outcomes and while PET modalities will continue to expand, without understanding the impact of these therapies on patients, choosing the best treatment for each individual patient becomes even more challenging.

As shown in Table 1, studies most often measured quality of life using the SF-36 and the EORTC quality of life instrument, which while validated, are not disease-specific for chronic pancreatitis. The remaining studies assessed quality of life by simply asking about quality of life, speaking to need for more rigorous research in quality of life within this field of endotherapy. The PANcreatitis Quality of Life Instrument is a validated chronic pancreatitis-specific quality of life instrument consisting of 18 items that includes sub-scores for physical function, role function, emotional function, and self-worth domains[33]. Additionally, the National Institute of Health has developed the Patient-Reported Outcomes Measurement Information System instruments to standardize measurement of patient-reported outcomes such as quality of life and pain. Incorporating instruments such as these can facilitate future research in this arena by capturing critical quality of life aspects pertinent to this patient population.

Pain remains the center point of quality of life in patients with CP as constant pain and severe pain, in particular, are associated with worse quality of life[2,34]. Similar to quality of life, pain has been poorly measured in prior PET studies with most reporting a visual analog scale score or the Izbicki pain score, which are simplified assessments of pain[35]. The Initiative on Methods, Measurement, and Pain Assessment in Clinical Trials has recently called for improved phenotyping of pain in an effort to deliver the most appropriate therapy based on an individual patient's pain characteristics[36]. In line with this, pancreatic quantitative sensory testing (QST) represents a novel method of characterizing sensory processing in the peripheral and central pain pathways[37]. While data has demonstrated how QST can be used to predict the efficacy of pregabalin in CP patients, much work is needed to determine if QST can help predict a priori which patients will respond to PET[38]. Nevertheless, there remains much promise in using tools such as QST to better characterize pain profiles in patients with CP to ultimately develop an algorithm-based approach to the management of this challenging disease.

In addition to the quantitative analysis done in these studies, qualitative studies are needed to truly encapsulate subjects' experiences with PET and better understand how PET affects their disease. Quantitative assessment of quality of life captures only a portion of the patient's overall well-being and given the lack of qualitative studies centered around endotherapy, future endeavors are certainly needed to incorporate the patient's perspective. Understanding factors such as patient expectations, regret, suffering, and coping may help design future randomized sham-controlled trials with patient-centered outcomes to help determine which PET modalities are most effective in which patients.

CONCLUSION

In summary, given the dearth of treatment options for CP, PET offers a viable therapy for patients with CP-related complications such as PD stones and strictures. Much work is needed, however, to elucidate the patient experience with PET and identify who will respond to PET with the ultimate goal of providing individualized treatment plans for these patients.

ARTICLE HIGHLIGHTS

Research background

While pancreatic endotherapy is frequently performed for the treatment of chronic pancreatitis-related complications, most studies examining endotherapy have focused on technical success outcomes, such as stricture resolution or stone clearance. Studies reporting patient-centered outcomes such as quality of life are lacking, however, making it difficult to determine how endotherapy affects these patients.

Research motivation

The motivation for this systematic review stems from the primary criticism of pancreatic endotherapy on whether endotherapy improves the lives of patients with chronic pancreatitis. While it is well-known that endotherapy can treat the structural complications of chronic pancreatitis, the effect of endotherapy on patient-centered outcomes is poorly studied.

Research objectives
The primary objective of this systematic review was to detail the literature regarding how pancreatic endotherapy affects quality of life in chronic pancreatiits patients.

Research methods
A systematic review was performed to identify studies reporting on various pancreatic endotherapy modalities and quality of life.

Research results
The search yielded 13 studies for review out of 10242 articles. All of the modalities examined found an improvement in quality of life.

Research conclusions
Pancreatic endotherapy does appear to improve quality of life, but the assessment of quality of life is very heterogeneous and not disease-specific. Furthermore, there is a lack of evidence regarding many modalities such as transmural fluid drainage, pancreatoscopy-guided therapy and celiac plexus block.

Research perspectives
Further studies are clearly needed to elucidate the patient experience with receiving pancreatic endotherapy and future trials will benefit from having patient-centered outcomes as the primary outcome.

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META-ANALYSIS

Efficacy and safety of endoscopic transpapillary gallbladder drainage in acute cholecystitis: An updated meta-analysis

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Abstract

BACKGROUND

Percutaneous transhepatic gallbladder drainage has been the most frequently performed treatment for acute cholecystitis for patients who are not candidates for surgery. Endoscopic transpapillary gallbladder drainage (ETGBD) has evolved into an alternative treatment. There have been numerous retrospective and prospective studies evaluating ETGBD for acute cholecystitis, though results have been variable.

AIM

To evaluate the efficacy and safety of ETGBD in the treatment of inoperable patients with acute cholecystitis.

METHODS

We performed a systematic review of major literature databases including PubMed, OVID, Science Direct, Google Scholar (from inception to March 2021) to identify studies reporting technical and clinical success, and post procedure adverse events in ETGBD. Weighted pooled rates were then calculated using fixed effects models for technical and clinical success, and post procedure adverse events, including recurrent cholecystitis.

RESULTS

We found 21 relevant articles that were then included in the study. In all 1307 patients were identified. The pooled technical success rate was 82.62% [95% confidence interval (CI): 80.63-84.52]. The pooled clinical success rate was found to be 94.87% (95%CI: 93.54-96.05). The pooled overall complication rate was 8.83% (95%CI: 7.42-10.34). Pooled rates of post procedure adverse events were bleeding 1.03% (95%CI: 0.58-1.62), perforation 0.78% (95%CI: 0.39-1.29), peritonitis/bile leak 0.45% (95%CI: 0.17-0.87), and pancreatitis 1.98% (95%CI: 1.33-2.76). The

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pooled rates of stent occlusion and migration were 0.39% (95%CI: 0.13-0.78) and 1.3% (95%CI: 0.75-1.99) respectively. The pooled rate of cholecystitis recurrence following ETGBD was 1.48% (95%CI: 0.92-2.16).

CONCLUSION
Our meta-analysis suggests that ETGBD is a feasible and efficacious treatment for inoperable patients with acute cholecystitis.

Key Words: Endoscopic transpapillary gallbladder drainage; Acute cholecystitis; Inoperable treatment; Double pigtail stent; Nasobiliary drainage

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Core Tip: We offer the most updated meta-analysis evaluating the efficacy, feasibility and safety of endoscopic transpapillary gallbladder drainage for the treatment of inoperable acute cholecystitis. We included 21 studies in our analysis. Our results conclude that this modality of gallbladder drainage is safe and efficacious.

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INTRODUCTION

Cholelithiasis is a common condition that affects 6% of men and 9% of women in the United States[1]. Acute cholecystitis is a syndrome of right upper quadrant abdominal pain, fevers and leukocytosis that is associated with inflammation of the gallbladder. Occurring in about 6%-11% of patients with symptomatic gallstones, it is the most common gallbladder syndrome[2]. The standard of care treatment for acute cholecystitis is antibiotic therapy and definitive surgical intervention with cholecystectomy. For patients unsuitable for surgery, the ideal choice has been percutaneous transhepatic drainage.

Percutaneous drainage is well established in the literature with strong technical success rates of nearly 97%, and with more variable clinical response rates ranging from 56%-100%[3-5]. Though effective, complications related to externalized drainage including bile leakage, peritonitis, bleeding and catheter misplacement/removal have been noted[6]. Patient satisfaction and quality of life have also been of concern, with patient discomfort occurring in up to 25% of patients[7]. Coagulopathy and decompensated liver disease with ascites have also been contraindications to percutaneous drainage[8,9]. Another drawback to percutaneous drainage is that it may be an impermanent solution. Patients who did not undergo cholecystectomy following percutaneous catheter removal had significant recurrence rates of cholecystitis ranging from 22%-47%[10,11].

Endoscopic techniques for gallbladder drainage have been evaluated in inoperable patients with cholecystitis who are not suitable for percutaneous drainage. Two endoscopic approaches to gallbladder drainage exist, they include a transmural approach performed with endoscopic ultrasound (EUS), and endoscopic transpapillary gallbladder drainage (ETGBD) which utilizes endoscopic retrograde cholangiopancreatography (ERCP). EUS guided gallbladder drainage was first described in 2007, with well-established efficacy. Technical and clinical success rates of 84.6%-100% and 86.7%-100% respectively have been demonstrated[12,13]. Drawbacks, such as the need for a high level of expertise, procedure costs and the risk of adverse events in the setting of technical failure, have been noted. The development of lumen opposing stents (LAMS) has improved the feasibility and efficacy and has helped to decrease the rate of procedure related complications. Nevertheless, there is uncertainly of the effects of retained LAMS and its contribution to adverse events as well as its effect on future surgical options.

Transpapillary gallbladder drainage is an important option for inoperable patients requiring treatment of acute cholecystitis. It consists of ERCP bile duct cannulation followed by endoscopic transpapillary gallbladder stenting or endoscopic nasobiliary gallbladder drainage (ENGBD). Both approaches have been useful in patients with concomitant choledocholithiasis or in the presence of biliary stricture. Unlike ENGBD, a transpapillary approach has evolved as an especially advantageous method due to its relatively non-invasive nature with improved patient quality of life without the need for externalized drainage. Drawbacks to this method include the potential for post ERCP complications, along with the technical difficulty of the procedure itself, though there have been variable results in the literature. We performed a systematic review including more recent studies evaluating ETGBD in inoperable patients with acute cholecystitis. We present an updated meta-analysis evaluating the technical and clinical success of ETGBD. We also evaluate the safety of ETGBD by analyzing pooled rates of procedural adverse events.

MATERIALS AND METHODS

Search methodology

We performed a literature search using the electronic database engines PubMed, OVID, ScienceDirect, Google scholar from inception to March 2021 to identify published articles and reports which addressed the use of ETGBD as treatment for acute cholecystitis. The search terms "endoscopic transpapillary gallbladder drainage", "acute cholecystitis", "complications", "technical success", "clinical success", "adverse events" in different combinations were used. The reference lists of eligible studies were reviewed to identify additional studies. The retrieved studies were carefully examined to exclude potential duplicates or overlapping data. Resultant titles and abstracts were selected from the initial search, they were scanned, and the full papers of potential eligible studies were reviewed.

Study eligibility

The relevance of the studies was initially screened based on title, abstract and the full manuscript. Published studies were eligible for inclusion if they reported the use of ETGBD for the treatment of acute cholecystitis. Studies that evaluated technical and clinical success, along with procedure related adverse events were included. Articles were excluded if they were not available in English, or if they did not have reported outcomes. In studies that compared multiple methods of treatment for acute cholecystitis, data from the cohort of patients who underwent EGTBD were collected and analyzed. Each article title and abstract was reviewed by two investigators (Jandura DM and Puli SR). They obtained full articles that met the inclusion and exclusion criteria, and after an independent review of the full content of each article, they extracted the data. Any differences were resolved by mutual agreement. The agreement between reviewers gave a Cohen's κ 1.0.

Data extraction and quality assessment

The following data was independently abstracted into a standardized form: Study characteristics (primary author, year of publication), study design, baseline characteristics of study population (number of patients enrolled, patient demographics) and intervention details (procedure indications) and outcomes (technical and clinical success, adverse events). The risk of bias was rated by two authors independently.

Outcome definition

The primary outcome of interest was assessment of ETGBD efficacy in terms of technical and clinical success. Clinical success was calculated based on the cohort of patients that achieved technical success in each study. The secondary outcomes that were assessed were overall and individual procedure related adverse events, and the rates of recurrent cholecystitis following the intervention.

Statistical analysis

This meta-analysis was performed by calculating pooled proportions. First, the individual study proportions was transformed into a quantity using a Freeman-Tukey variant of the arcsine square root transformed proportion. The pooled proportion was calculated as the back-transform of the weighted mean of the transformed proportions, using inverse arcsine variance weights for the fixed effects model and DerSimonian-

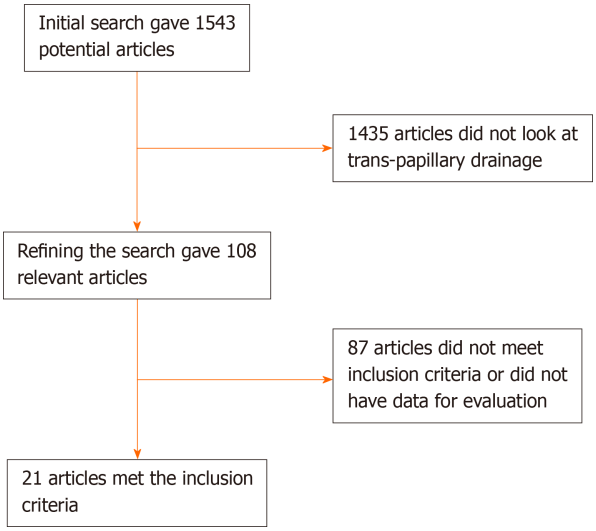

Figure 1 Flowchart of search results.

Laird weights for the random effects model[14,15]. Forest plots were drawn to show the point estimates in each study in relation to the summary pooled estimate. The width of the point estimates in the forest plots indicates the assigned weight to that study. The effect of publication and selection bias on the summary estimates was tested by the Harboud-Egger indicator[16]. Also, funnel plots were constructed to evaluate potential publication bias[17,18].

RESULTS

Study selection

In summary, 21 studies identified by our search using the literature databases were included for our analysis. A flow diagram of this systematic review is included in Figure 1.

Characteristics of the included studies

In all, 8 studies were performed in Japan, 6 were performed in the United States, and 4 were performed in South Korea. 3 of the remaining studies included in our meta-analysis were originally performed in Germany, Denmark and Italy. Most of the studies were retrospective, however prospective and one random controlled trial was included.

Participants

A total of 1307 patients from 21 studies were included in the meta-analysis. In this meta-analysis, 61.44% of the patients included were males and 38.56% were females. The median age of study subject was 68.41 (range: 48.5-79.7).

Interventions

ETGBD was performed in inoperable patients with acute cholecystitis with placement of a double pigtail stent in 57.1% of studies. Plastic stents were used in 40.0% of studies. Nasobiliary stenting was performed in 45.0% of the studies included in the meta-analysis.

Outcomes

Technical success was reported by all the studies included in the analysis. The prevalence of successfully performed procedures ranged from 70.59%-100%. The pooled rate of technical success of ETGBD was 82.62% [95% confidence interval (CI): 80.63-84.52]. The individual study rates and the pooled proportion of technical success is shown as a forest plot in Figure 2.

Efficacy

Procedure efficacy, as represented by clinical success was described by all the studies

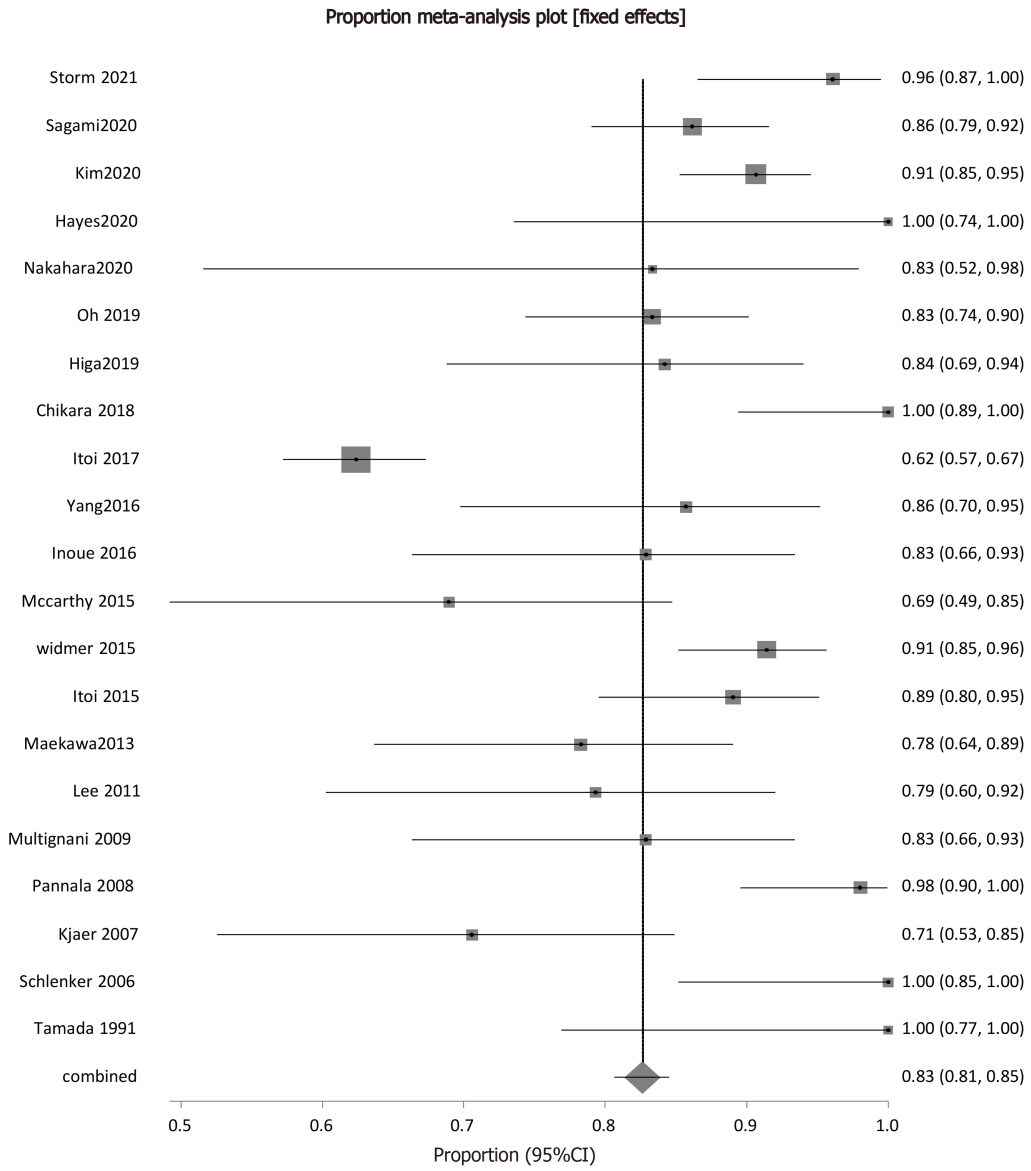

Figure 2 Forest plot showing the individual study proportions of endoscopic transpapillary gallbladder drainage technical success in relation to the pooled rate[7,9,22,24-40].

included in the analysis. Prevalence of ETGBD efficacy in successful treatment of cholecystitis ranged from 64.29%-100%. The pooled proportion of clinical success of ETGBD was 94.87% (95%CI: 93.54-96.05). Figure 3 shows the forest plot of the pooled proportion of clinical success.

Safety

The overall pooled rate of post procedural complications was 8.83% (95%CI: 7.42-10.34). The forest plot depicting the pooled proportion of complications is in Figure 4. The pooled proportion of patients with bleeding as an adverse event following ETGBD was 1.03% (95%CI: 0.58-1.62). Pooled proportion of patients with perforation as an adverse event following ETGBD was 0.78% (95%CI: 0.39-1.29). Peritonitis/bile leak as an adverse event following ETGBD was calculated as a pooled proportion and was 0.45% (95%CI: 0.17-0.87). The pooled proportion of patients with pancreatitis following ETGBD was 1.98% (95%CI: 1.33-2.76).

Stent related procedure complications were also featured in the analysis as adverse events in all the included studies. They included both stent occlusion and stent migration. The pooled proportion of patients with stent occlusion following ETGBD was 0.39% (95%CI: 0.13-0.78). The pooled proportion of patients with stent migration was 1.3% (95%CI: 0.75-1.99).

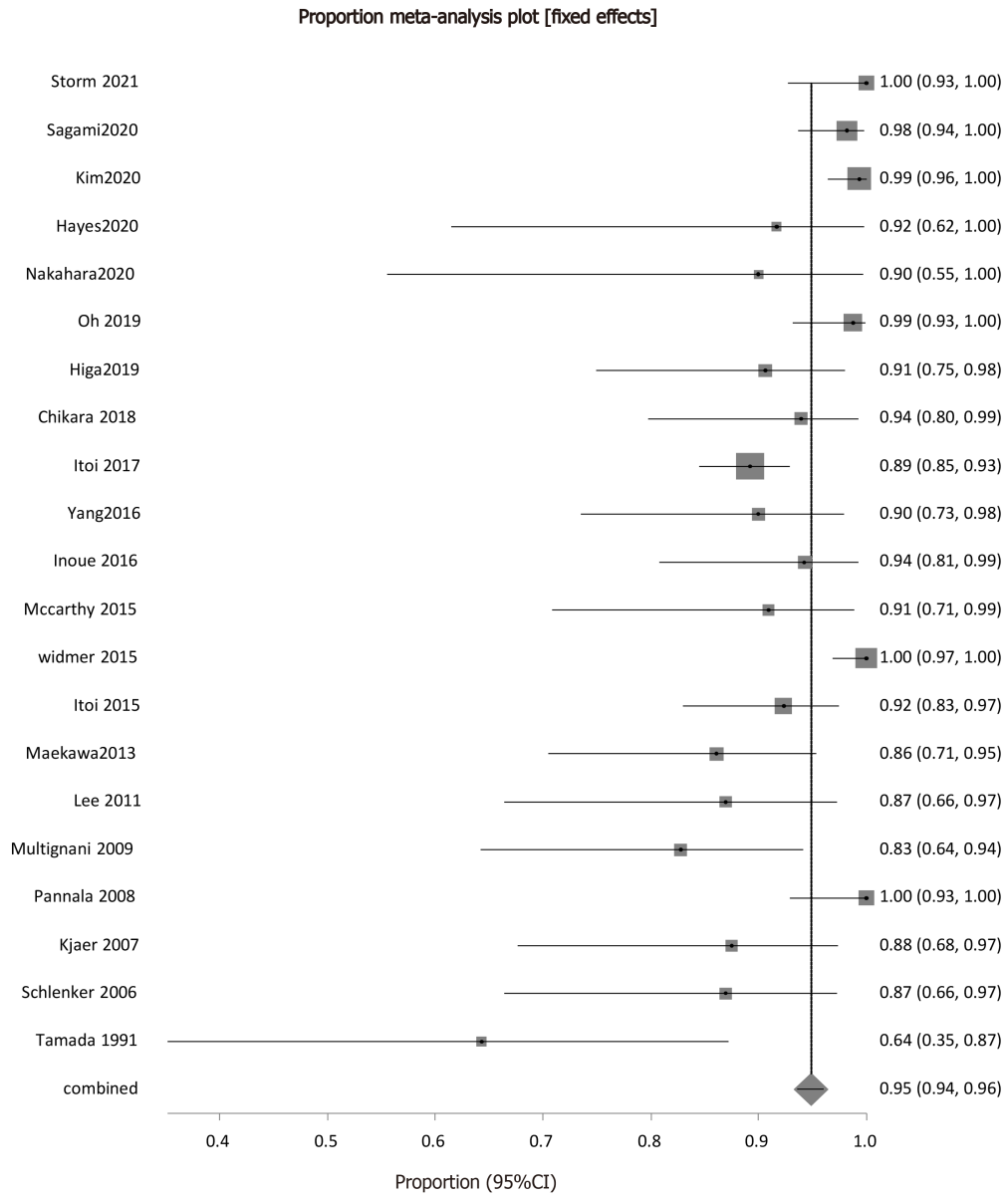

Figure 3 Forest plot showing the individual study proportions of endoscopic transpapillary gallbladder drainage clinical success in relation to the pooled rate[7,9,22,24-40].

Recurrent cholecystitis was also included as a secondary outcome measure. There were 6 studies which reported a recurrence of cholecystitis following ETGBD. The pooled proportion of patients with recurrent cholecystitis following ETGBD was 1.48% (95%CI: 0.92-2.16).

Publication bias calculation using the Harbord-Egger bias indicator gave a value of -1.61 (95%CI: -4.70-1.49) (P = 0.29), indicating that there was no publication bias. The funnel plot in Figure 5 shows no publication bias for ETGBD clinical success.

DISCUSSION

Cholecystectomy is the standard of care for the treatment of acute cholecystitis, however a subset of patients exists with co-morbidities or poor clinical status that are not candidates for surgery. Based on Tokyo guidelines from 2018, the standard non-surgical approach recommendation for high-risk patients has been percutaneous guided gallbladder drainage[19]. It has remained the most frequently used intervention for inoperable patients due to the vast procedural expertise that exists as well as its significant representation within the literature. The management of cholecystitis has evolved to include endoscopic methods of treatment, and choosing the appropriate intervention requires consideration of multiple factors including

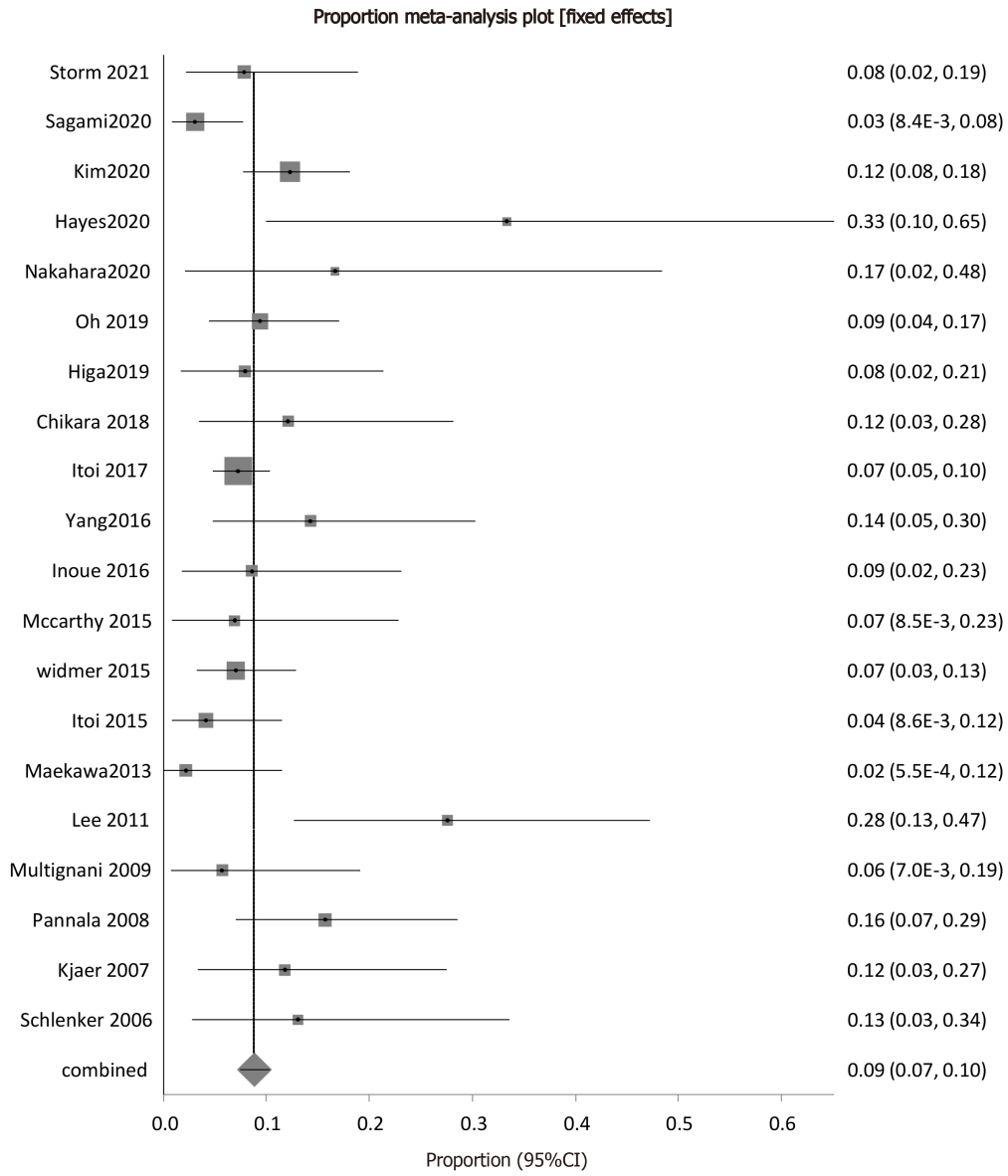

Figure 4 Forest plot showing the individual study proportions of endoscopic transpapillary gallbladder drainage related adverse events in relation to the pooled rate[7,9,22,24-39].

patient co-morbidities and preferences, technical factors, and local expertise. Endoscopic therapies have been advantageous over percutaneous drainage when tolerability of externalized drainage is an issue due to patient discomfort and given the potential for these drains to migrate, occlude or become secondarily infected. Other patient factors such as ascites or coagulopathy also need to be considered. Technical factors such as suspected biliary obstruction due to choledocholithiasis and biliary stricture, also support the preferential use of transpapillary gallbladder drainage.

Transpapillary drainage can be technically challenging, specifically due to the difficult nature of cannulation of the bile duct and traversal of the cystic duct. Our pooled rates of technical and clinical success were 83% and 95% respectively. Rates of initial failure are not negligible, however if successfully performed the vast majority of patients found clinical success. Studies have shown that centers with high volume and expertise have benefited from their increased experience, with improved technical success rates. Kjaer *et al*[20] demonstrated an improvement in technical success from 50% in the first 4 years of the study to 89% in the final 5 years of the study, indicating that there is a learning curve that could be overcome with experience. Prior studies have demonstrated similar results when evaluating efficacy of endoscopic drainage in regards to technical and clinical success compared to percutaneous methods[21], though further comparison trials are required.

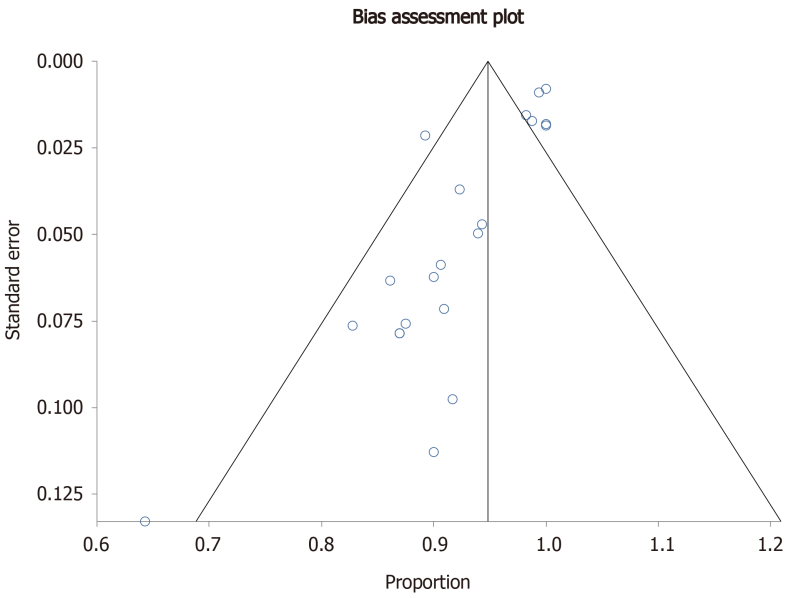

Figure 5 Funnel plot evaluating the effect of publication bias on individual studies rates of endoscopic transpapillary gallbladder drainage success.

Lyu *et al*[23] demonstrated that the adverse event and mortality rates amongst EUS guided gallbladder drainage, transpapillary gallbladder drainage and percutaneous gallbladder drainage were comparable. Nonetheless, post-operative complications related to endoscopic interventions such as EUSGBD and ETGBD tended to have higher risk adverse events that had a higher propensity to lead to death, such as perforation, bleeding, and pancreatitis. Our overall pooled complication rate was about 9%, with the highest being pooled rates of pancreatitis. ERCP related complications have been an increased concern, given the need for cannulation of the bile duct for successful transpapillary gallbladder drainage and stenting to occur. Given the burden of potentially severe adverse events, ETGBD should be reserved for patients who are otherwise not candidates for standard percutaneous drainage. Such therapies should also be performed in centers with high expertise and specifically when other biliary interventions are called for, such as in the case of concomitant choledocholithiasis.

Based on our results, recurrent cholecystitis occurred in about 1% of patients undergoing transpapillary drainage and stenting. These patients with recurrence may require repeat transpapillary drainage, or other methods of gallbladder drainage. A subset of patients can eventually undergo definitive cholecystectomy when clinically stabilized. A particular benefit of ETGBD over other endoscopic interventions such as EUS guided stenting is the avoidance of creating a chole-duodenal or gastric fistula, which can make eventual surgical intervention difficult. Stents placed during ETGBD may be removed just prior to planned cholecystectomy.

Our study had several limitations. Most of the studies included were retrospective analysis, with only one randomized controlled trial. This could have led to selection and time bias. The exclusion of non-English studies could have also led to bias. Inclusion of these studies could have led to more randomized control trials in our analysis. Many of the studies included in the pooled analysis, included the use of nasobiliary drainage. Over the past several years, this method that has been utilized less frequently, in favor of double pigtail stents making the application of our data to everyday practice more difficult. Though based on prior subgroup analysis, double pigtail stenting was compared to nasobiliary drainage with similar rates of technical (85% *vs* 81%), and clinical success (95% *vs* 93%)[21]. Outcome definitions, including technical success and clinical success varied among the included studies. This may have confounded the pooled results, though publication bias was not significant based on indicators that were used.

CONCLUSION

In conclusion, our study supports that ETGBD is a safe and efficacious procedure for

inoperable patients with cholecystitis. Given its relative technical difficulty, which is inherent to ERCP, it should be performed in high volume centers and when patients are unfit for percutaneous drainage. Its clinical success rates were comparable to prior analyses, and rates of adverse events were acceptable. At this time further data and prospective trials would be beneficial in evaluating the long-term outcomes of ETGBD.

ARTICLE HIGHLIGHTS

Research background

Percutaneous gallbladder drainage has been the standard treatment of acute cholecystitis in patients who are not surgical candidates. Our study sought to evaluate the efficacy and safety of transpapillary drainage for acute cholecystitis in this subset of patients.

Research motivation

The key topics of interest include non-surgical, less-invasive techniques to treat acute cholecystitis. The evolution of safe and effective treatments in acute cholecystitis can lead to improved patient outcomes and quality of life following treatment. Future research can also have a positive effect on cost effectiveness and health care utilization.

Research objectives

The main objectives were to evaluate feasibility, efficacy and safety of transpapillary gallbladder drainage in inoperable patients for the treatment of acute cholecystitis. This can positively affect further research and direct comparison trials.

Research methods

A systematic review was performed followed by updated meta-analysis.

Research results

The pooled technical success rate of endoscopic transpapillary gallbladder drainage (ETGBD) was 82.62% [95% confidence interval (CI): 80.63-84.52]. The pooled clinical success rate was found to be 94.87% (95%CI: 93.54-96.05). The pooled overall complication rate was 8.83% (95%CI: 7.42-10.34). Pooled rates of post procedure adverse events were bleeding 1.03% (95%CI: 0.58-1.62), perforation 0.78% (95%CI: 0.39-1.29), peritonitis/bile leak 0.45% (95%CI: 0.17-0.87), and pancreatitis 1.98% (95%CI: 1.33-2.76). The pooled rates of stent occlusion and migration were 0.39% (95%CI: 0.13-0.78) and 1.3% (95%CI: 0.75-1.99) respectively. The pooled rate of cholecystitis recurrence following ETGBD was 1.48% (95%CI: 0.92-2.16).

Research conclusions

Our results demonstrated that transpapillary gallbladder drainage for treatment of acute cholecystitis is both an efficacious and safe procedure in patients that are inoperable. This particular method of gallbladder drainage may offer an alternative to a certain subset of inoperable patients who are otherwise not candidates for percutaneous drainage. Patients who demonstrate signs of concomitant choledocholithiasis or cholangitis also benefit. Comparison between percutaneous drainage, and endoscopic drainage methods with endoscopic ultrasound or a transpapillary approach has been explored however results remain inconclusive.

Research perspectives

Future research should involve randomized controlled trials to compare the different non-surgical techniques used in treatment of acute cholecystitis. In regards to ETGBD, emphasis should be placed on different stenting methods, along with assessment of long term outcomes.

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MINIREVIEWS

Endoscopic management of colorectal polyps: From benign to malignant polyps

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Abstract

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer related death in the world. The early detection and removal of CRC precursor lesions has been shown to reduce the incidence of CRC and cancer-related mortality. Endoscopic resection has become the first-line treatment for the removal of most precursor benign colorectal lesions and selected malignant polyps. Detailed lesion assessment is the first critical step in the evaluation and management of colorectal polyps. Polyp size, location and both macro- and micro- features provide important information regarding histological grade and endoscopic resectability. Benign polyps and even malignant polyps with superficial submucosal invasion and favorable histological features can be adequately removed endoscopically. When compared to surgery, endoscopic resection is associated with lower morbidity, mortality, and higher patient quality of life. Conversely, malignant polyps with deep submucosal invasion and/or high risk for lymph node metastasis will require surgery. From a practical standpoint, the most appropriate strategy for each patient will need to be individualized, based not only on polyp- and patient-related characteristics, but also on local resources and expertise availability. In this review, we provide a broad overview and present a potential decision tree algorithm for the evaluation and management of colorectal polyps that can be widely adopted into clinical practice.

Key Words: Colorectal cancer; Colon polyps; Malignant polyps; Endoscopic resection; Endoscopic mucosal resection; Endoscopic submucosal dissection

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Core Tip: Endoscopic resection is a proven strategy for the management of benign and selected malignant colorectal polyps. When compared to surgery, endoscopic resection is less costly and associated with improved clinical outcomes and patient satisfaction. Detailed lesion assessment, including endoscopic imaging and histopathology, play a critical role in directing subsequent treatment strategies. Ultimately, the most appropriate intervention will depend on various factors, including patient and lesion characteristics, as well as local resources and expertise availability. Establishing the multidisciplinary collaboration between referring physicians, endoscopists, surgeons and pathologists is the basis for ensuring best practices for the management of colorectal polyps.

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INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer worldwide and the second leading cause of cancer death in the world[1]. A well-recognized characteristic of CRC carcinogenesis is that most cancers arise from precursor benign polyps[2]. The increasingly widespread adoption of colonoscopy has reduced CRC incidence and mortality *via* the early detection and removal of these precursor lesions and even early cancers[3,4]. In this review, we provide a broad overview and decision algorithm on the endoscopic evaluation and management of colorectal polyps.

DEFINITIONS

Colorectal polyps are growths or protuberances into the lumen above the adjacent colonic mucosa. The two major histologic types of neoplastic polyps that serve as direct precursors to most CRCs are conventional adenomas and serrated polyps[5].

Adenomas

Adenomas are commonly regarded as the prototypical precursor of CRC, given that nearly 85%-90% of sporadic CRCs derive from adenomas[6]. These lesions are identified histologically by epithelial clusters of dysplastic glands; and are divided into tubular, tubulovillous, or villous types according to the World Health Organization (WHO) classification system[7]. The adenoma-carcinoma sequence is characterized by chromosomal instability and a stepwise progression of gradual genetic and epigenetic mutations that culminate in the transformation of these precancerous lesions to CRC [8-10].

Serrated polyps

Serrated polyps encompass three main types:

Hyperplastic polyps (HPs): are the most common type of serrated polyp. They are usually small (less than 5 mm), predominantly located in the rectosigmoid colon, and are not associated with a risk for malignant transformation[6].

Sessile serrated lesions (SSLs): The term SSL is often used interchangeably with sessile serrated adenomas (SSAs). These lesions are traditionally larger than HPs, predominantly in the right colon, and according to the WHO criteria, distinguished from HPs based on the presence of crypt distortion on histology[7].

Traditional serrated adenomas (TSAs): TSAs are more commonly located in the distal colon and may have an erythematous "pine cone" gross appearance on endoscopy[11, 12]. Histologically, TSAs feature prominent cytoplasmic eosinophilia, elongated nuclei and ectopic crypts[7].

Unlike HPs, both SSL/SSAs and TSAs have malignant potential and account for approximately 15%-30% of all sporadic CRCs[6,11]. The inactivation of tumor suppressor genes *via* hypermethylation plays a critical role in the progression of serrated polyps to cancer, which is the basis of the CpG island methylator phenotype pathway[11-13]. From a histological standpoint, it is important to note that unlike conventional adenomas, not all SSL/SSAs have dysplasia. As opposed to SSL/SSAs without dysplasia, serrated polyps with dysplasia have advanced molecular changes; although there is some controversy in what constitutes these dysplasia patterns[14]. Irrespectively, SSL/SSAs with dysplasia should be distinguished from those without dysplasia given their significantly higher risk for progression to CRC[15].

CRC and the malignant polyp

CRC is defined as the invasion of neoplastic cells beyond the muscularis mucosa. As opposed to other organs in the gastrointestinal tract, the colonic mucosa is devoid of lymphatics. Therefore, neoplastic lesions confined to the muscularis mucosa have a negligible risk for lymph node metastasis (LNM) and, according to the National Comprehensive Cancer Network, do not meet the clinically accepted definition for CRC[16]. These lesions are defined as benign (non-malignant) polyps.

The term malignant polyp is used to describe a colorectal lesion in which neoplastic cells have invaded into, but not beyond the submucosa[17]. Hence, a malignant polyp represents early CRC and is categorized as pT1 according to the American Joint Committee on Cancer tumor-node metastasis classification system[18]. It has been estimated that at least 0.2% to 8.3% of colorectal polyps are malignant polyps[19-22].

ENDOSCOPIC ASSESSMENT OF COLORECTAL POLYPS

Detailed lesion assessment is the first critical step in the evaluation and management of colorectal polyps. Every polyp should be evaluated according to its size, location, and carefully inspected for macro- and micro- features. These details may provide important information regarding its histological grade and direct subsequent management decisions.

Polyp gross morphology

Paris classification: The Paris classification is a consensus system widely used to describe colorectal polyp morphology[23]. Although studies have shown only moderate agreement among experts using the Paris classification, it serves as a validated standardized nomenclature that helps categorize colorectal polyps and stratify according to the risk of CRC. Broadly speaking, lesions are categorized as polypoid (type 0-I) or non-polypoid (type 0-II) (Figure 1). The polypoid type can be either pedunculated (type 0-Ip) or sessile (type 0-Is). Nonpolypoid type 0-II can be further subdivided into those that are superficially elevated (0-IIa), flat (0-IIb), or depressed (0-IIc). Excavated lesions are designated type 0-III. The risk of CRC [*i.e.* submucosal invasion (SMI)] has been shown to be directly proportional to polyp size and the presence of depression: with the risk being as high as 40% in smaller lesions (6-10 mm) to nearly all lesions measuring more than 20 mm[24-26].

Lateral spreading tumors: Superficial non-polypoid colorectal lesions measuring more than 10 mm in diameter extending laterally rather than vertically are commonly referred as laterally spreading tumors (LSTs). The incidence of LSTs on routine colonoscopy is approximately 9%[25], and these can be broadly subdivided into the granular (LST-G) or non-granular (LST-NG) types (Figure 2). Similar to the Paris classification, LST morphology provides prognostic information regarding the risk for SMI. LST-G with a homogenous nodular pattern have a low risk of local invasion (< 2%) compared to LST-G with mixed-size nodules, in which the risk can be as high as 30% for those measuring more than 30 mm in size[27]. As opposed to the nodularity in LST-Gs, LST-NGs are characterized by a smooth surface and can be either flat or pseudo-depressed. In all, LST-NG with pseudo-depression carries the highest risk of SMI among LSTs (31.6%; 95%CI: 19.8%-43.4%)[28]. In addition to morphology, location is another important factor, with LST-G mixed type or LST-NG lesions in the rectosigmoid colon carrying the highest risk for malignancy[29].

Polyp surface pattern

In addition to its gross morphology, the surface vascular and pit pattern of a polyp can provide information about the risk of SMI and thereby assist with management

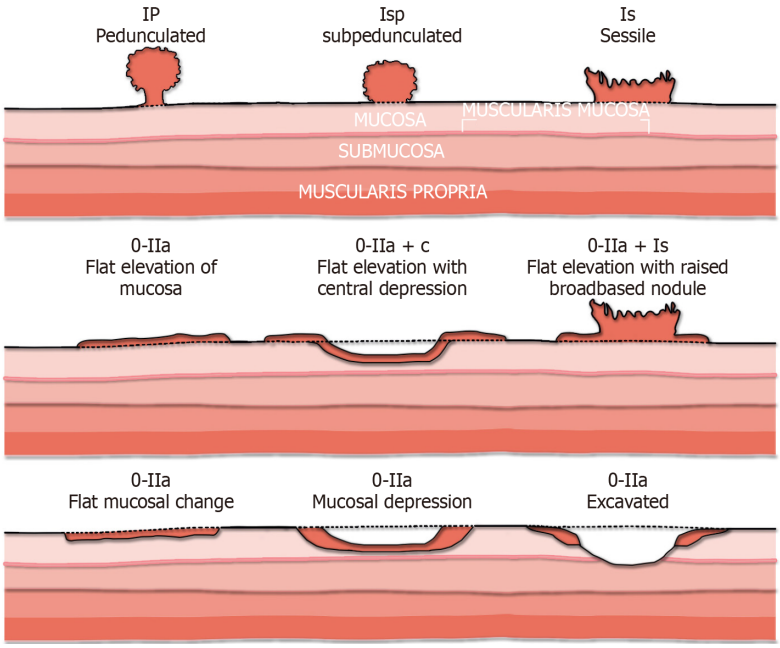

Figure 1 The Paris endoscopic classification of colorectal polyps. Adapted from[23].

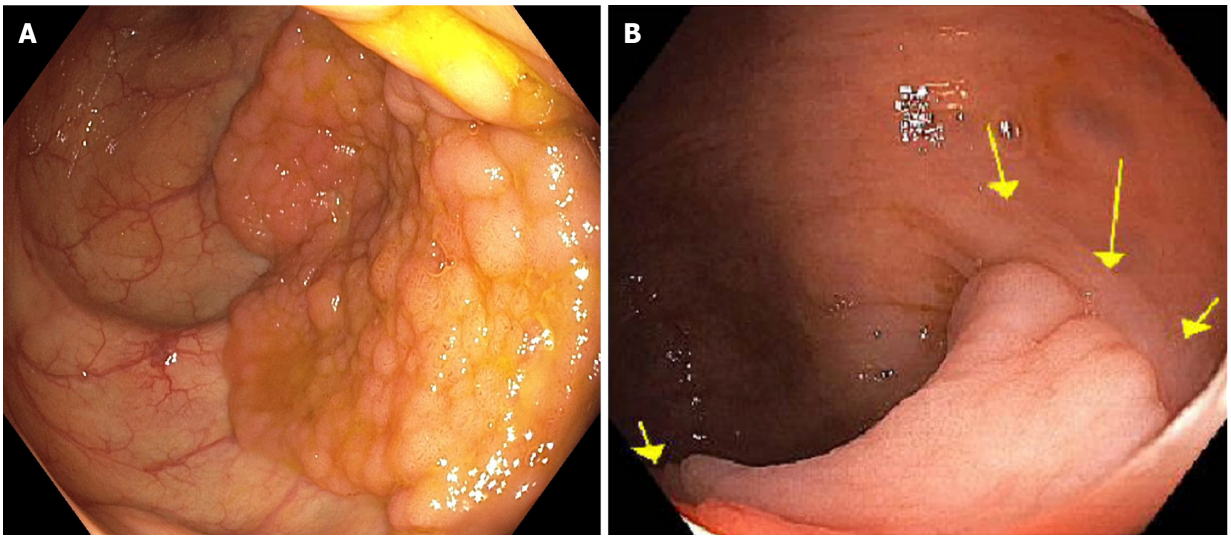

Figure 2 Lateral spreading tumor. A: Lateral spreading tumor with granular surface; B: Lateral spreading tumor non-granular type highlighted by arrows.

decisions. Multiple classification systems have been developed for polyp characterization and are outside the scope of this review. As part of this overview, we briefly discuss the Narrow Band Imaging International Colorectal Endoscopic (NICE) classification system and Kudo pit pattern nomenclature, which are possibly the most commonly utilized classification systems in the West.

NICE classification system: Narrow-band imaging (NBI) is a form of digital chromoendoscopy that enables detailed assessment of the capillary mucosal pattern of polyps by filtering white light into specific wavelengths to enhance the superficial microvascular structures. Using NBI, the NICE classification system provides a validated criterion for the optical diagnosis of colorectal polyps[30,31]. In this classification scheme, polyps can be divided into three categories (type 1, 2 or 3) based on their appearance (Table 1). NICE type 1 and 2 polyps are benign and can be resected endoscopically. Conversely, type 3 Lesions, characterized by disrupted/missing vessel pattern and amorphous or absent surface pattern on NBI, are highly suggestive of deep SMI, and thereby not amenable to endoscopic resection.

Table 1 Narrow-Band Imaging International Colorectal Endoscopic classification system

	Color	Vessels	Pits	Association
Type 1	Same or lighter than background	No or lacy vessels	Dark or white spots of uniform size	Hyperplastic or serrated polyps
Type 2	Browner than background	Brown vessels	Oval or tubular white pits	Adenomatous polyps
Type 3	Dark brown	Disrupted or missing vessels	Amorphous or absent pits	Deep submucosal invasion

This system uses color, vessel and surface pattern on Narrow-band imaging to predict the most likely polyp histology

Japan NBI Expert Team classification system: The Japan NBI Expert Team (JNET) introduced an NBI magnifying endoscopic classification system for colorectal polyps in 2014[32]. The JNET system is mainly used in Asian countries and less frequently in the Western Hemisphere. By focusing on vessel and surface pattern, the JNET system classifies colorectal polyps into four types (Types 1, 2A, 2B, and 3); each type representing the histological feature of the polyps (Table 2). Similar to NICE, irregular /amorphous vessel and surface patterns on the JNET classification system are indicative of a higher likelihood of submucosal invasive cancer.

Kudo pit pattern: Kudo and colleagues first highlighted the feasibility of examining and classifying pit patterns to distinguish type of polyps by using magnifying endoscopy[33]. This scheme broadly categorizes pit patterns into 7 types based on the pit appearance and structure (Figure 3). Most colorectal polyps (Kudo pit pattern types I through IV) fall within the spectrum of benign polyps that can be managed endoscopically. On the other hand, lesions with Kudo pit pattern V (amorphous, non-structured pit pattern) are often indicative of deep SMI, CRC and therefore the need for surgery[26,34].

HISTOLOGICAL ASSESSMENT OF COLORECTAL POLYPS

Accurate histopathological assessment is critical in determining adequacy of endoscopic resection. In this section, we briefly discuss some of the specific histopathological criteria associated with risk of recurrence and LNM in the context of malignant polyps.

Depth of invasion

Haggitt classification of pedunculated polyps: Haggitt *et al*[35] developed a classification system to describe the level of invasion in pedunculated polyps. This system categorizes polyps into five classes: level 0 to 4 (Figure 4). Level 0 corresponds to neoplastic cells limited to the mucosa without breaching the muscularis mucosa, thereby not meeting the clinical definition of CRC. Level 1 corresponds to those pedunculated polyps in which cancer cells have invaded the submucosa of the polyp head. Level 2 and 3 indicate cancer cells invading into the submucosa of the neck (junction between head and stalk) and any region of the stalk, respectively. Lastly, level 4 denotes invasion of cancer cells into the submucosa of the colorectal wall below the stalk of the polyp, but not into the muscularis propria.

Kudo and Kikuchi classification of sessile polyps: Both Kudo *et al*[36] and Kikuchi *et al*[37] introduced the concept of classifying sessile polyps into three levels based on the degree of SMI: Sm^1–invasion into the upper third of the submucosa; Sm^2–invasion into the middle third; and Sm^3–invasion into the lower third (Figure 5). The main challenge of implementing this classification system in routine clinical practice is the need for a significant portion of the submucosa within the resected specimen to define the deepest border of the submucosa. Hence, for practical purposes, this scheme has been largely modified to measure the depth of SMI from the muscularis mucosa. A SMI depth of 1000 μm is used to differentiate those lesions with superficial (< 1000 μm) *vs* deep (≥ 1000 μm) invasion. Deep SMI has been shown to be highly associated with risk for lymph node spread (10%-18%), independent of other histological features[38-40].

Tumor differentation, lymphosvacular invasion and tumor budding

In addition to depth of invasion, several histological features have been identified as

Table 2 Japan Narrow-band imaging Expert Team classification system

	Type 1	Type 2A	Type 2B	Type 3
Vessel pattern	Invisible	Regular caliber and distribution (meshed/spiral)	Variable caliber, irregular distribution	Loose vessel areas, interruption of thick vessels
Surface pattern	Uniform dark or white spots similar to surrounding mucosa	Regular (tubular/branched/papillary)	Irregular or obscure	Amorphous areas
Most likelyhistology	Hyperplastic or sessile serrated polyps	Low grade dysplasia	High grade dysplasia/shallow submucosal invasive cancer	Deep submucosal invasive cancer

This system uses vessel and surface pattern evaluation under magnified endoscopy with narrow-band imaging to predict the most likely polyp histopathology.

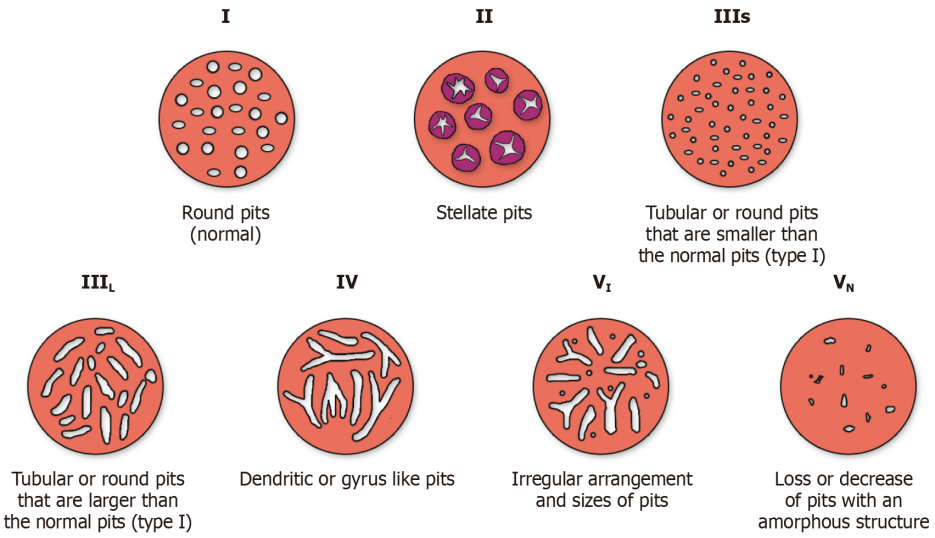

Figure 3 Kudo classification of pit pattern (Adapted from Kudo *et al*[33]).

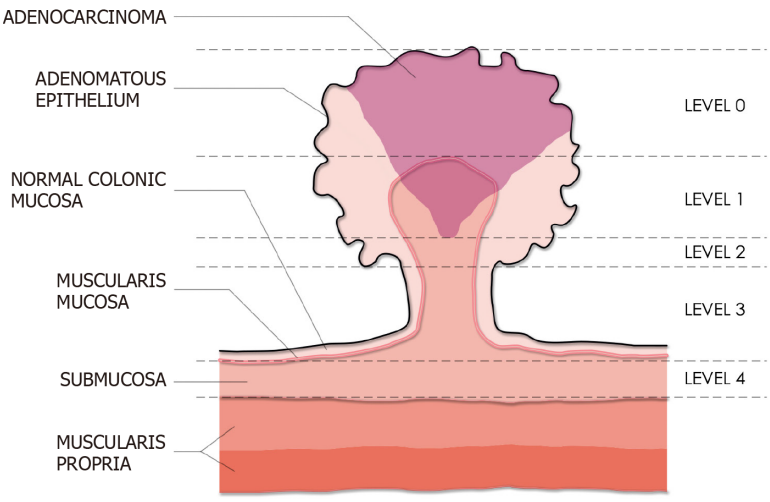

Figure 4 Haggitt classification system of pedunculated polyps (Adapted from Haggitt *et al*[35]). This system categorizes polyps into five levels (level 0 to 4) based on the degree of invasion. In this illustration, an adenocarcinoma confined to the head of the polyp would be classified as Level 1.

predictors for LNM.

Tumor differentiation: Three tumor grades have been used to described CRC based on the degree of glandular differentiation: grade 1 (well-differentiated), grade 2 (moderately differentiated), and grade 3 (poorly differentiated). When compared to

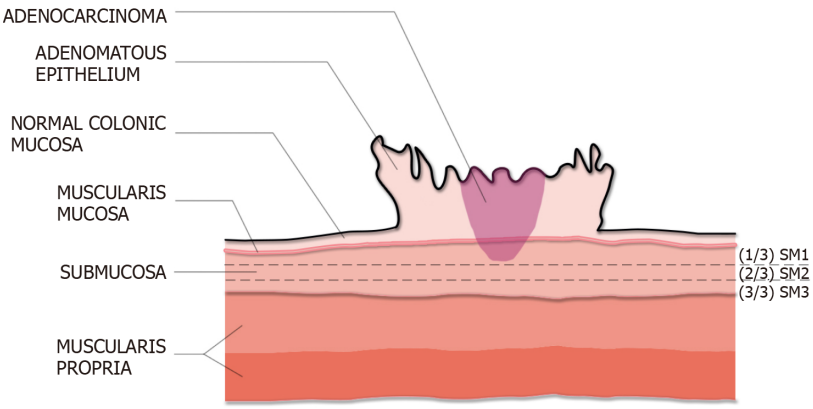

Figure 5 Kudo and Kikuchi classification (adapted from Kikuchi *et al*[37]). Depth of submucosal invasion is divided into Sm^1 (invasion into the upper third of the submucosa), Sm^2 (invasion into the middle third), Sm^3 (invasion into the lower third). In this illustration, the adenocarcinoma is a superficial lesion with Sm1 invasion.

grade 1 or 2, poorly differentiated adenocarcinomas have been shown to be associated with a significantly higher incidence of lymphatic spread [odds ratio (OR): 5.60; 95%CI: 2.90-10.82; $P < 0.00001$] and cancer-related mortality[39].

Lymphovascular invasion: Lymphovascular invasion (LVI) is recognized as a poor prognostic indicator and predictor of patient outcome. The presence of LVI in malignant polyps has been associated with an increased risk of regional LNM (OR: 4.81; 95%CI: 3.14-7.37; $P < 0.0001$)[39].

Tumor budding: Tumor budding is defined as a single or cluster of up to 5 tumor cells at the advancing front of the tumor[5,40]. This phenomenon has been recognized as a potential indicator of aggressive tumor biology with substantial evidence identifying it as a significant risk factor for LNM (OR: 7.74; 95%CI: 4.47-13.39, $P < 0.001$)[39].

Clinical ambiguity of the terms "intramucosal carcinoma" and "carcinoma in-situ"

Endoscopic resection should be the first-line preferred approach for the management of non-malignant polyps. Multiple studies have shown that endoscopic resection is more cost-effective, associated with less adverse events and higher patient quality of life when compared to surgery[41-45]. Nonetheless, despite the data favoring endoscopic resection, surgery remains a common practice and increasing trend in the United States over the past two decades[46]. In a recent study on referral patterns for the management of colorectal polyps, we demonstrated that polyps with a baseline histopathology diagnosis of "intramucosal adenocarcinoma" or "carcinoma in-situ" were associated with a significant higher likelihood of being scheduled for surgery as compared to endoscopic resection (OR: 5.72; 95%CI: 1.16-28.19, $P = 0.03$)[7]. The terms intramucosal adenocarcinoma, intraepithelial carcinoma, carcinoma in-situ or high-grade dysplasia are commonly used interchangeably by pathologists to define lesions in which neoplasia has invaded into the lamina propria but without extension through the muscularis mucosa. In all, these lesions can be adequately treated endoscopically given the absence of lymphatics within the colon mucosa and the aforementioned negligible risk for LNM. However, the inclusion of the word "carcinoma" on the diagnosis can be easily misinterpreted by providers as equivalent to CRC, which in turn can lead to inappropriate management decisions[7,17]. More recently, the terminology for these precursor lesions has been somewhat standardized in the recent 2019 WHO classification of tumors of the digestive system (5th edition)[7,47]. Indeed, the term "dysplasia" is preferred for these precursor lesions in the colon, with the two-tiered system (low- *vs* high-grade) considered the standard grading system. Conversely, the use of "carcinoma in-situ" and "intramucosal adenocarcinoma" is strongly discouraged so as to reduce the clinical ambiguity associated with these terms [5,7,47].

This standardization of pathological diagnostic reporting unifies these diagnoses under the term high-grade dysplasia, potentially reducing the likelihood of misinterpreting these non-malignant polyps as CRC, and thereby the surgical referrals for otherwise endoscopically resectable lesions.

MANAGEMENT OF COLORECTAL POLYPS: A PROPOSED ALGORITHM

The optimal management of colorectal polyps can be complex and dependent on various factors, including patient and lesion characteristics, as well as local resources and expertise availability. In this section, we propose a potential strategy for the evaluation and management of colorectal polyps that can be adapted in clinical practice. The decision tree is depicted in Figure 6.

Polyps with signs of deep submucosal invasion

Lesions should be carefully evaluated endoscopically for "overt" signs of deep SMI including NICE type 3, Kudo class V, surface ulceration without prior manipulation (*i.e.* biopsies or resection attempts), or stiffness of the lesion and colon wall[17]. According to the recent recommendations by the United States Multi-Society Task Force (USMSTF) on CRC, non-pedunculated lesions with features of deep SMI should be biopsied (in the area with surface feature disruption), tattooed near the base of the polyp and on the opposite lumen wall, and referred to surgery[48]. These recommendations by the USMSTF stem from data showing that both NICE type 3 and Kudo type V patterns are highly specific predictors of deep SMI, which are associated with LNM and need for surgery[49,50]. However, it should be highlighted that these outcomes on real-time optical diagnosis are derived from endoscopists highly trained in advanced imaging and may not reflect performance in routine clinical practice. In fact, optical diagnosis alone is notoriously endoscopist-dependent and its performance outside of specialized academic centers has been disappointing[51].

Hence, reliance on optical diagnosis alone, as proposed by the USMSTF, may have some potential drawbacks. For one, misclassification of endoscopically resectable polyps as having deep SMI can lead to premature surgical referral and a slew of potentially unnecessary diagnostic staging tests (*i.e.* EUS, CT, MRI, PET-scan, *etc*), directly impacting the patient's mental health and resource utilization[52]. Secondly, tattooing a lesion at or near its base is associated with significant submucosal fibrosis, which in turn can render subsequent endoscopic resection attempts significantly more difficult if not impossible[53-55]. Therefore, if a tattoo is deemed necessary, we recommend strictly tattooing 3 cm distal to the polyp, with appropriate photo documentation of its location with respect to the lesion[56]. Based on the aforementioned issues, we suggest that surgical referral be initiated only for those lesions with biopsy-proven invasive adenocarcinoma (Figure 6). When biopsies are performed, they should be directed to the area exhibiting features of deep SMI. This targeted biopsy strategy increases the yield for histological diagnosis and minimizes the risk of inducing submucosal fibrosis for those lesions that may be amenable for endoscopic intervention. For lesions with the following indeterminate characteristics, we recommend considering referral to a high-volume center with expertise in both endoscopic imaging and resection of complex polyps: Lesions with endoscopic appearance suggestive of deep SMI yet negative for invasive cancer on biopsies[55,57]; Lesions with equivocal endoscopic appearance for deep SMI; Lesions with equivocal biopsy results (*i.e.* histopathology showing "at least" high-grade dysplasia yet deeper invasion cannot be excluded based on the limited sample).

While we recognize that this biopsy-driven algorithm is not without its limitations, including false negative histopathology for invasive disease due to sampling error, it may potentially curtail the current trend of surgical referrals for endoscopically resectable colorectal polyps. Of note, the exception to this approach includes pedunculated polyps with either biopsy-proven and/or signs of deep SMI limited to the head of the polyp (Haggitt level 0-2). In these cases, even when invasive CRC is present, *en-bloc* resection at the level of the stalk is associated with favorable prognosis and is often curative[48,58]. Most of these pedunculated polyps can be adequately transected at the stalk with endoscopic polypectomy. In select cases, maneuvering a snare around the large head of a pedunculated polyp with a long, wide stalk can be technically challenging and endoscopic submucosal dissection (ESD) has been reported as an alternate approach to ensure *en-bloc* resection[59,60].

Polyps with probable superficial submucosal invasion

In the absence of endoscopic features of overt deep SMI, the next step is to evaluate for morphological features associated with an increased risk for superficial SMI, as this may influence the endoscopic resection strategy. Predictors associated with a relative high risk of superficial SMI include the following; polyps with depressed morphology (Paris IIc), LST-NG with depression or bulky sessile appearance (Paris Is component), and LST-G with dominant nodules[26]. While neither lesion size nor location by itself

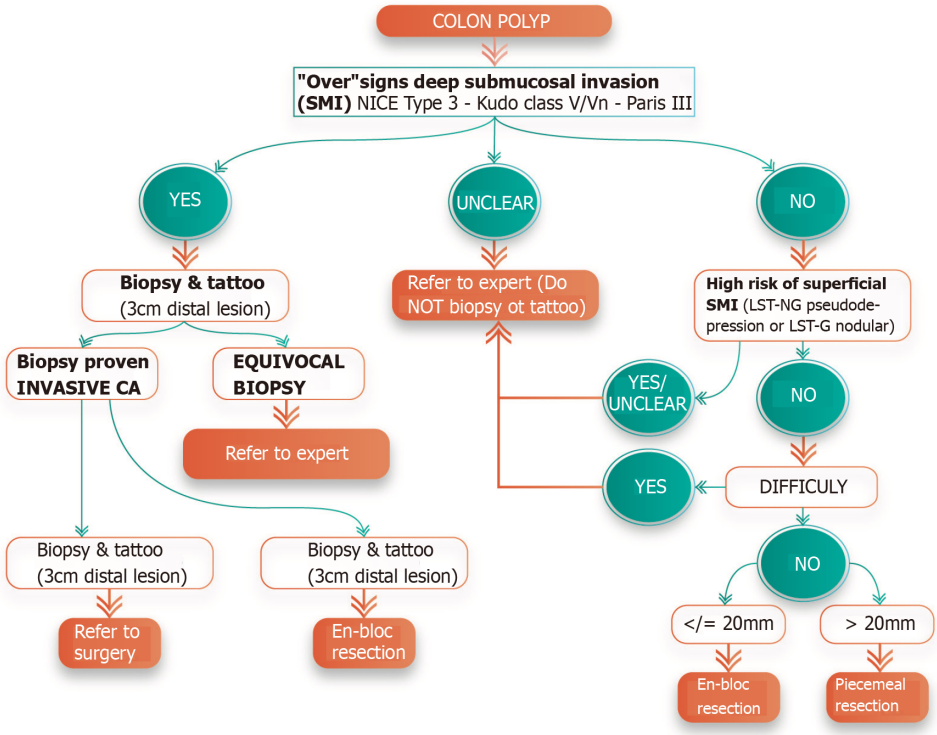

Figure 6 Decision tree algorithm for the evaluation and management of colorectal polyps.

can reliably predict superficial SMI, multiple studies have shown that the risk increases with lesions ≥ 20 mm and LSTs located in the right colon, rectosigmoid, and rectum[26,48].

As outlined by the recent recommendations by the USMSTF on CRC, lesions with suspected superficial SMI should ideally be approached with *en-bloc* endoscopic resection[48]. *En-bloc* removal of these lesions is necessary for accurate histological assessment, as piecemeal resection results in fragmented tissue specimens that compromise specimen orientation and interpretability of the resection margins. Inasmuch, the National Comprehensive Cancer Network practice guidelines specify that patients with otherwise endoscopically curable malignant polyps (*i.e.* those with superficial SMI and favorable histopathological features) who undergo piecemeal endoscopic resection will inevitably still require surgery due to the high risk of understaging the lesion because of compromised pathological interpretation[61]. Hence, the approach to a lesion with suspected superficial SMI is largely dependent on polyp size.

Lesions ≤ 20 mm in size: *En-bloc* resection may be achievable with endoscopic mucosal resection (EMR) for lesions ≤ 20 mm. Although a recent systematic review and meta-analysis suggested that underwater EMR may be associated with superior *en-bloc* resection rate when compared to conventional EMR (OR: 1.49; 95%CI: 1.02-2.16; P = 0.04), high-quality comparative studies are scarce. Therefore, the most appropriate strategy remains to be determined[62]. When performing EMR for these lesions, it is important to ensure that the snare encloses an additional margin of normal tissue around the polyp. By including a wider margin, risk of inadvertent incomplete *en-bloc* resection is decreased, which would otherwise require piecemeal removal.

Lesions > 20 mm in size: These polyps usually require ESD to achieve *en-bloc* resection. Attempt to *en-bloc* resect polyps > 20 mm with EMR is associated with a higher risk of potential complications and failure. A recent meta-analysis showed that the pooled proportion of successful *en-bloc* resection for polyps > 20 mm with either conventional or underwater EMR was unacceptably low (49.7%-58.7%)[62]. Hence, the European Society of Gastrointestinal Endoscopy, the Japan Gastroenterological Endoscopy Society and a recent American Gastroenterological Association clinical practice update recommend ESD as the preferred strategy for the resection of select colorectal lesions with suspected superficial SMI[63-65]. When compared to EMR, ESD is associated with a higher *en-bloc* and curative resection rate, and lower risk of recurrence[66]. However, ESD is a technically more complex procedure, associated

with a steep learning curve and higher rate of serious adverse events[66,67]. Due to these and other factors, the adoption of colonic ESD in the Western Hemisphere has been slower; albeit recent studies from North America have shown comparable outcomes to those reported in Asia. In a recent North American multicenter study, rectal ESD (n = 171) was associated with an *en-bloc* and complete (R0) resection rate of 82.5% and 74.9%, respectively[54]. Importantly, this study demonstrated that ESD was curative for 82% of these rectal malignant polyps[54]. It is worth noting that compared to surgery in the proximal colon, rectal operations for malignant polyps have an exceedingly high morbidity (40%-45%)[68,69]. Based on the above, referral for ESD to a center with expertise should be the preferred approach for the management of rectal lesions with suspected superficial SMI.

ESD in the proximal colon is more challenging than in the rectum, given issues with bowel peristalsis, scope positioning, and the relatively thinner colon wall[70]. As such, we recommend referring these lesions to a dedicated center with appropriate endoscopic and surgical expertise for multi-disciplinary discussion regarding the most optimal approach on a case-by-case basis.

Polyps without signs of submucosal invasion

All colorectal polyps without signs of superficial or deep SMI are benign and have no risk for LNM. Endoscopic resection should be the preferred management strategy over surgery, given the well-established advantages as previously mentioned in this review.

EMR remains the treatment of choice for the removal of benign colorectal polyps [71]. For lesions ≤ 20 mm in size, *en-bloc* resection should be attempted as this is associated with a lower risk of recurrence and need for re-intervention when compared to piecemeal removal[66,70]. Piecemeal EMR will invariably be necessary for the removal of larger non-pedunculated polyps, which increases the risk of recurrence, reportedly as high as 40%[70]. Recent strategies, including endoscopic ablation of the resection margins appear to decrease recurrence rate following piecemeal EMR[72], albeit future studies are needed to corroborate its efficacy in routine clinical practice.

Irrespective of the EMR approach, complete endoscopic resection (no visible residual tissue) should be the procedural benchmark. Partial resection or endoscopic ablation of residual visible tissue is associated with a prohibitively high risk for recurrence and even more concerning, significantly jeopardizes the ability to endoscopically remove the lesion on subsequent attempts. Notably, colorectal EMR can be technically challenging for complex polyps. Thereby, the USMSTF recommends that lesions ≥ 20 mm should be removed by endoscopists with experience in advanced polypectomy[48].

Approach to the "difficult" polyp

Several features have been commonly used to define a "difficult polyp", including variables such as size (usually ≥ 40 mm) and challenging location (*i.e.* involving the ileocecal valve, appendiceal orifice, dentate line, behind folds)[73]. More broadly, a "difficult polyp" should be defined as any lesion that the endoscopist feels he/she may not be able to completely resect endoscopically with high confidence; therefore, needing to be referred to a center with the appropriate expertise. When referring these lesions, we recommend against routine biopsy. Pretreatment biopsies do not necessarily change the management strategy in the absence of signs of SMI and can induce submucosal fibrosis, leading to prolonged procedure times and higher incomplete resection rates during succeeding endoscopic resection[74,75]. Furthermore, tattooing is not necessary if the lesion is in the cecum or rectum. If the lesion cannot be easily identified on colonoscopy, tattoo for lesion localization should be placed approximately 3 cm distal to the polyp and documented in the endoscopy report.

CONCLUSION

Endoscopic resection is a proven strategy for the management of benign and select malignant colorectal polyps. When compared to surgery, endoscopic resection is less costly and associated with improved clinical outcomes and patient satisfaction. Detailed lesion assessment, including endoscopic imaging and histopathology, play a critical role in directing subsequent treatment strategies. Ultimately, the most

appropriate intervention will depend on various factors, including patient and lesion characteristics, as well as local resources and expertise availability. Establishing the multidisciplinary collaboration between referring physicians, endoscopists, surgeons and pathologists is the basis for ensuring best practices for the management of colorectal polyps.

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ORIGINAL ARTICLE

Retrospective Study

Outcomes of inpatient cholecystectomy among adults with cystic fibrosis in the United States

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Author contributions: Ramsey ML designed and performed the research and wrote the paper; Sobotka LA, Krishna SG designed the research and supervised the report; Hinton A performed the statistical analysis and supervised the report; Kirkby SE, Li SS, Meara MP, Conwell DL supervised the report; Stanich PP designed and performed the research and supervised the report; all authors approved the final version of the article.

Institutional review board statement: As the NIS is a publicly available database of de-identified patients, The Ohio State University Institutional Review Board deemed studies utilizing this resource as exempt.

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Abstract

BACKGROUND

Symptomatic biliary and gallbladder disorders are common in adults with cystic fibrosis (CF) and the prevalence may rise with increasing CF transmembrane conductance regulator modulator use. Cholecystectomy may be considered, but the outcomes of cholecystectomy are not well described among modern patients with CF.

AIM

To determine the risk profile of inpatient cholecystectomy in patients with CF.

METHODS

The Nationwide Inpatient Sample was queried from 2002 until 2014 to investigate outcomes of cholecystectomy among hospitalized adults with CF compared to controls without CF. A propensity weighted sample was selected that closely matched patient demographics, patient's individual comorbidities, and hospital

meet criteria for human subject research. Therefore, there is no risk to any individual subject so informed consent is not necessary and was not obtained.

Conflict-of-interest statement: Stanich PP receives research support from Emtora Biosciences, Janssen Pharmaceuticals Inc., Pfizer Inc. and the PTEN Research foundation. Ramsey ML, Sobotka LA, Krishna SG, Hinton A, Kirkby SE, Li SS, Meara MP, Conwell DL has no conflicts of interest to report.

Data sharing statement: The data is available online from the Healthcare Costs and Utilization Project.

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characteristics. The propensity weighted sample was used to compare outcomes among patients who underwent laparoscopic cholecystectomy. Hospital outcomes of open and laparoscopic cholecystectomy were compared among adults with CF.

RESULTS

A total of 1239 inpatient cholecystectomies were performed in patients with CF, of which 78.6% were performed laparoscopically. Mortality was < 0.81%, similar to those without CF (P = 0.719). In the propensity weighted analysis of laparoscopic cholecystectomy, there was no difference in mortality, or pulmonary or surgical complications between patients with CF and controls. After adjusting for significant covariates among patients with CF, open cholecystectomy was independently associated with a 4.8 d longer length of stay (P = 0.018) and an $18449 increase in hospital costs (P = 0.005) compared to laparoscopic cholecystectomy.

CONCLUSION

Patients with CF have a very low mortality after cholecystectomy that is similar to the general population. Among patients with CF, laparoscopic approach reduces resource utilization and minimizes post-operative complications.

Key Words: Laparoscopic cholecystectomy; Nationwide Inpatient Sample; Cystic fibrosis; Mortality; Length of stay; Symptomatic biliary disorders

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Core Tip: Cholecystectomy has been considered to be a high-risk intervention in adults with cystic fibrosis (CF). Our study used a sample of adults with closely matched baseline characteristics to compare hospital outcomes among patients with and without CF. There was no difference in mortality or pulmonary or surgical complications between adults with and without CF. Patients with CF who underwent an open cholecystectomy had a longer length of stay than those who underwent a laparoscopic cholecystectomy. This study suggests that cholecystectomy is safe in selected adults with CF and that a laparoscopic approach should be preferred.

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INTRODUCTION

Cystic fibrosis (CF) is a multisystem disease resulting from defects in the CF transmembrane conductance regulator (CFTR) apparatus. The highest incidence of CF is seen in people of northern European descent, where CF occurs in one out of 3000 live births and approximately one in 25 people carry a pathogenic allele[1]. When initially described in the 1930s, median survival was only a few months but advances in pulmonary treatments have since increased the median predicted survival beyond 40 years[2,3]. While the natural history and treatment of pulmonary and pancreatic diseases in CF have been well characterized, other affected organs, such as the biliary tree and gallbladder, have less epidemiologic and clinical data to guide care. Management of these other organ systems which affect quality of life will become increasingly important as median survival improves.

Biliary disorders are thought to be common in CF due to the high expression of the CFTR gene in the gallbladder and biliary tree[4]. The mechanism of gallstone formation in CF is incompletely understood, but is likely the result of biliary stasis due to gallbladder dysmotility and prolonged transit through the bile ducts[4,5]. Cholelithiasis is reported in 20%-30% of patients with CF, and symptomatic biliary colic is experienced by 4% to 40% of subjects in retrospective studies[6-8]. One case

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series suggested that the incidence of cholelithiasis increases with age, from 0.1% in those less than 5 years of age, to nearly 10% in those aged 30-40[8]. Additionally, the use of CF transmembrane conductance regulator (CFTR) modulators may increase the risk of biliary colic[9]. The population of patients with CF are aging and CFTR modulators are increasingly used, which are leading to a greater number of patients at risk for biliary and gallbladder disorders.

In patients without CF, symptomatic biliary disorders are managed surgically by cholecystectomy. However, few CF patients undergo cholecystectomy, due at least in part to concerns for perioperative complications[3,10]. The few published case series of cholecystectomy show an aggregate mortality rate of 4% (3/71) among patients with CF, which is considerably higher than the 0.15% mortality reported in the general population[6,8,10-15]. However, the CF surgical case series were completed over 25 years ago, and surgical technique and patient characteristics have changed dramatically since then. We hypothesized that the outcomes of cholecystectomy in a modern cohort of subjects with CF will be no different than the general population, especially when controlling for comorbidities. We aimed to evaluate the safety of cholecystectomy in subjects with CF compared to non-CF controls using a large national database.

MATERIALS AND METHODS

Data source

A retrospective analysis was performed using the Nationwide Inpatient Sample (NIS) (2002 to 2014), available through the Healthcare Cost and Utilization Project (HCUP) of the Agency for Healthcare Research and Quality. The NIS represents more than 35 million individual hospitalizations annually across the United States and is one of the largest publicly available databases. This database can be used to evaluate patient and hospital characteristics as well as resource utilization such as costs, mortality, and length of stay[16]. As the NIS is a publicly available database of de-identified patients, The Ohio State University Institutional Review Board deemed studies utilizing this resource as exempt.

Study sample

Subjects were required to have a procedure code for cholecystectomy, defined as open, laparoscopic, or laparoscopic converted to open (Supplementary Table 1). Subjects were excluded if they were under the age of 18, pregnant, had cirrhosis, or underwent a partial cholecystectomy. Patients who underwent laparoscopic converted to open approach were categorized as open cholecystectomy. The cohorts were then defined by the presence or absence of CF diagnosis codes.

Outcomes of interest

The primary outcome of interest was mortality following cholecystectomy. As secondary outcomes, we evaluated length of stay, cost of hospitalization, and the rates of post-operative complications based on a validated set of diagnosis and procedure codes (Supplementary Table 1)[17,18]. Additionally, we analyzed the indications for cholecystectomy among patients with CF using previously defined diagnosis codes (Supplementary Table 1)[19-21]. Patients with choledocholithiasis and gallstone pancreatitis were included in the category of gallstone disease without cholecystitis (Supplementary Table 1). All outcomes were compared between patients with and without CF using survey weighting and propensity weighting and between patients with CF who received open or laparoscopic cholecystectomy using univariate and multivariate analyses. A study flowchart of patient inclusion and analyses is presented in Figure 1.

Definition of variables

Other variables evaluated include age, gender, race, income, type of insurance, hospital size, type of hospital, and hospital region. The presence of comorbid conditions were evaluated using the Elixhauser comorbidity index, which has been used widely since it was developed in 2005[22].

Statistical analysis

All analyses were performed using SAS version 9.4 (SAS Institute, Cary, NC, United States) on weighted data and accounted for the complex survey designs of the NIS.

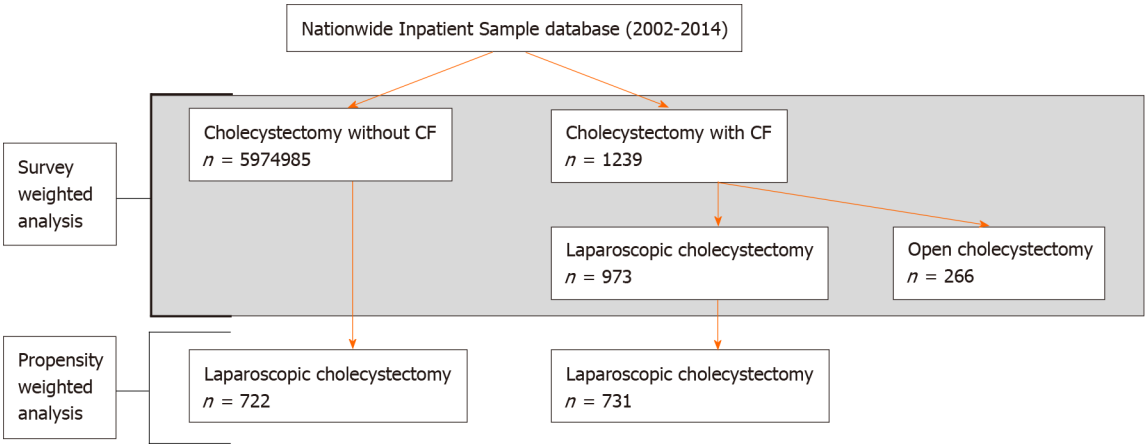

Figure 1 Study flowchart demonstrating survey weighted and propensity weighted analyses. CF: Cystic fibrosis.

Differences between patient characteristics, hospital characteristics, and outcomes were compared between patients with and without CF through the use of chi-square tests for categorical variables and *t*-tests for continuous variables. Similar comparisons were made between the populations of patients with CF who underwent open or laparoscopic cholecystectomy. Multivariate linear regression models were created for length of stay and hospital costs using a stepwise selection process. Where less than 10 observations are recorded, the exact number is censored to protect subject privacy, per NIS regulations. Missing data is listed in Supplementary Table 2.

Propensity weighted analysis

Among patients who underwent a laparoscopic cholecystectomy, propensity scores were calculated using a multivariable logistic regression model for CF containing all patient and hospital characteristics and indications for cholecystectomy as well as all individual Elixhauser comorbidities. The logistic regression model was weighted and accounted for all aspects of the complex survey design.

After deriving propensity scores (e) for each subject, propensity score weights were defined as 1 for subjects with CF and as $e/(1-e)$ for subjects without CF. These propensity score weights were then multiplied by the original survey weights defined by HCUP to arrive at the new weights which were used in place of the original HCUP weights in the following propensity weighted analysis, as previously described[23]. After propensity weighting was applied, all variables were well balanced between the two groups. The propensity weights were then used to evaluate differences in outcomes between patients with and without CF.

RESULTS

Demographics

From 2002 to 2014, a total of 5976224 adults underwent inpatient cholecystectomy, of which 1239 (0.021%) had CF (Table 1, Figure 1). Subjects with CF were younger and were more likely to be white, have private insurance, be treated at an urban teaching hospital, and have comorbid chronic respiratory failure (Table 1). A laparoscopic approach was used more often in CF subjects than in controls (78.6% *vs* 70.2%, P = 0.003) (Table 1). The indications for surgery between these groups were different: subjects with CF were less likely to undergo cholecystectomy for acute cholecystitis (48.1% *vs* 60.4%, P < 0.001), but more likely to have gallstone disease without cholecystitis (26.6% *vs* 18.0%, P < 0.001) or biliary dyskinesia (5.0% *vs* 1.2%, P < 0.001) (Table 1). Mortality was not significantly different between those with CF and those without (≤ 0.81% *vs* 0.99%, P = 0.719) (Supplementary Table 3). Length of stay and total hospitalization costs were higher for CF patients than controls (10.1 d *vs* 5.4 d, P < 0.001; $27561 *vs* $14059, P < 0.001) (Supplementary Table 3).

Propensity weighted analysis

After propensity weighting was applied to patients who underwent laparoscopic cholecystectomy, the variables were well balanced between groups

Table 1 Comparison of characteristics between subjects with and without cystic fibrosis who underwent cholecystectomy from 2002 to 2014

	Without cystic fibrosis (*n* = 5974985)		With cystic fibrosis (*n* = 1239)		
	n	**%**	***n***	**%**	***P* value**
Patient and hospital characteristics					
Age (mean ± SE)	53.81	0.05	31.28	0.80	< 0.001
Gender					0.342
Male	2113648	35.45	475	38.35	
Female	3848224	64.55	764	61.65	
Race					< 0.001
White	3377462	68.16	917	90.92	
Black	486644	9.82	15	1.51	
Hispanic	784975	15.84	38	3.81	
Other	306042	6.18	38	3.75	
Income quartile					0.669
First	1443591	26.81	270	23.36	
Second	1423075	26.43	322	27.83	
Third	1342530	24.94	313	27.06	
Fourth	1174730	21.82	251	21.76	
Primary payer					< 0.001
Medicare	2013023	33.76	255	20.62	
Medicaid	689680	11.57	215	17.34	
Private insurance	2550634	42.77	646	52.16	
Other	710118	11.91	122	9.88	
Elixhauser co-morbidity score					0.095
< 3	4425355	74.06	974	78.62	
≥ 3	1549630	25.94	265	21.38	
Chronic respiratory failure	16136	0.27	24	1.96	< 0.001
Hospital bed size					0.044
Small	744565	12.50	89	7.27	
Medium	1569622	26.36	306	24.87	
Large	3639976	61.13	835	67.86	
Hospital location/teaching status					< 0.001
Rural	786013	13.20	57	4.67	
Urban non-teaching	2724014	45.75	252	20.52	
Urban teaching	2444135	41.05	920	74.82	
Hospital region					0.184
Northeast	1048152	17.54	210	16.93	
Midwest	1248121	20.89	335	27.00	
South	2369451	39.66	467	37.65	
West	1309262	21.91	228	18.42	
Cholecystectomy approach					0.003

Laparoscopic	4192051	70.16	973	78.55	
Open	1782934	29.84	266	21.45	
Indication for cholecystectomy[1]					< 0.001
Acute cholecystitis	3606140	60.35	597	48.14	
Chronic cholecystitis	317489	5.31	98	7.90	
Gallstone disease without cholecystitis	1077090	18.03	329	26.58	
Biliary dyskinesia	71204	1.19	62	5.03	
Other	903063	15.11	153	12.35	

[1]Hierarchy model.

(Supplementary Table 4). Hospital mortality was low among both groups, with less than 10 events observed (Table 2). Subjects with CF experienced a mean length of stay (LOS) of 9.4 d, compared to 5.2 d in those without CF ($P < 0.001$) (Table 2). Similarly, total hospital costs were greater for subjects with CF ($25891 *vs* $14103, $P = 0.003$) (Table 2). There was no difference between CF and controls in post-operative surgical complications (4.5% *vs* 2.3%, $P = 0.094$) or pulmonary complications (6.6% *vs* 4.1%, $P = 0.109$) (Table 2).

Impact of surgical route on outcomes in CF

Of the 1239 patients with CF who underwent cholecystectomy, 973 (78.6%) had a laparoscopic approach. Compared to an open approach, patients with a laparoscopic cholecystectomy were more likely to be female, but other demographics were similar (Table 3). There was no significant difference in mortality (≤ 1.0% *vs* ≤ 3.8%, $P = 0.286$) but the LOS was longer and total hospital costs were greater in the open cholecystectomy group (14.5 d *vs* 8.9 d, $P = 0.009$; $43024 *vs* $23288, $P = 0.005$) (Supplementary Table 4). After adjusting for significant covariates, open route at surgery was associated with longer LOS (4.82 d, 95%CI: 0.82 d, 8.83 d, $P = 0.018$) and increased hospital costs ($18449, 95%CI: $5582, $31316, $P = 0.005$) (Table 4 and Supplementary Table 5). There were insufficient observations of mortality and post-operative complications to fit a multivariate model for these outcomes.

DISCUSSION

More patients with CF are reaching adulthood due to advances in CF care and CFTR modulators are increasingly used. With this, clinicians are likely to see an increasing prevalence of biliary disorders for which cholecystectomy will be considered as a definitive treatment. Therefore, it is important to clarify the safety of cholecystectomy. In this study, we used a nationally-representative database to evaluate the post-operative outcomes among adult patients with CF who undergo cholecystectomy. Importantly, we found that cholecystectomy had very low in-hospital mortality that was not significantly different from the general population. The surgical indications and approach were different between patients with and without CF. Open cholecystectomy was independently associated with longer LOS and greater hospital costs compared to laparoscopic approach. Finally, there is increased healthcare utilization among patients with CF compared to a propensity weighted cohort following laparoscopic cholecystectomy.

Our data shows a low mortality rate in a large and nationally representative cohort of CF patients, comparable to previous case series of cholecystectomy among CF patients. Aggregate data from case series show no deaths out of 12 patients who underwent laparoscopic surgery and 3/59 (5.1%) who underwent open cholecystectomy (although many of these surgeries were performed over 25 years ago)[6,8,10-12,15]. The previous case series also reported long lengths of stay after open cholecystectomy, up to 22 d in one series, partially due to prolonged pre- and post-operative intravenous antibiotics and frequent respiratory care[12]. Compared to these older studies, the current mean length of stay for laparoscopic cholecystectomy (8.9 d, standard error 0.71 d) is shorter. Similarly, CF patients experience longer LOS after sinus surgery compared to non-CF patients[24]. In one study using the American College of Surgeons' National Surgical Quality Improvement Program-Pediatric

Table 2 Univariate analysis of outcomes between propensity weighted cohort of patients with and without cystic fibrosis who underwent laparoscopic cholecystectomy in the Nationwide Inpatient Sample 2002-2014

	Without cystic fibrosis (*n* = 722)		With cystic fibrosis (*n* = 731)		
	n	**%**	***n***	**%**	***P* value**
Mortality[1]	≤ 10	≤ 1.39	≤ 10	≤ 1.37	0.662
Length of stay (mean ± SE)	5.18	0.33	9.36	0.89	< 0.001
Cost ($) (mean ± SE)	14103	842	25891	3859	0.003
Pulmonary complications	29	4.05	49	6.64	0.109
Surgical complications	16	2.27	33	4.48	0.094

[1]Where $n \leq 10$, the exact value is censored to protect patient privacy, per Nationwide Inpatient Sample regulation.

database, the authors suggested that the longer LOS was not due to complications but rather due to extended monitoring and intravenous antibiotics[24]. Our study shows this also appears to be true for cholecystectomy: Patients with CF have longer LOS than controls despite similar rates of post-operative complications.

Post-operative pulmonary decompensation and infection has been reported in previous case series, with an overall incidence of 7.0% (5/71) that is similar to our study[6,8,10-13,15]. To mitigate this risk, chest physiotherapy and antibiotics were used pre- and post-operatively. One group targeted pre-operative pulmonary function tests at the "highest level attained in the past 2 years, or until a prolonged period of therapy reaches a plateau of improvement" for elective surgery[10]. Increased pulmonary complications after open cholecystectomy may be attributed to derangements in respiratory mechanics due to the surgical incision near the diaphragm and increased post-operative pain[25]. Accordingly, laparoscopic cholecystectomy is recommended over open cholecystectomy for subjects with chronic pulmonary comorbidities to minimize risks of post-operative complications[25,26]. These data suggest that optimal outcomes are attained by elective laparoscopic intervention, and further study may be required to determine the best approach for pre- and post-operative pulmonary optimization among patients with CF.

While the incidence of post-cholecystectomy pulmonary complications has been described, the risk of surgical complications including soft tissue infections, perforation during surgery and need for recurrent surgery in CF compared to the general population has not been previously reported. We demonstrate an increased risk of surgical complications in patients with CF compared to the general population in the survey weighted cohort, and an increased risk with open compared to laparoscopic cholecystectomy among patients with CF. In the propensity weighted analysis, we found no significant difference in the rate of surgical complications. Patients with CF have an increased risk of infections with drug resistant bacteria, which may place this population at higher risk of infection after surgical intervention as these organisms may not be treated by routine pre-operative antibiotics[27].

Our study has several limitations inherent to the use of a large database, such as the potential for coding errors. Additionally, we cannot account for characteristics that are not included in the NIS which may influence outcomes, such as medication use, nutritional status, and baseline pulmonary function, nor can we evaluate survival beyond the inpatient period. Lastly, there may be selection bias, as only patients with acceptable surgical risk would have undergone cholecystectomy. Due to these limitations, "causality" cannot be inferred from large database analyses. However, in the absence of a prospectively collected surgical registry among patients with CF, the NIS remains an excellent data source due to its large number of observations and sophisticated sampling design. The NIS included 1239 inpatient cholecystectomies among patients with CF which greatly outnumbers the 71 cases reported in the literature to date. Additionally the NIS represents national demographics so the reported outcomes are likely to be generalizable to similar CF patients encountered in clinical practice. Finally, the volume of cholecystectomy in the control population allowed for a propensity weighted analysis to approximate a randomized trial, which could not be reasonably accomplished outside of a large database.

Table 3 Comparison of characteristics between subjects with cystic fibrosis who underwent open compared to laparoscopic cholecystectomy from 2002 to 2014

	Laparoscopic CCY (*n* = 973)		Open CCY (*n* = 266)		
	n	**%**	***n***	**%**	***P* value**
Patient and hospital characteristics					
Age (mean ± SE)	30.78	0.86	33.11	1.95	0.272
Gender					0.005
Male	330	33.92	145	54.60	
Female	643	66.08	121	45.40	
Race					0.911
White	718	90.92	199	90.93	
Black	≤ 10	≤ 1.03	≤ 10	≤ 3.76	
Hispanic	29	3.65	≤ 10	≤ 3.76	
Other	33	4.13	≤ 10	≤ 3.76	
Income quartile					0.110
First	210	23.22	60	23.86	
Second	221	24.47	100	39.95	
Third	264	29.20	48	19.34	
Fourth	209	23.11	42	16.85	
Primary payer					0.265
Medicare	221	22.73	34	12.86	
Medicaid	177	18.23	37	14.07	
Private insurance	482	49.56	164	61.69	
Other	92	9.47	30	11.38	
Elixhauser co-morbidity score					0.311
< 3	778	79.93	196	73.81	
≥ 3	195	20.07	70	26.19	
Chronic respiratory failure	24	2.50	0	0.00	-
Hospital bed size					0.244
Small	71	7.29	19	7.21	
Medium	219	22.58	87	33.34	
Large	679	70.13	155	59.45	
Hospital location/teaching status					0.476
Rural	53	5.45	≤ 10	≤ 3.76	
Urban non-teaching	193	19.94	59	22.67	
Urban teaching	723	74.61	197	75.56	
Hospital region					0.812
Northeast	167	17.15	43	16.12	
Midwest	258	26.53	76	28.73	
South	378	38.85	88	33.27	
West	170	17.47	58	21.88	
Indication for cholecystectomy[1]					
Acute cholecystitis	527	54.17	69	26.07	

Chronic cholecystitis	84	8.61	14	5.28
Gallstone disease without cholecystitis	285	29.25	45	16.82
Biliary dyskinesia[2]	58	5.95	≤ 10	≤ 3.76
Other	20	2.02	133	50.18

[1]Hierarchy model.
[2]Where $n \leq 10$, the exact value is censored to protect patient privacy, per Nationwide Inpatient Sample regulation. CCY: Cholecystectomy.

Table 4 Multivariate comparison of post-operative outcomes between subjects with cystic fibrosis who underwent open compared to laparoscopic cholecystectomy from 2002 to 2014

	Length of stay			Hospitalization cost		
	Days	95%CI	*P* value	$	95%CI	*P* value
Open cholecystectomy	4.82	(0.82, 8.83)	0.018	18449	(5582, 31316)	0.005
Elixhauser co-morbidity score ≥ 3	8.35	(4.28, 12.43)	< 0.001	28344	(10548, 46141)	0.002
Hospital location/teaching status			< 0.001			< 0.001
Rural	-5.88	(-11.53, -0.24)		-13801	(-22490, -5111)	
Urban non-teaching	-3.69	(-5.71, -1.68)		-13709	(-20684, -6734)	
Urban teaching	Ref.			Ref.		

Adjusted for significant covariates.

CONCLUSION

Cholecystectomy among adult patients with CF did not carry an increased risk of in-hospital mortality compared to controls. Length of stay and hospital costs are higher in patients with CF and there is a higher risk of post-operative surgical complications and a tendency to develop more pulmonary complications, although this risk of complications is no longer seen when demographic and health variables are taken into account. A laparoscopic approach is safer and reduces healthcare utilization compared to an open approach in adults with CF. These results should inform the discussion between clinicians and patients with CF when cholecystectomy is considered.

ARTICLE HIGHLIGHTS

Research background

Symptomatic biliary disorders are common in cystic fibrosis (CF) and may become more common now that patients with CF are living longer. Biliary disorders are often managed with cholecystectomy but this surgery carries high risk of morbidity and mortality among adults with CF. However, the reported rate of complications is based on older studies, and may not represent modern surgical outcomes.

Research motivation

Currently, there is insufficient data examining the safety of cholecystectomy among adults with CF using modern surgical techniques.

Research objectives

To investigate the outcomes of inpatient cholecystectomy among adults with and without CF.

Research methods

The Nationwide Inpatient Sample was used to collect data on inpatient cholecystectomies between 2002 and 2014. Subjects without CF were matched 1:1 to subjects with CF, accounting for over 20 variables including age, sex, and comorbidities.

Research results

Among patients with CF, 1239 cholecystectomies were performed during the study period. Open cholecystectomy was independently associated with an $18449 increase in hospital costs (P = 0.005) and a 4.8 d longer length of stay (P = 0.018) compared to laparoscopic cholecystectomy. The mortality rate among patients with CF was < 0.81%, which was similar to the mortality rate among patients without CF (P = 0.719). Similarly, there was no significant difference in mortality or post-operative surgical complications (4.5% *vs* 2.3%, P = 0.094) or pulmonary complications (6.6% *vs* 4.1%, P = 0.109) after laparoscopic cholecystectomy between patients with and without CF in the propensity weighted analysis.

Research conclusions

With modern anesthesia and surgical techniques, cholecystectomy is equally safe for patients with and without CF.

Research perspectives

Cholecystectomy may be increasingly considered for the management of biliary symptoms among adults with CF. Future research will need to clarify if there are unique indications for cholecystectomy among patients with CF.

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ORIGINAL ARTICLE

Retrospective Study

Endoscopic balloon dilation for management of stricturing Crohn's disease in children

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Abstract

BACKGROUND

Crohn's disease (CD) has a multitude of complications including intestinal strictures from fibrostenotic disease. Fibrostenotic disease has been reported in 10%-17% of children at presentation and leads to surgery in 20%-50% of cases within ten years of diagnosis. When symptoms develop from these strictures, the treatment in children has primarily been surgical resection. Endoscopic balloon dilation (EBD) has been shown to be a safe and efficacious alternative to surgery in adults, but evidence is poor in the literature regarding its safety and efficacy in children.

AIM

To evaluate the outcomes of children with fibrostenosing CD who underwent EBD *vs* surgery as a treatment.

METHODS

In a single-center retrospective study, we looked at pediatric patients (ages 0-18) who carry the diagnosis of CD, who were diagnosed after opening a dedicated Inflammatory Bowel Disease clinic on July 1, 2012 through May 1, 2019. We used

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diagnostic codes through our electronic medical record to identify patients with CD with a stricturing phenotype. The type of intervention for patients' strictures was then identified through procedural and surgical billing codes. We evaluated their demographics, clinical variables, whether they underwent EBD *vs* surgery or both, and their clinical outcomes.

RESULTS

Of the 139 patients with CD, 25 (18%) developed strictures. The initial intervention for a stricture was surgical resection in 12 patients (48%) and EBD in 13 patients (52%). However, 4 (33%) patients whom initially had surgical resection required follow up EBD, and thus 17 total patients (68%) underwent EBD at some point in their treatment process. For those 8 patients who underwent successful surgical resection alone, 4 of these patients (50%) had a fistula present near the stricture site and 4 (50%) had strictures greater than 5 cm in length. All patients who underwent EBD had no procedural complications, such as a perforation. Twenty-two (88%) of the treated strictures were successfully managed by EBD and did not require any further surgical intervention during our follow up period.

CONCLUSION

EBD is safe and efficacious as an alternative to surgery for palliative management of strictures in selected pediatric patients with CD.

Key Words: Crohn's disease; Intestinal strictures; Endoscopic dilation; Pediatrics; Endoscopic balloon dilation

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Core Tip: Endoscopic balloon dilation (EBD) has been shown to be a safe and efficacious alternative to surgery in adults, but evidence is poor in the literature regarding its safety and efficacy in children. In our retrospective cohort, 22 of the 25 (88%) treated strictures were successfully managed by EBD and did not require any further surgical intervention during our follow up period. All patients who underwent EBD had no procedural complications, such as a perforation, showing that EBD is safe and efficacious as an alternative to surgery for palliative management of strictures in selected pediatric patients with Crohn's disease.

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INTRODUCTION

In pediatric Crohn's disease (CD), intestinal strictures are a major cause of morbidity and one of leading causes for surgery with cumulative incidence of 20%-50% after 10 years of diagnosis[1]. It is estimated that strictures, defined by a luminal narrowing and thickening of the intestinal wall that results in obstructive clinical symptoms, are present in approximately 10%-17% of children at the time of diagnosis[2]. Strictures can appear at any point in the gastrointestinal tract, but most commonly appear in the ileocecal region and can cause symptoms, such as abdominal pain, bloating, emesis, decreased energy, and growth failure[3]. Surgery has been a mainstay treatment for intestinal strictures in pediatric CD with resection for longer strictures (> 5 cm in length) or strictureplasty for simple, shorter strictures[4]. Strictureplasty is a surgical procedure that repairs a stricture by widening the narrowed area with intestinal conservation[5,6]. Post-operative complications from surgical resection include fistulas, leaks, short bowel syndrome, and recurrence of the stricture at the anastomosis site[7]. One study shows that clinical recurrence of strictures occurs in 55% of patients in the first two years after initial surgery, which leads to the need for

subsequent surgical interventions[6]. Overall, 75% of CD patients undergo surgery for disease related complications at least once in the course of their disease[8].

Given the high likelihood of surgery in a CD patient, attempts should be made to find alternatives to surgery in these patients. One such alternative is endoscopic balloon dilation (EBD), through which an endoscopist traverses the stricture with a balloon device that is then inflated in an effort to increase the diameter of the intestinal lumen. EBD has been demonstrated to be a safe and efficacious alternative to surgery in adults with CD, but there was a paucity of evidence regarding use in children until our initial publication in 2008[3,7]. Evolution of our knowledge regarding outcomes from fibrostenosing CD and anti-inflammatory effects of biologic therapy suggested stenosing disease evolves independently, which is propelled by local myofibroblast activity, soluble chemokines, and growth factors[9]. The accumulation of this understanding led to the eventual guidelines published by the European Crohn's and Colitis Organization in 2016[10]. The aim of our study is to evaluate the longitudinal outcomes of children with CD who underwent EBD *vs* surgical resection as a treatment of their strictures in order to show that EBD is efficacious as an alternative to surgery for management of simple strictures in pediatric fibrostenosing CD.

MATERIALS AND METHODS

Study design

In a single-center retrospective study, we looked at pediatric patients (ages 0-18) who carry the diagnosis of CD who were diagnosed after opening a dedicated Inflammatory Bowel Disease clinic on July 1, 2012 through May 1, 2019. We used diagnostic codes through our electronic medical record to identify patients with CD with a stricturing phenotype. The type of intervention for patients' strictures was then identified through procedural and surgical billing codes. Patient demographics, disease characteristics and longitudinal clinical outcomes were obtained through review of the electronic medical record. Demographic data included: age at diagnosis of CD, age at time of procedure, body mass index (BMI) at time of procedure, and race. Disease characteristics included: modality of CD diagnosis, time (years) from diagnosis of CD until the development of symptomatic strictures, the Paris classification of disease, and medication at the time of the procedure. Symptomatic strictures were defined as new onset or worsening of baseline abdominal pain, postprandial bloating, and/or emesis. Information obtained about the intestinal stricture and procedure(s) included the location, length, number of strictures, the presence of penetrating disease near the stricture site, the type of stricture intervention (EBD, surgery, or both), and if any medication was injected into the stricture at the time of EBD. Strictures were classified as simple, which were defined as single and < 5 cm, or complex, which were defined by multiple, > 5 cm or associated with a fistula.

EBD

All patients with complex strictures underwent surgical resection of their stricture sites rather than strictureplasty. All EBDs were done by a single provider, using the same technique (JAQ). First, a 0.25 mm soft tip guidewire was passed through the stricture. In the case of medication injected at the stricture site, 2 mg/kg up to 80 mg of triamcinolone was diluted in 5 mL of saline and was then injected into all four quadrants of the stricture area prior to dilation. A single patient received an injection of an infliximab biosimilar (0.5 mg/kg) diluted in 25 mL of saline at the stricture site before dilation. After the injection of the stricture, a through the scope controlled radial release (CRR) colonic balloon dilator was placed over the guidewire and serial dilations were done until the desired diameter was achieved to allow endoscope passage for inspection of the proximal bowel (Figure 1).

RESULTS

Stricturing CD

Of the 139 active patients diagnosed with CD in the study period, 25 (18%) developed intestinal strictures; 13 patients (52%) were male and 22 patients (88%) were Caucasian (Table 1). BMI was recorded in the 25 patients and nine (36%) were in the overweight BMI category (BMI > 85th and < 95th percentiles). Six of those patients had complex strictures and went directly to surgical resection. The mean age at diagnosis of CD was

Table 1 Patient demographics and clinical variables

	Surgery only, *n* = 8	EBD only, *n* = 11	Surgery and EBD, *n* = 6
Sex, *n* (%)			
Male	4 (50)	6 (55)	3 (50)
Female	4 (50)	5 (45)	3 (50)
Age at diagnosis, *n* (%)			
0-10	1 (12)	1 (9)	1 (17)
11-18	7 (88)	10 (91)	5 (83)
Race, *n* (%)			
Caucasian	7 (88)	11 (100)	4 (67)
African-American	1 (12)	0	2 (33)
BMI, *n* (%)			
Underweight	2 (25)	2 (18)	0 (0)
Normal	0	7 (64)	5 (83)
Overweight	6 (75)	2 (18)	1 (17)
On biologic, *n* (%)	6 (75)	10 (91)	5 (83)
On steroids, *n* (%)	0	2 (18)	1 (17)
Location of stricture, *n* (%)			
Terminal ileum	6 (75)	2 (18)	4 (66)
Ileocecal valve	2 (25)	5 (46)	1 (17)
Colon	0	1 (9)	0
Duodenum	0	1 (9)	0
Rectum/anus	0	2 (18)	1 (17)
Average years of disease until development of stricture	2.1	1.9	1
Stricturing disease only, *n* (%)	4 (50)	8 (73)	2 (33)
Stricturing and penetrating disease, *n* (%)	4 (50)	3 (27)	4 (67)

EBD: Endoscopic balloon dilation; BMI: Body mass index.

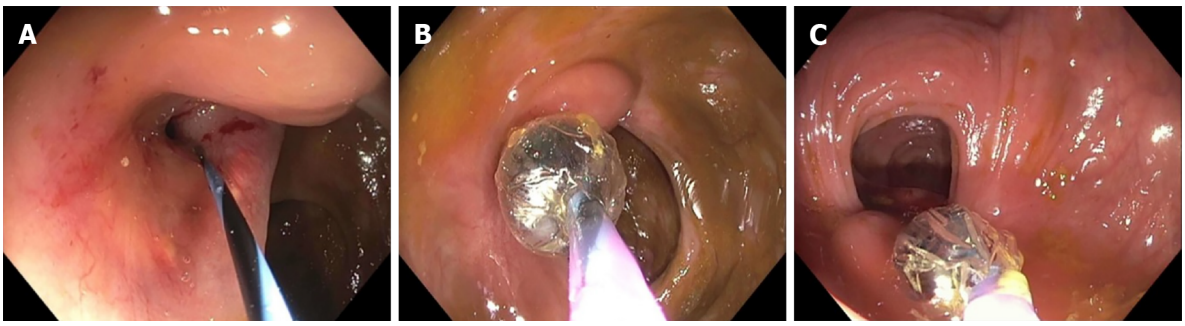

Figure 1 Endoscopic appearance. A: Endoscopic appearance of a Crohn's disease fibrostenotic lesion in the ileocecal valve; B: Wire-guided 18 mm balloon dilation catheter (CRE PRO, Boston Scientific, Marlborough, MA, United States); C: Appearance after dilation.

13 years. In 23 of the 25 patients, diagnosis was made *via* upper and lower endoscopy with biopsies confirming CD, and the other two patients had stricturing and penetrating disease at the time of diagnosis, and CD was confirmed on histologic review of the surgically-resected specimen. Using the Paris Classification, CD location was classified as: ileocolonic (*n* = 20, 80%), distal 1/3 of the ileum with limited cecal disease (*n* = 3, 12%), colonic (*n* = 1, 4%), or upper disease proximal to the ligament of

Treitz and ileocolonic (n = 1, 4%). CD behavior was classified as: stricturing (n = 11, 44%), stricturing and penetrating (n = 9, 36%), stricturing and perianal disease (n = 3, 12%), or stricturing, penetrating and perianal disease (n = 2, 8%). The mean time of development of symptomatic strictures from time of diagnosis was 1.5 years. Twenty (80%) of these strictures were located in the terminal ileum, 3 (12%) in the rectum, 1 (4%) in the duodenum, and 1 (4%) in the ascending colon (Figure 1).

At the time of intervention, most patients (n = 21, 84%) were on biologic therapy; 11 patients were on infliximab or an infliximab biosimilar, 9 patients were on adalimumab, and one patient was on vedolizumab. Of the four patients not receiving biologic therapy, three patients were managed with azathioprine and one was managed with mesalamine alone. Three patients (12%) were on low-dose corticosteroids in addition to biologic therapy.

EBD outcomes

The initial intervention for a stricture was surgical resection in 12 patients (48%) and EBD in 13 patients (52%). However, 4 (33%) patients whom initially had surgical resection required follow-up EBD, and thus 17 total patients (68%) underwent EBD at some point in their treatment process. The frequency of EBD procedures performed on an individual patient was: one EBD (n = 7, 41%), 2-3 EBD (n = 8, 47%), 4 or more EBD (n = 2, 12%) (Figure 2). All patients that underwent EBD had strictures with a length less than or equal to 5 cm in length and inflammation was controlled with medications prior to EBD. Fifteen patients received a triamcinolone injection into the stricture site and one patient received an infliximab biosimilar injection at the stricture site. There were no post-EBD perforations, bleeding requiring intervention, or infections. Of the 8 patients who underwent successful surgical resection alone, 4 patients (50%) had a fistula present near the stricture site and 4 (50%) had strictures greater than 5 cm in length. Overall, 88% (15/17) with stricturing disease treated endoscopically did not require any further surgical interventions.

DISCUSSION

The natural history of CD in children suggests that most children present with inflammatory disease but a proportion will develop more complicated stricturing or penetrating disease[11]. Given the high overall rate of surgery in CD, the rate of recurrence of strictures post-surgery, and the risk of complications post-surgery, there exists the need for alternative interventions[6,7,12]. EBD offers a minimally invasive, therapeutic approach that can reduce or obviate the need for surgical intervention[13]. It has been shown to be efficacious in adult stricturing CD with overall reported technical success rate of 89.1% to 94.9% and associated clinical efficacy of 80.8%-82.3% [14,15]. Complications are also minimal in EBD compared to surgery with a complication rate averaging around 2% overall[16]. Here, we aim to demonstrate similar efficacy and safety in our pediatric CD cohort.

In our single-center cohort, 88% (15/17) of patients with stricturing CD treated *via* EBD did not require any further surgical interventions. This is a higher success rate than the adult literature where a meta-analysis of 33 studies showed that surgical intervention was avoided in 57% of adult patients who had undergone EBD[14]. In our cohort, there was a need for repeat EBD in 6/17 (35%) patients whom had initial EBD and a need for EBD after surgical resection in 4/12 (33%) patients. The adult literature cites that need for repeat EBD as 73.5% in a meta-analysis and 47% in another study, and the need for EBD after surgical resection at 62%[14,17]. It is difficult to compare our rates of success and need for repeat dilations to adult studies given the small number of patients in our study and a different range in follow up time. In our study, follow up ranged from 6 mo to 2 years compared to the two years used in adult literature[14,17].

In our population, there were no complications of perforation, bleeding, or infection for any patient who underwent EBD. Although this is reassuring, our study is again limited by the small number of patients making it difficult to compare to the rate of complications in the literature which is around 2%[8]. In addition, patients who were deemed high risk by the adult literature, those with longer strictures (≥ 5 cm) and the presence of a nearby abscess or fistula, were not candidates for EBD and underwent primary surgical resection instead[14,17,18]. Our data does support previous literature about the safety of EBD in patients with uncomplicated, fibrostenotic, non-inflammatory and short segment strictures (< 5 cm in length) (Figure 3)[18].

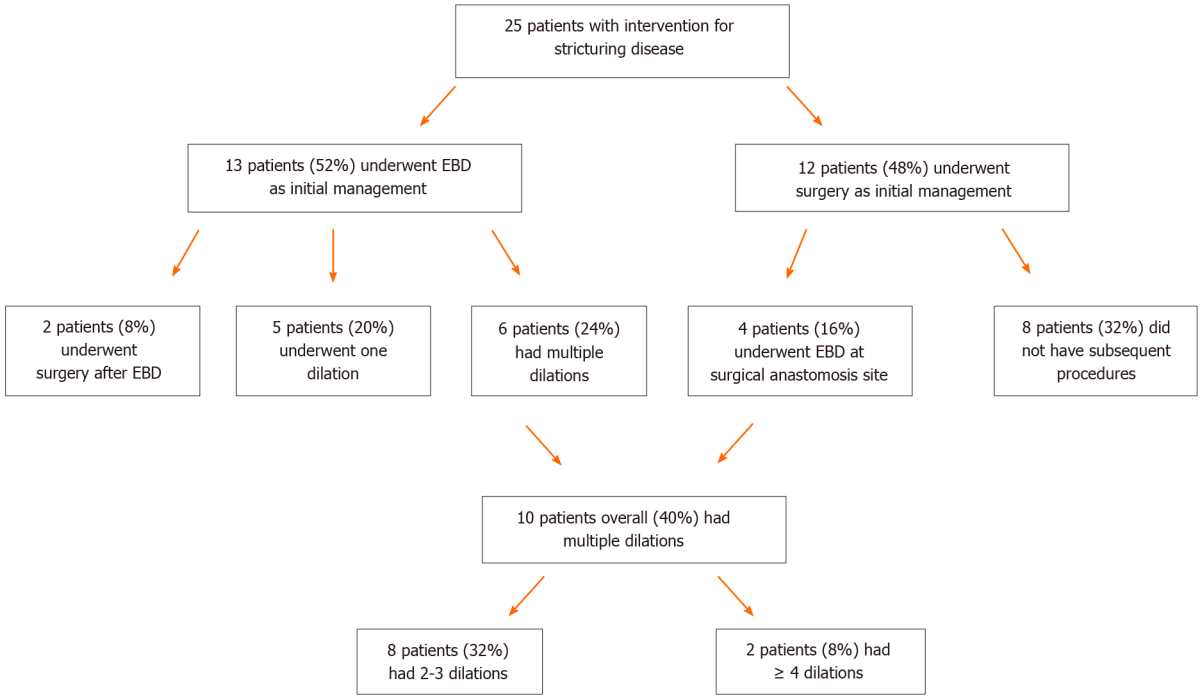

Figure 2 Management of patients with stricturing Crohn's disease *via* surgery or endoscopic balloon dilation. EBD: Endoscopic balloon dilation.

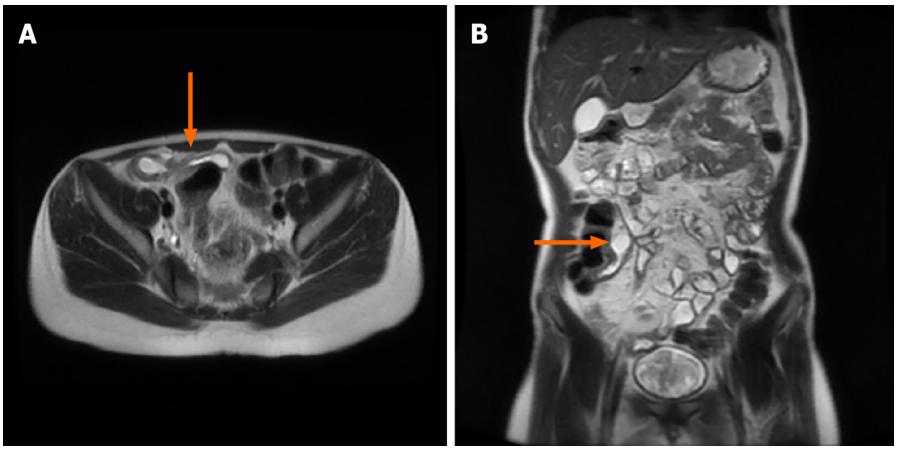

Figure 3 Magnetic resonance imaging of fibrostenosing Crohn's disease. A: Cross sectional magnetic resonance imaging showing the lesion in the distal ileum; B: Coronal cut on magnetic resonance imaging of fibrostenosing Crohn's disease with proximal dilation.

The majority of our patients (15/17) also received intralesional steroid injection into the stricture site. This has been documented as effective by showing the reduction in the need for further endoscopic dilations and surgical interventions in a double-blinded controlled trial in pediatric patients[5]. One patient in our study received an injection of an infliximab biosimilar at the stricture site prior to dilation. This patient had a high-grade duodenal stricture at presentation of her disease which did not allow for tolerance of enteral nutrition. Due to severity of her clinical condition, surgical risk and after internal discussion and family approval, the suitability of this approach was felt to be acceptable. One study in the adult literature showed that injection of 40 mg of infliximab into strictures in six patients was successful[19]. All six patients at the final follow-up at six months described relief of obstructive symptoms and no patients were referred to surgery during the follow-up period[19]. Our patient did require two dilations with infliximab biosimilar injection, and she eventually had resolution of her symptoms and was able to advance to a regular diet. Although there are some smaller studies describing success of injection of biologics into strictures, this has not been proven to be fully efficacious due to the small number of patients that have received a

biologic injection into their stricture site. In contrast, a multicenter study from the United States did not show that intra-lesional steroids or biologics lower the risk of further interventions or surgery[20].

In addition, our data suggests that there seems to be an interesting correlation with higher BMI and worsening disease. Six patients (66%) in the overweight BMI category (BMI > 85th and < 95th percentiles) were those patients with complex strictures that went directly to surgical resection. This correlates with a study that was published in the journal of Biomolecules in 2019 which showed that increased visceral adipose tissue, "creeping fat," can worsen intestinal inflammation through increased altered adipocyte function and through deregulated leptin and adiponectin production[21]. Another recent prospective study from Australia suggested that visceral adipose tissue to subcutaneous adipose tissue ratio was positively associated with risk of stricturing disease behavior and elevated fecal calprotectin in patients with ileocolonic disease; however, these findings are controversial and ongoing research is required to better classify this correlation[22].

Though EBD is shown to be safe and efficacious based on our initial data and the data in the literature, it does have limitations. Surgical resection is still recommended as initial management in longer strictures or for complicated strictures due to an increased risk for perforation[18]. Before EBD is performed, it is recommended to characterize the number, nature and length of the stricture using magnetic resonance enterography or small intestine contrast ultrasonography[18]. Furthermore, EBD requires a skilled endoscopist who is comfortable performing these procedures, and this may not be available at all pediatric centers.

There has been a small amount of published data on EBD in pediatric fibrostenosing CD since our first publication in 2008. Our initial experience suggested that EBD was safe and efficacious in children with short and uncomplicated strictures secondary to fibrostenosing CD which we proceeded to implement in our active day to day care of pediatric CD with these results. Our study is limited by a modest follow-up interval and relatively small number of patients. Further research is most definitely needed in order to find the ideal role for EBD in the management of fibrostenosing CD in children and to further assess the long-term efficacy of the procedure when comparing to surgical intervention in children. We also need to determine if biologic injection at the site of a stricture is a superior option in prevention of stricture recurrence at the dilation site and need to develop ideal tools and techniques to reproducibly manage patients with CD-related intestinal strictures.

CONCLUSION

EBD is safe and efficacious as an alternative to surgery for palliative management of strictures in selected pediatric patients with CD with a high response rate and low complication rate directly related to the procedure.

ARTICLE HIGHLIGHTS

Research background

Currently up to 75% of patients with Crohn's disease (CD) are expected to need surgery due to disease related complications. Intestinal fibrostenosing disease is a common complication and biologic therapy has not limited its appearance even with much improved clinical response rates. Due to a high risk for surgery, attempts to find alternatives to surgery need to be made. Endoscopic balloon dilation with adequate technique promises to have an important role in his area.

Research motivation

Endoscopic balloon dilation has already been shown to be efficacious in adults but no large case series involving pediatric patients exists currently in literature.

Research objectives

We aimed to evaluate the short and long term outcomes of CD who developed fibrostenosing disease and underwent endoscopic balloon dilation as primary or secondary therapy.

Research methods

This is a single-center case series in which all subjects who were diagnosed with diagnosed between 2012 and 2019 were included in the study, and those that developed fibrostenosing disease were identified. Their records were then reviewed for types of interventions performed and outcomes. Patients were classified into primary surgical or endoscopy-treated subjects and those that subsequently required surgery or endoscopy were thus classified. Demographic data included: age at diagnosis of CD, age at time of procedure, body mass index (BMI) at time of procedure, and race. Disease characteristics included: modality of CD diagnosis, time (years) from diagnosis of CD until the development of symptomatic strictures, the Paris classification of disease, and medication at the time of the procedure.

Research results

We identified 139 subjects diagnosed with CD in this study period. Of these patients, 25 (17%) were noted to have a fibrostenotic lesion anywhere in the small and large bowel. 13 (52%) underwent primary endoscopic therapy *vs* 12 (48%) who underwent surgical management. Of the patients who went to surgery, 4 (16%) had to have further endoscopic treatment after surgery, compared to just 2 (8%) of those who had endoscopy as primary therapy. Of note, 5 (20%) required just one endoscopic therapy session for resolution of their stricture.

Research conclusions

Endoscopic balloon dilation is a safe and effective treatment in children with CD-related fibrostenosing disease. Adequate patient selection is key to ensure a high success rate. Pediatric patients undergoing surgery for fibrostenosing disease should be cautioned that a 1 in 5 risk of requiring further endoscopic therapy is a distinct possibility.

Research perspectives

Our data suggested an interesting correlation between higher BMI and risk of stricturing disease. Pediatric patients with BMI > 85% and < 95% had a higher risk of complex strictures requiring surgery. This brings into new light publications associating an increase in visceral adipose tissue with intestinal inflammation through dysregulated leptin and adiponectin production.

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ORIGINAL ARTICLE

Retrospective Study

Gastrointestinal hemorrhage in the setting of gastrointestinal cancer: Anatomical prevalence, predictors, and interventions

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Author contributions: Minhem MA contributed to study concept and design, statistical analysis of data, and drafting of manuscript; Nakshabandi A supervised the report and contributed to interpretation of data and editing of manuscript; Mirza R contributed to interpretation of data and drafting of manuscript; Alsamman MA contributed to interpretation of data and editing of manuscript; Mattar MC supervised the report and provided critical revision of important intellectual concepts.

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Abstract

BACKGROUND

Gastrointestinal hemorrhage (GIH) is a common complication with gastrointestinal cancers (GIC). There is no comprehensive research that examines GIH in different types of GIC.

AIM

To study the prevalence, predictors, and interventions of GIH based on the anatomical location of GIC.

METHODS

This is a retrospective analysis of the 2016-2018 National Inpatient Sample database, the largest inpatient care database in the United States. All adult inpatients (≥ 18-year-old) were included. ICD-10-CM codes were used to identify patients with GIH and GIC. Prevalence of GIH was obtained based on the anatomical location of GIC. Predictors of GIH in the GIC population were studied using multivariate analysis. Interventions including endoscopy were compared to the non-intervention group to determine the differences in inpatient mortality.

RESULTS

Out of a total of 18173885 inpatients, 321622 (1.77%) cases had a diagnosis of GIC. Within GIC patients, 30507 (9.5%) inpatients had GIH, which was significantly ($P < 0.001$) more than the prevalence of GIH in patients without GIC (3.4%). The highest to lowest GIH rates are listed in the following order: Stomach cancer (15.7%), liver cancer (13.0%), small bowel cancer (12.7%), esophageal cancer

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(9.1%), colorectal cancer (9.1%), pancreatic cancer (7.2%), bile duct cancer (6.0%), and gallbladder cancer (5.1%). Within gastric cancer, the GIH rate ranged from 14.8% in cardia cancer to 25.5% in fundus cancer. Within small bowel cancers, duodenal cancers had a higher GIH rate (15.6%) than jejunal (11.1%) and ileal cancers (5.7%). Within esophageal cancers, lower third cancers had higher GIH (10.7%) than the middle third (8.0%) or upper third cancers (6.2%). When studying the predictors of GIH in GIC, socioeconomic factors such as minority race and less favorable insurances (Medicaid and self-pay) were associated with significantly higher GIH on multivariate analysis ($P < 0.01$). Chemotherapy and immunotherapy were also identified to have a lower risk for GIH [odds ratios (OR) = 0.74 (0.72-0.77), $P < 0.001$]. Out of 30507 GIC inpatients who also had GIH, 16267 (53.3%) underwent an endoscopic procedure, *i.e.*, upper endoscopy or colonoscopy. Inpatient mortality was significantly lower in patients who underwent endoscopy compared to no endoscopy [5.5% *vs* 14.9%, OR = 0.42 (0.38-0.46), $P < 0.001$].

CONCLUSION

The prevalence of GIH in patients with GIC varies significantly based on the tumor's anatomical location. Endoscopy, which appears to be associated with a substantial reduction in inpatient mortality, should be offered to GIC patients with GIH. Nevertheless, the decision on intervention in the GIC population should be tailored to individual patient's goals of care, the benefit on overall care, and long-term survival.

Key Words: Gastrointestinal hemorrhage; Gastrointestinal cancer; Anatomy; Risk factors; Gastrointestinal endoscopy

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Core Tip: This is a retrospective analysis of the National Inpatient Sample database aiming to study the prevalence, predictors, and interventions of gastrointestinal hemorrhage (GIH) in the setting of gastrointestinal cancer (GIC). The prevalence of GIH varies based on the anatomical location of cancer, ranging between 15.7% in gastric cancer and 5.1% in gallbladder cancer. Many risk factors, including socioeconomic factors such as insurance and race, can affect the rates of GIH. Endoscopy is significantly associated with lower inpatient mortality in bleeding patients with GIC.

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INTRODUCTION

Gastrointestinal hemorrhage (GIH) is a common complication in patients with gastrointestinal cancers (GIC). In terms of incidence and mortality, GICs are among the highest globally[1]; and thus remain an ongoing challenge as to management and treatment. GIH often serves as the initial symptom for GIC, locally invasive, and metastatic disease[2]. It can also carry a high mortality rate, as in the case of upper GIH [3]. An earlier study documented that bleeding gastrointestinal (GI) tumors accounted for roughly 12 percent of cases involving GIH[4]. Another analysis of studies purported that neoplasia constituted between 3%-11% of lower GIH[5]. On the other hand, in 5% of patients with upper GI bleeds, biopsy-proven tumors were the source of bleeding[6]. While existing literature studied the prevalence of GIC in GIH, and some assess GIH as a clinical symptom of a specific type of tumor[2,4,7,8], there are no inclusive studies that assess GIH in different types of GIC. Therefore, a more comprehensive and large sample size analysis is warranted to study GIH in all types of GIC.

Bleeding in GIC patients could be the result of many causes and risk factors. One study revealed that bleeding from the tumor site is the predominant source of upper GI bleeds in patients with cancer[9]. Another study found GIH common after chemoradiotherapy in patients with locally advanced pancreatic cancer[10]. Some existing literature examines the risk factors behind GIH in specific tumors, such as gastrointestinal stromal tumors[11]. In one study, risk factors implicated in GIH included initial tumor stage, smoking, and carbohydrate antigen 19-9 Levels at the time of pancreatic cancer diagnosis[8]. This current retrospective analysis assesses predictors of GIH in the setting of GIC. Another study found that GIH rate can vary based on pancreatic cancer location; however, the study was limited by the small sample size[8]. Therefore, further analysis on the prevalence of GIH regarding the anatomical location of neoplasm would assist in future clinical management of GIH in these patients.

Most importantly, investigating different interventions for GIH in the setting of GIC would provide vital information in developing treatment plans for these patients and preventing mortality. For example, literature reviews endoscopic hemostasis of GIH in both cancer and non-cancer settings, but data remains limited in specifically the setting of tumor bleeding[2,6,12,13]. Endoscopic therapy is often recommended for non-cancer related GIH, as it may decrease overall morbidity and the need for invasive surgery [14,15]. However, while hemostasis is often successfully achieved by endoscopic therapy for bleeding GIC, rebleeding rates, unfortunately, remain common[6,13].

This study's goals involve estimating the prevalence of GIH in patients with GIC based on the anatomical location of tumors, evaluating the predictors of GIH in GIC, and the outcomes of different procedure modalities used in bleeding GIC patients.

MATERIALS AND METHODS

Study setting

This study is a retrospective analysis of the 2016 to 2018 National (Nationwide) Inpatient Sample (NIS) database, the largest national inpatient database. NIS is drawn from 48 states and includes more than 97% of the United States population. The NIS does not contain any patient identifier; therefore, it does not require review by the institutional review board.

Inclusion/exclusion criteria

All adult inpatients (≥ 18-year-old) were included.

Outcomes

(1) Estimate GIH prevalence in patients with GIC based on the anatomical location of cancer; (2) Study the predictors of GIH in patients with GIC; and (3) Study the mortality outcome of various procedural modalities used in GIH patients with GIC: (a) Endoscopy; (b) Surgery; (c) Trans-arterial embolization; and (d) Radiation therapy.

Exposure

(1) In all adult inpatients, the prevalence of GIH was compared between patients with and without GIC; (2) In inpatients with GIC, the prevalence of GIH was determined according to the anatomic location of GIC; (3) In inpatients with GIC, demographics, socioeconomic factors, comorbidities, and other disease-related factors were compared based on GIH status; and (4) In inpatients with GIC and GIH, mortality outcome was compared between patients who underwent or did not undergo interventions such as endoscopy, surgery, embolization, and radiation therapy.

Definitions

All diagnoses and procedures were reported based on ICD-10-CM and PCS coding listed in Table 1. GIH was defined as the presence of upper or lower GIH or the presence of hematemesis, melena, hematochezia, or unspecified source of GIH.

Statistical analysis

Continuous variables were presented as mean and standard deviation. Categorical variables were presented as frequencies and percentages (%). Student *t*-test was used for the comparison of continuous variables, and Pearson's χ^2 test was used for categorical variables. *P* values were adjusted according to the Bonferroni method when pairwise comparisons were used. In a few instances, analysis was not performed

Table 1 ICD-10-CM and PCS codes for diagnoses and procedures

Diagnosis	ICD-10-CM
GI hemorrhage	Upper: I85.x1; (K25-K28).0,2,4,6; K29.x1; K318.11 K31.82
	Lower: K50.x11; K51.x11; K55.21; K57.x1; K57.x3
	Total = upper + lower + K62.5; K92.0-2
GI cancer	
Esophageal cancer	C15; C49.A1; D00.1
Upper third	C15.3
Middle third	C15.4
Lower third	C15.5
Other/unspecified	C15.8-9; C49.A1; D00.1
Gastric cancer	C16; C49.A2; D00.2
Cardia	C16.0
Fundus	C16.1
Body	C16.2
Pyloric antrum	C16.3
Pylorus	C16.4
GIST	C49.A2
Other/unspecified	C16.5-9; D00.2
Small bowel cancer	C17; C49.A3; D01.49
Duodenum	C17.0
Jejunum	C17.1
Ileum	C17.2
GIST	C49.A3
Other/unspecified	C17.3-9; D01.49
Liver cancer	C22; D01.5
Hepatocellular carcinoma	C22.0
Other primary liver	C22.2-8; D01.5
Biliary cancer	C22.1; C24
Intrahepatic	C22.1
Extrahepatic	C24.0
Ampulla of Vater	C24.1
Other/unspecified	C24.8-9
Gallbladder cancer	C23
Pancreatic cancer	C25
Head	C25.0
Body	C25.1
Tail	C25.2
Duct	C25.3
Endocrine	C25.4
Other/unspecified	C25.7-9
Colorectal cancer	C18; C19; C20; C26.0; C49.A4-5; D01.0-4
Cecum	C18.0

Appendix	C18.1
Ascending colon	C18.2
Hepatic flexure	C18.3
Transverse colon	C18.4
Splenic flexure	C18.5
Descending colon	C18.6
Sigmoid	C18.7
Rectosigmoid junction	C19
Rectum	C20
Other/unspecified	C188.9-9; C26.0; C49.A4-5; D01.0-4
Acute kidney injury	N17; N19; N99.0; O90.4
Chronic kidney disease	D63.1; (E08-E13).22; I12.0,9; I13.10,11,20; N18; R88.0; Z49
Congestive heart failure	I50; I97.13x; O29.12x; Z95.812; I09.81; I11.0; I13.0,2
Cirrhosis and liver failure	K70.4; K70.3; K72; K91.82; K71.7; K74; K76.(6,7); K65.2; I85
Radiation gastroenteritis/proctitis	K52.0; K62.7
Metastasis	C77; C78; C79; C80.0
Chemotherapy and immunotherapy	Z92.21; Z51.11-12; T45.1X; K12.31; D61.81; D64.81
Severe malnutrition and cachexia	E40-43; R64
Obesity	E66.01; E66.09; E66.(1,2,8,9); Z68.3-4
Palliative care	Z521.5
Aspirin/antiplatelets	Z79.82; Z79.02
Anticoagulants	Z79.01
Intestinal infection	A00-09; A18.32; A21.3; A22.2; B37.82; B25.8-9
Hypovolemic shock	R57.1
Procedures	ICD-10-PCS
Upper endoscopy	06L34CZ; 0D5(1-9)8ZZ; 0DB(1-9)8ZX; 0DB(1-9)8ZZ; 0DBA8ZX; 0DJ08ZZ; 0DQ(6,7,9)8ZZ; 3E0G8TZ
Colonoscopy	06LY4CC; 0D5(E-Q)8ZZ; 0DB(B-Q)8ZZ; 0DB(B-Q)8ZX; 0DJD8ZZ
Surgery	0D(1,5,B,J,T); 0F(5,B,T); OW(J,3) excluding endoscopic approach
Trans-arterial embolization	04(L,V)(1,2,3,5,6,7,9,B)3DZ
Radiation therapy	D(D,F,W)0(0-7)(0-6)Z(0,Z)

GI: Gastrointestinal; GIST: Gastrointestinal stromal tumor.

due to lack of enough sample size (≤ 10 patients in a table cell), and the affected cells were left unfilled in the table.

Binary multiple logistic regression was performed for the following outcomes: (1) GIH (to assess the predictors of GIH in patients with GIC); and (2) Inpatient mortality (to assess the association between mortality and interventions such as endoscopy, surgery, embolization, and radiation therapy).

Multivariate analysis was used in the backward stepwise regression to select statistically significant variables. The binary logistic regression results were represented with adjusted OR and 95% confidence interval. Statistical significance was set at the 5% level. Statistical analysis was performed using IBM SPSS, version 27 (IBM Inc., Armonk, NY, United States).

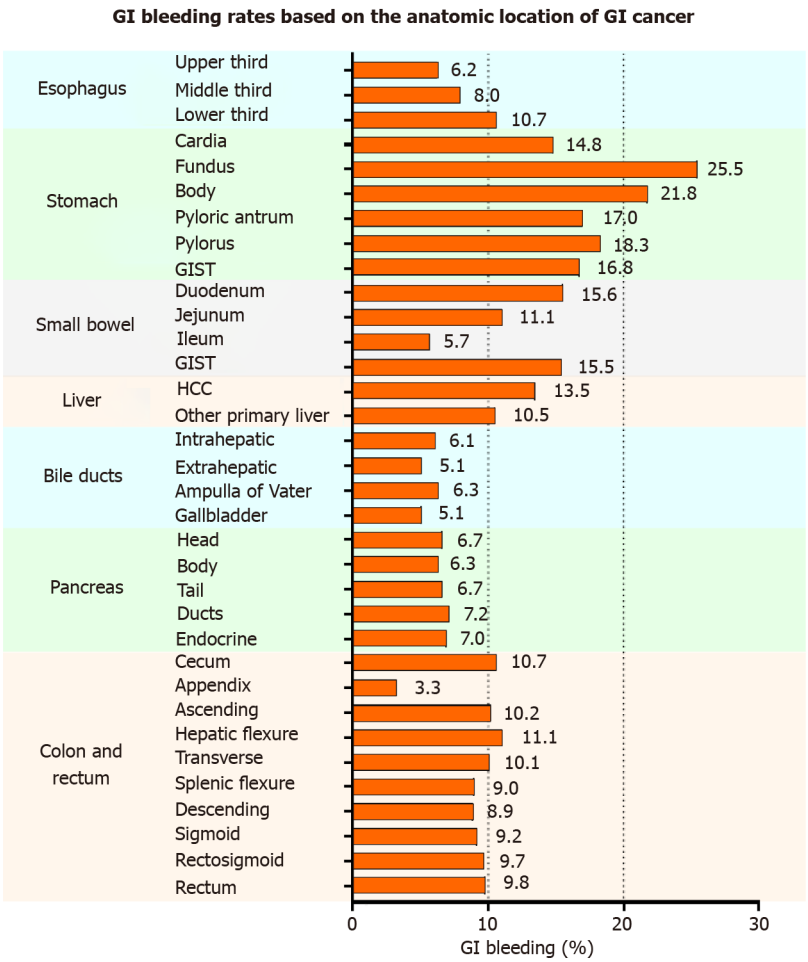

Figure 1 The proportion of gastrointestinal bleeding in inpatients according to the anatomical location of gastrointestinal cancer. GI: Gastrointestinal; GIST: Gastrointestinal stromal tumor; HCC: Hepatocellular carcinoma.

RESULTS

Prevalence of GIH in the setting of GIC

The prevalence of GIH in adult inpatients was compared based on GIC (Table 2). Out of a total of 18173885 inpatients, 321622 (1.77%) cases had a diagnosis of GIC. Within patients with GIC, 30507 (9.5%) inpatients had GIH, which was significantly (P < 0.001) more than the prevalence of GIH in patients without GIC (3.4%).

Prevalence of GIH based on the anatomical location of GIC

The highest to lowest GIH rates are listed in the following order: stomach cancer (15.7%), liver cancer (13.0%), small bowel cancer (12.7%), esophageal cancer (9.1%), colorectal cancer (9.1%), pancreatic cancer (7.2%), bile duct cancer (6.0%), and gallbladder cancer (5.1%). The prevalence of GIH was dissected more in detail by the anatomical location of GIC, as displayed in Figure 1. In esophageal cancer, GIH appears to become more prevalent in lower esophageal lesions (GIH in upper third esophageal cancer: 6.2% < middle third: 8.0% < lower third: 10.7%). Patients with stomach cancer have the highest GIH rates compared to other locations. The highest GIH rate occurs in patients with cancer of the stomach fundus (25.5%), and the lowest rate occurs in the cancer of the stomach cardia (14.8%). In the small bowel, cancer of the duodenum had the highest rate of GIH (15.6%), followed by jejunum (11.1%) and ileum (5.7%). Hepatocellular carcinoma was associated with a GIH rate of 13.5%, whereas biliary and gallbladder cancers had a GIH rate approximately 5%-6%, slightly differing by location. Patients with pancreatic cancers had GIH of approximately 6%-7%, slightly differing by location. Patients with cancers of the colon and rectum had comparable GIH rates (approximately 9%-11%) except for appendiceal cancer with a low bleeding rate (3.3%). The highest GIH rate in colorectal cancer patients belonged to hepatic flexure tumors (11.1%), and the lowest GIH (after appendiceal cancer) was for descending colon cancer (8.9%). Detailed data showing the patient counts

Table 2 Comparison of gastrointestinal hemorrhage between inpatients who have and do not have gastrointestinal cancer

		GI cancer				Total	
		No		Yes			
		Count	Within GI cancer (%)	Count	Within GI cancer (%)	Count	Within total (%)
GI bleeding	No	17242568	96.6	291115	90.5	17533683	96.5
	Yes	609695	3.4	30507	9.5	640202	3.5
	Total	17852263	100	321622	100	18173885	100

$P < 0.001$. GI: Gastrointestinal.

determining the percentages mentioned above are available in Table 3. No statistical comparison was performed between different anatomical locations due to the numerous possibilities for comparisons and combinations; however, assessing the clinical significance of percentages and their differences is still valuable in making comparisons.

Predictors of GIH in patients with GIC

In this section, the predictors of GIH were studied in the population of patients with GIC. Table 4 shows a comparison of various demographic, socioeconomic, and other disease-related factors based on GIH status. Patients with GIH were slightly older compared to patients without GIH (68.2 ± 13.2 *vs* 66.2 ± 12.8 years old, $P < 0.001$). Patients with GIH were less likely to be females (37.8% *vs* 43.3%, $P < 0.001$). While minority races, including Black, Hispanic, Asian, and Native American, were more prevalent in patients with GIH, White race was less common in GIH patients (63.0% *vs* 68.3%, $P < 0.001$). Socioeconomic factors also were associated with varying GIH rates. Patients with GIH were more likely to be Medicare (60.3% *vs* 55.5%, $P < 0.001$), Medicaid, or self-pay patients, and they were less likely to have private insurance (21.3% *vs* 28.1%, $P < 0.001$). Likewise, GIH patients had a lower median household income compared to patients without GIH. Comorbidities such as acute kidney injury, chronic kidney disease, heart failure, cirrhosis, and liver failure were more common in patients with GIH. For cancer-related variables, patients with GIH had less metastatic disease (39.7% *vs* 43.1%, $P < 0.001$), were less treated with chemotherapy or immunotherapy (14.1% *vs* 19.6%, $P < 0.001$), and had more radiation gastroenteritis or proctitis (0.6% *vs* 0.3%, $P < 0.001$). GIH patients were also less obese and were more diagnosed with severe malnutrition and cachexia compared to non-GIH patients.

Table 5 shows the multivariate analysis results, which validates the results of the bivariate analysis discussed above. In summary, predictors (in favor) of GIH were age, minority races (Black, Hispanic, Asian, Native American compared to White race), Insurance (Medicaid and Self-pay compared to Medicare), acute kidney injury, chronic kidney disease, heart failure, cirrhosis, and liver failure, radiation gastroenteritis or proctitis, severe malnutrition and cachexia, use of aspirin, antithrombotic and anticoagulants. Predictors against having GIH were female gender, private insurance (compared to Medicare), higher median household income, presence of metastatic disease, patient on chemotherapy or immunotherapy, and obesity. The factor with the highest OR for GIH was radiation gastroenteritis and proctitis [OR = 2.39 (2.02-2.81)]. The factor with the lowest OR for GIH was chemotherapy or immunotherapy [OR = 0.74 (0.72-0.77)].

Interventions for GIH

Interventions that have been proposed and utilized in GIH patients with GIC were studied. Inpatient mortality was the outcome of interest. The four studied interventions were endoscopy, surgery, trans-arterial embolization, and radiation therapy. Multivariate analysis, using stepwise binary logistic regression, accounted for the following factors: Age, female, race, income, acute kidney injury, chronic kidney disease, heart failure, cirrhosis and liver failure, intestinal infection, metastasis, chemotherapy and immunotherapy, radiation gastroenteritis, palliative care, hypovolemic shock, endoscopy, surgery, embolization, and radiation therapy.

Endoscopy

Out of 30507 inpatients with GIC who also had GIH, 16267 (53.3%) underwent an

Table 3 Tabulated representation of data of Figure 1 which shows to the prevalence of gastrointestinal hemorrhage according to the anatomic location of gastrointestinal cancer

Anatomic location of cancer		GI hemorrhage			
		No		Yes	
	n	Count	Row (%)	Count	Row (%)
Esophagus	23674	21508	90.90	2166	9.10
Upper third	773	725	93.80	48	6.20
Middle third	1467	1349	92.00	118	8.00
Lower third	6540	5843	89.30	697	10.70
Other/unspecified	15161	13842	91.30	1319	8.70
Stomach	27409	23103	84.30	4306	15.70
Cardia	6829	5815	85.20	1014	14.80
Fundus	471	351	74.50	120	25.50
Body	1284	1004	78.20	280	21.80
Pyloric antrum	1881	1561	83.00	320	17.00
Pylorus	398	325	81.70	73	18.30
GIST	2477	2060	83.20	417	16.80
Other/unspecified	14410	12256	85.10	2154	14.90
Small bowel	6469	5646	87.30	823	12.70
Duodenum	3270	2760	84.40	510	15.60
Jejunum	513	456	88.90	57	11.10
Ileum	540	509	94.30	31	5.70
GIST	872	737	84.50	135	15.50
Other/unspecified	1322	1228	92.90	94	7.10
Liver	33452	29111	87.00	4341	13.00
HCC	27601	23877	86.50	3724	13.50
Other primary liver	5988	5357	89.50	631	10.50
Bile ducts	18706	17577	94.00	1129	6.00
Intrahepatic	12515	11749	93.90	766	6.10
Extrahepatic	2749	2608	94.90	141	5.10
Ampulla of Vater	2143	2008	93.70	135	6.30
Other/unspecified	1464	1368	93.40	96	6.60
Gallbladder	4268	4049	94.90	219	5.10
Pancreas	63636	59063	92.80	4573	7.20
Head	17643	16469	93.30	1174	6.70
Body	3077	2882	93.70	195	6.30
Tail	3892	3630	93.30	262	6.70
Ducts	774	718	92.80	56	7.20
Endocrine	589	548	93.00	41	7.00
Other/unspecified	38379	35489	92.50	2890	7.50
Colon and rectum	148943	135410	90.90	13533	9.10
Cecum	12171	10863	89.30	1308	10.70
Appendix	3967	3835	96.70	132	3.30

Ascending	16104	14458	89.80	1646	10.20
Hepatic flexure	3280	2916	88.90	364	11.10
Transverse	7439	6687	89.90	752	10.10
Splenic flexure	2033	1851	91.00	182	9.00
Descending	4239	3862	91.10	377	8.90
Sigmoid	17602	15976	90.80	1626	9.20
Rectosigmoid	17199	15527	90.30	1672	9.70
Rectum	29634	26730	90.20	2904	9.80
Other/unspecified	40531	37341	91.50	3190	8.50

GI: Gastrointestinal; GIST: Gastrointestinal stromal tumor; HCC: Hepatocellular carcinoma.

endoscopic procedure, *i.e.*, upper endoscopy or colonoscopy. Figure 2 displays a significant decrease in mortality associated with endoscopy performance in patients with GIH and GIC (mortality with endoscopy: 5.5% *vs* no endoscopy: 14.9%, $P < 0.001$). Multivariate adjusted analysis (Table 6) shows a mortality reduction associated with endoscopy [OR = 0.42 (0.38-0.46)]. This association also applied to cancer subtypes, particularly esophageal, gastric, primary hepatic, biliary, pancreatic, and colorectal cancer. Gallbladder and small bowel cancer patients did not show a statistically significant association between mortality and endoscopy.

Colorectal cancer had a sufficient patient population to study the types of endoscopy performed and their association with inpatient mortality. Figure 3 shows that, in colorectal cancer patients with GIH, the lowest mortality was reported in patients who underwent either colonoscopy (2.6%) or dual (upper and lower) endoscopy (2.6%). This was significantly lower compared to mortality in patients who underwent upper endoscopy (6.5%) or no endoscopy (9.0%) ($P < 0.001$ for colonoscopy or dual endoscopy *vs* upper endoscopy or non-endoscopy group). Eight percent of all GIH causes in colorectal cancer patients were attributed to upper GIH, including 4.1% peptic ulcer disease and 0.9% esophageal varices.

Surgery

Out of 30507 inpatients with GIC who also had GIH, 4568 (15.0%) underwent surgical exploration with or without bowel resection during hospitalization. Unadjusted analysis displays a significant decrease in mortality associated with the performance of surgery in GIH patients with GIC (total) (5.6% *vs* 10.6%, $P < 0.001$) and colorectal cancer (4.6% *vs* 6.5%, $P < 0.001$). On multivariate (adjusted) analysis shown in Table 6, results were different from unadjusted analysis. Surgery was not associated with any statistical difference decrease in mortality in GIC (total) but had increased odds of mortality in patients with gastric [OR = 1.73 (1.00-3.00)] and colorectal cancer [OR = 1.33 (1.09-1.62)]. Small bowel, hepatic, and pancreatic cancer patients did not show a statistical difference between surgery and non-surgery groups.

Trans-arterial embolization

Out of 30507 inpatients with GIC who also had GIH, 516 (1.7%) underwent trans-arterial embolization. Unadjusted analysis displays a significant increase in mortality associated with the performance of trans-arterial embolization in GIH patients with GIC (total) (14.7% *vs* 9.8%, $P < 0.001$). Gastric cancer (15.1% *vs* 8.7%, $P = 0.01$) and colorectal cancer (21.9% *vs* 5.9%, $P < 0.001$) were also associated with increased mortality in patients who underwent embolization. Similarly, on multivariate (adjusted) analysis in Table 6, embolization was associated with increased odds of mortality in GIC (total) [OR = 1.35 (1.02-1.80)] and colorectal cancer [OR = 2.52 (1.23-5.15)]. Gastric, hepatic, and pancreatic cancer patients did not show a statistical association between embolization and mortality on multivariate analysis.

Radiation therapy

Out of 30507 inpatients with GIC who also had GIH, radiation therapy was performed in 210 (0.7%) patients during the hospitalization. On bivariate analysis, the inpatient mortality of patients who underwent inpatient radiation therapy was lower than those who did not undergo radiation therapy (5.7% *vs* 9.9%, $P = 0.04$). On multivariate

Table 4 Bivariate analysis comparing various factors based on gastrointestinal hemorrhage status in a population of inpatients with gastrointestinal cancer

Inpatients with GI cancer		No GI hemorrhage		GI hemorrhage		*P* value
		n = 291115		*n* = 30507		
		Count/mean	Column%/SD	Count/mean	Column%/SD	
Demographic factors						
Age (yr)		66.2	± 12.8	**68.2**	**± 13.2**	< 0.001
Female		**125898**	**43.30**	11543	37.80	< 0.001
Race	White	**192544**	**68.30**	18633	63.00	< 0.001
	Black	37986	13.50	**4727**	**16.00**	< 0.001
	Hispanic	29010	10.30	**3462**	**11.70**	< 0.001
	Asian or Pacific Islander	11482	4.10	**1562**	**5.30**	< 0.001
	Native American	1494	0.50	**189**	**0.60**	0.015
	Other	9345	3.30	999	3.40	0.543
Socioeconomic factors						
Insurance	Medicare	161272	55.50	**18371**	**60.30**	< 0.001
	Medicaid	33523	11.50	**3859**	**12.70**	< 0.001
	Private	**81599**	**28.10**	6483	21.30	< 0.001
	Self-pay	6348	2.20	**894**	**2.90**	< 0.001
	No charge	628	0.20	71	0.20	0.544
	Other	7379	2.50	799	2.60	0.373
Median household income for patient ZIP Code	1st quartile	78840	27.60	**8905**	**29.70**	< 0.001
	2nd quartile	73759	25.80	7733	25.80	0.965
	3rd quartile	**69806**	**24.40**	7072	23.60	0.003
	4th quartile	**63693**	**22.30**	6241	20.80	< 0.001
Comorbidities						
Acute kidney injury		55007	18.90	**7849**	**25.70**	< 0.001
Chronic kidney disease		38425	13.20	**5766**	**18.90**	< 0.001
Heart failure		8704	3.00	**1289**	**4.20**	< 0.001
Cirrhosis and liver failure		32194	11.10	**6154**	**20.20**	< 0.001
Intestinal infection		6694	2.30	753	2.50	0.06
Cancer related						
Metastasis		**125345**	**43.10**	12120	39.70	< 0.001
Chemo and Immunotherapy		**57005**	**19.60**	4314	14.10	< 0.001
Radiation gastroenteritis/proctitis		849	0.30	**189**	**0.60**	< 0.001
Palliative care		38129	13.10	**5318**	**17.40**	< 0.001
Nutritional status						
Severe malnutrition and cachexia		41008	14.10	**4952**	**16.20**	< 0.001
Obesity		**32691**	**11.20**	3127	10.30	< 0.001
Use of antithrombotic/anticoagulants						
Aspirin/antiplatelets		30778	10.60	**3605**	**11.80**	< 0.001
Anticoagulants		22753	7.80	**3345**	**11.00**	< 0.001

Bold values represent a statistically significant higher column proportion. GI: Gastrointestinal.

analysis (Table 6), inpatient radiation therapy for GI bleeding patients with GIC was not significantly associated with any inpatient mortality difference. Analysis was not performed on individual GIC types (esophageal, gastric, small bowel, …) due to insufficient sample in the radiation group.

DISCUSSION

This was a retrospective review of the 2016-2018 NIS database, which is one of the largest national inpatient databases. Our results, as presented in Table 2, our results showed that hospitalized patients with GIC have a significantly higher prevalence of GIH (9.5%) compared to that of the general inpatient population (3.4%). This estimate underscores that GIH is a common complication of GIC and corroborates this study's importance.

Our study showed that GIH is note common in GIC patients and varies significantly based on the anatomical location of cancer. The highest to lowest GIH rates are listed in the following order: stomach cancer (15.7%), liver cancer (13.0%), small bowel cancer (12.7%), esophageal cancer (9.1%), colorectal cancer (9.1%), pancreatic cancer (7.2%), bile duct cancer (6.0%), and gallbladder cancer (5.1%). Figure 1 shows a more detailed representation of GIH rates based on the anatomical location of GIC. The rate of GIH can significantly vary with different tumor locations, even for locations within the same organ. The pattern of bleeding, displayed in Figure 1, shows the highest GIH rate in gastric cancers (ranging between 14.8% in the cardia and 25.5% in cancers of the fundus) followed by cancers adjacent to the stomach, such as cancer of the duodenum (15.6%) and lower third of the esophagus (10.7%). This could be related to the effect of the stomach's acidic medium that can cause erosion and ulceration of the friable intraluminal cancerous tissue and subsequently bleeding. Thus, the further the cancerous tissue from the stomach, the less risk of GIH. Following the same logic, jejunal (11.1%) and ileal cancers (5.7%) have lower GIH rate than duodenal cancers (15.6%), and cancers of the upper (6.2%) and middle third (8.0%) of the esophagus have lower GIH than lower third cancers (10.7%). The correlation between the high incidence of GIH in hepatocellular carcinoma and underlying severe liver cirrhosis with resultant variceal hemorrhage has been demonstrated in previous studies.[16] Colorectal cancer's GIH rates based on different anatomical locations were relatively comparable in the range between 9% to 11%. Appendiceal cancer was an exception with 3.3% GIH, which is similar to the general inpatient population (3.4%).

While our study reports the prevalence of GIH among GIC patients, prior studies have reported the reciprocal prevalence of GIC among patients with GIH[3,17,18]. For example, Sheibani *et al*[6] stated that tumor bleeding comprised 5% (106 cases) of all upper GIH with gastric cancer representing 73%, esophageal cancer 16%, and duodenal cancer 11%. The aforementioned study serves another purpose and cannot estimate the rates of GIH as it examines another parameter. In addition, the large sample size of our patients (30507 bleeding GIC) robustly increases the power of our GIH estimates and analysis.

Notable findings were also reported in the study of the predictors of GIH in GIC. Multivariate analysis results are shown in Table 5. A closer look at the prevalence of GIH in GIC, stratified by race, raises concerning questions on healthcare disparities. Compared to the White race, certain minority races (Black, Hispanic, Asian, and Native American) were predictors of GIH. Lower median household income was also a concerning predictor of GIH. GIH outcomes, stratified by race, have been studied before in various contexts. One study of patients hospitalized for upper GIH found that rebleeding rates were significantly lower in White patients than in Hispanic or Black patients[19]. In the instance of cancer, healthcare disparities also play a significant role in disease onset and outcome. Black patients are observed to have the highest incidence and mortality of many GI tract malignancies, including esophageal, gastric, small bowel, pancreas, colorectal, and anal cancer[20]. Despite the decline in colorectal cancer mortality rates in the past years, the reduction is not as prominent in Black patients. The causes of this are likely multifactorial, many of which are modifiable risk factors such as socioeconomic status, insurance coverage, education level, and consistent access to medical care[21]. The results of this study potentially reinforce these conclusions, as Medicaid patients and non-White patients with GIC

Table 5 The results of multivariate analysis showing the predictors of gastrointestinal hemorrhage in a population of patients with gastrointestinal cancer

Predictors of GI hemorrhage				
		aOR	95%CI	*P* value
Demographic factors				
Age (yr)		**1.01**	**(1.01-1.02)**	**< 0.001**
Female		0.84	(0.81-0.86)	< 0.001
Race	White- Reference	1.00	-	-
	Black	**1.27**	**(1.22-1.31)**	**< 0.001**
	Hispanic	**1.19**	**(1.14-1.24)**	**< 0.001**
	Asian or Pacific Islander	**1.42**	**(1.34-1.50)**	**< 0.001**
	Native American	**1.24**	**(1.06-1.46)**	**0.007**
	Other	**1.13**	**(1.05-1.21)**	**0.001**
Socioeconomic factors				
Insurance	Medicare- Reference	1.00	-	-
	Medicaid	**1.17**	**(1.12-1.22)**	**< 0.001**
	Private	0.91	(0.88-0.94)	< 0.001
	Self-pay	**1.44**	**(1.34-1.56)**	**< 0.001**
	No charge	1.21	(0.94-1.56)	0.148
	Other	1.03	(0.95-1.12)	0.468
Median household income for patient ZIP Code	1st quartile- Reference	1.00	-	-
	2nd quartile	0.98	(0.95-1.01)	0.246
	3rd quartile	0.96	(0.93-0.99)	0.022
	4th quartile	0.94	(0.90-0.97)	< 0.001
Comorbidities				
Acute kidney injury		**1.17**	**(1.13-1.20)**	**< 0.001**
Chronic kidney disease		**1.22**	**(1.18-1.26)**	**< 0.001**
Heart failure		**1.19**	**(1.12-1.27)**	**< 0.001**
Cirrhosis and liver failure		**1.84**	**(1.78-1.90)**	**< 0.001**
Cancer related				
Metastasis		0.93	(0.90-0.95)	< 0.001
Chemo and Immunotherapy		0.74	(0.72-0.77)	< 0.001
Radiation gastroenteritis/proctitis		**2.39**	**(2.02-2.81)**	**< 0.001**
Palliative care		**1.21**	**(1.17-1.26)**	**< 0.001**
Nutritional status				
Severe malnutrition and cachexia		**1.12**	**(1.08-1.15)**	**< 0.001**
Obesity		0.94	(0.90-0.98)	0.001
Use of antithrombotic/anticoagulants				
Aspirin/antiplatelets		**1.09**	**(1.05-1.13)**	**< 0.001**
Anticoagulants		**1.48**	**(1.42-1.54)**	**< 0.001**

Bold values represent a statistically significant odds ratio > 1 [in favor of gastrointestinal hemorrhage (GIH)]; multivariate logistic regression of outcome (GIH) was performed using the backward stepwise method to determine statistically significant factors; variables included in the analysis: Age, female, race, insurance, income, acute kidney injury, chronic kidney disease, heart failure, cirrhosis and liver failure, intestinal infection, metastasis, chemotherapy

and immunotherapy, radiation gastroenteritis, palliative care, severe malnutrition and cachexia, obesity, aspirin/antiplatelet, and anticoagulant; intestinal infection was a statistically non-significant factor; GI: Gastrointestinal; CI: Confidence interval; OR: Odds ratio.

Table 6 The results of multivariate analysis showing the odds ratio of inpatient mortality associated with different interventions (endoscopy, surgery, embolization, radiation)

		GI bleeding patients with cancer								
		All GI Ca	Esophageal Ca	Gastric Ca	Hepatic Ca	Biliary Ca	Gallbladder Ca	Pancreatic Ca	Small bowel Ca	Colorectal Ca
Mortality aOR (95%CI)	Endoscopy	**0.42 (0.38-0.46)**	**0.42 (0.31-0.57)**	**0.42 (0.32-0.54)**	**0.36 (0.29-0.43)**	**0.43 (0.28-0.66)**	0.71 (0.24-2.11)	**0.36 (0.29-0.44)**	1.19 (0.59-2.43)	**0.45 (0.38-0.54)**
	Surgery	0.97 (0.84-1.13)	-	**1.73 (1.00-3.00)**	1.30 (0.67-2.53)	-	-	0.85 (0.49-1.48)	2.26 (0.95-5.36)	**1.33 (1.09-1.62)**
	Trans-arterial embolization	**1.35 (1.02-1.80)**	-	1.46 (0.81-2.62)	1.12 (0.55-2.30)	-	-	0.98 (0.56-1.69)	-	2.52 (1.23-5.15)
	Radiation therapy	0.55 (0.29-1.05)	-	-	-	-	-	-	-	-

Bold values: Statistically significant ($P < 0.05$). Adjusted odds ratio with 95% confidence interval; empty cells indicate that analysis for the corresponding intervention was not performed due to the insufficient sample size; multivariate logistic regression of outcome (mortality) was performed using the backward stepwise method to determine statistically significant factors; variables included in the analysis: Age, female, race, income, acute kidney injury, chronic kidney disease, heart failure, cirrhosis and liver failure, intestinal infection, metastasis, chemotherapy and immunotherapy, radiation gastroenteritis, palliative care, hypovolemic shock, endoscopy, surgery, embolization, and radiation therapy. GI: Gastrointestinal. CI: Confidence interval; Ca: Cancer; OR: Odds ratio.

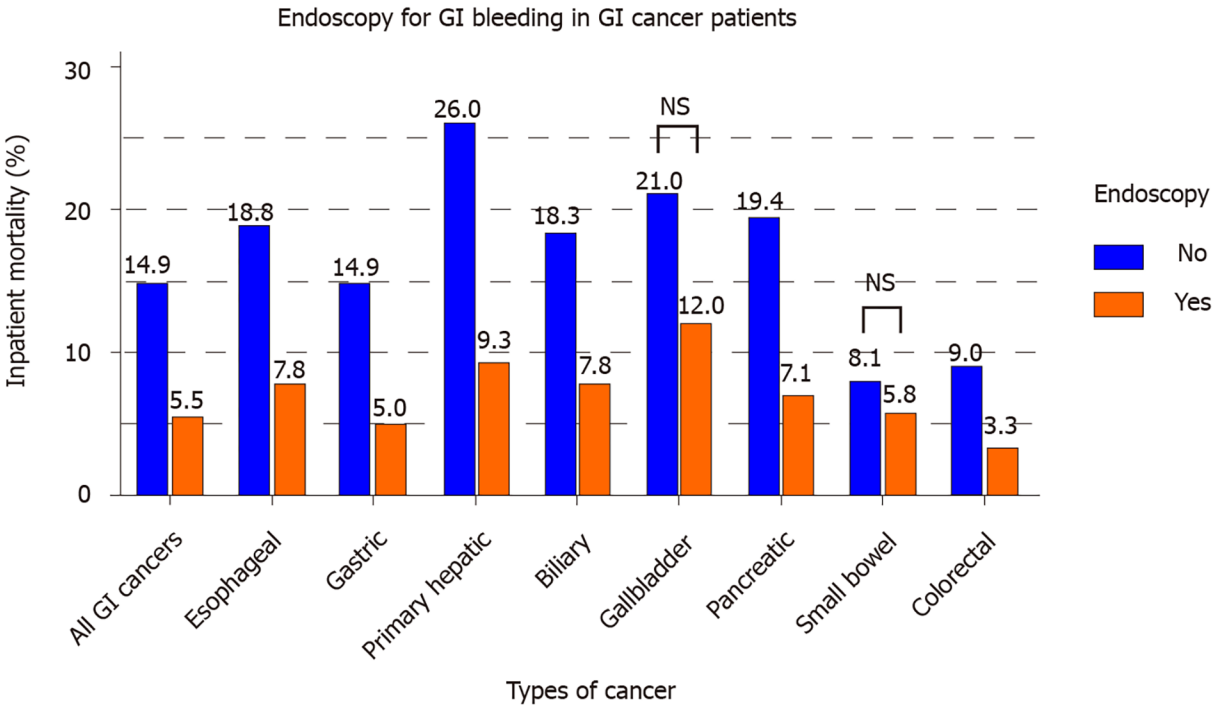

Figure 2 The mortality outcomes of endoscopy in gastrointestinal cancer patients who have gastrointestinal hemorrhage. GI: Gastrointestinal; NS: Not significant.

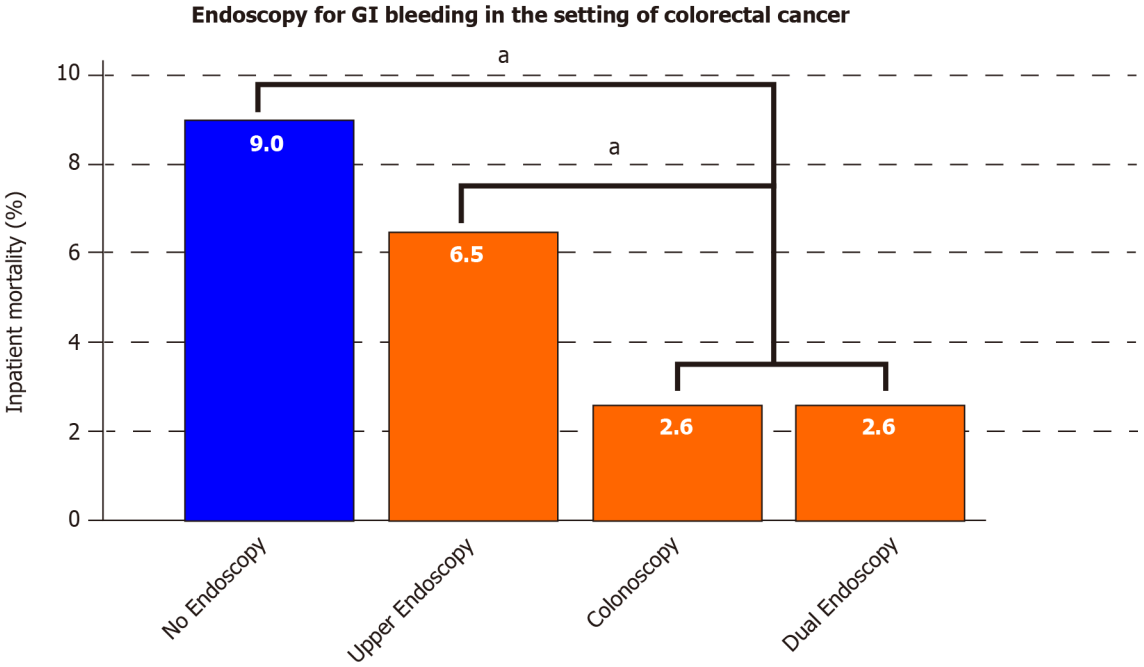

Figure 3 The mortality outcomes of different endoscopic approaches (upper, colonoscopy, or dual) in colorectal cancer patients who have gastrointestinal hemorrhage. [a]*P* < 0.05. GI: Gastrointestinal.

experienced higher rates of GIH. Future studies should continue to examine outcomes of GIH in cancer patients, stratified by factors that would affect access to quality healthcare. Such data would be important in driving targeted screening and prevention efforts to high-risk populations. Our analysis also found other significant predictors of GIH, including cancer-related factors. Chemotherapy and immunotherapy were associated with lower risk for GIH [OR = 0.74 (0.72-0.77), *P* < 0.001]. We speculate that the associated decreased risk is related to tumor involution in response to chemotherapy. Radiation gastroenteritis and proctitis was the strongest predictor of GIH [OR = 2.39 (2.02-2.81), *P* < 0.001]. The presence of metastasis was associated with a lower risk of GIH [OR = 0.93 (0.90-0.95), *P* < 0.001]. This could be confounded by other factors that are not retrospectively available for analysis in this database, such as patients' prior surgical history related to the malignancy.

In examining interventions for GIH in the setting of GIC, our data support that endoscopic therapy is associated with a substantial reduction in mortality. Figure 2 highlights the marked difference in mortality between endoscopy and non-endoscopy groups in various GICs (esophageal, gastric, liver, biliary, pancreatic, and colorectal cancer). There was no statistical difference in the subset of gallbladder and small bowel cancers. The type of endoscopy was studied particularly in our cohort of bleeding colorectal cancer patients. Performing either dual endoscopy or colonoscopy resulted in a statistically significant reduction in mortality compared to no endoscopy or upper endoscopy alone (Figure 3). We also have reported that eight percent of all GIH causes in colorectal cancer patients were attributed to upper GIH, including 4.1% peptic ulcer disease and 0.9% esophageal varices. From this standpoint, we can argue in favor of performing dual endoscopy, as upper endoscopy is a fast procedure that can generally be performed with ease along with colonoscopy. As discussed before, endoscopic therapy for GIH may decrease overall morbidity and the need for surgical intervention[14]. Multiple endoscopic methods such as injection, mechanical, and ablative therapies were suggested to stop bleeding from GI tumors; however, literature is mainly based on limited small sample size (10-100 patients) studies[22,23]. Based on our current knowledge, this current study has the largest analysis of endoscopy in bleeding GIC patients. Future studies should examine the different modalities of endoscopic therapy for the treatment of hemorrhage in the specific setting of cancer.

Trans-arterial embolization for GIH in GIC patients was associated with increased inpatient mortality, particularly for colorectal cancers. Surgical exploration with or without resection was not associated with mortality difference in bleeding GIC total population. However, it was associated with increased gastric and colorectal cancer mortality on multivariate analyses (Table 6). Surgery is usually reserved as a last resort

for rebleeding or hemorrhage refractory to endoscopic therapy, and these cancer patients usually have an initial poor prognosis or advanced disease[12]. Radiation therapy was not associated with mortality difference in patients with GIH and GIC. The limitations are mainly due to the retrospective nature of the study. Important factors, such as the severity of GIH, intensive care admission, rebleeding rates, tumor's size, and the stage and grade of cancer, were also not available for analysis in this database. Therefore, prospectively studying this patient population in the future would instead decrease potential information bias and would be able to fill in the gaps of the current research. However, our study's strength is numerous and related to its uniqueness, novelty, and robust analysis. The current study provides a detailed and comprehensive examination of the subject of GIH in GIC and provides evidence to support the use of endoscopy in this patient population.

CONCLUSION

The prevalence of GIH in patients with GIC varies significantly based on the anatomical location of the tumor. GICs with the highest to the lowest likelihood of GIH are stomach cancer, liver cancer, small bowel cancer, esophageal cancer, colorectal cancer, pancreatic cancer, bile duct cancer, and lastly, gallbladder cancer. Endoscopy is associated with a substantial reduction in inpatient mortality and therefore should be offered to GIH patients with GIC. Nevertheless, the decision on intervention in the GIC population should be tailored to individual patient's goals of care, the benefit on overall care, and long-term survival.

ARTICLE HIGHLIGHTS

Research background

Gastrointestinal hemorrhage (GIH) is a common complication with gastrointestinal cancers (GIC).

Research motivation

There is no comprehensive research that examines GIH in different types of GIC. Furthermore, endoscopic therapy is insufficiently studied in this setting.

Research objectives

We aim to study the prevalence, predictors, and interventions of GIH based on the anatomical location of GIC.

Research methods

This is a retrospective analysis of the 2016-2018 National Inpatient Sample database, the largest inpatient care database in the United States. Adult inpatients were evaluated for the prevalence and predictors of GIH in the setting of GIC. In addition, inpatient mortality was compared between patients who underwent or did not undergo endoscopy.

Research results

The highest to lowest GIH rates are listed in the following order: stomach cancer (15.7%), liver cancer (13.0%), small bowel cancer (12.7%), esophageal cancer (9.1%), colorectal cancer (9.1%), pancreatic cancer (7.2%), bile duct cancer (6.0%), and gallbladder cancer (5.1%). Inpatient mortality was significantly lower in patients who underwent endoscopy compared to no endoscopy [5.5% *vs* 14.9%, OR = 0.42 (0.38-0.46)], $P < 0.001$).

Research conclusions

The prevalence of GIH in patients with GIC varies significantly based on the tumor's anatomical location. Endoscopy appears to be associated with a substantial reduction in inpatient mortality and should be offered to GIC patients with GIH.

Research perspectives

Future studies, prospective and randomized trials, would help confirm the effectiveness of endoscopic therapy for GIH in patients with GIC.

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ORIGINAL ARTICLE

Observational Study

Clinical characteristics and prognosis of patients with ulcerative colitis that shows rectal sparing at initial diagnosis

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Data sharing statement: Technical appendix, statistical code, and dataset available from the corresponding author at [yschoi427@naver.com]. Participants gave informed consent for data sharing.

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Abstract

BACKGROUND

Ulcerative colitis (UC) is characterised by mucosal inflammation from the rectum to its proximal area in a symmetric and continuous fashion. However, although uncommon, we encounter cases of UC with rectal sparing in the initial stage.

AIM

To evaluate the clinical characteristics and clinical course for rectal sparing UC compared with typical UC.

METHODS

We looked at records from 2004 to 2015, and selected patients who were newly diagnosed with UC, and who could be followed up for at least 5 years in our hospital. We then retrospectively analysed the medical records and endoscopic findings of those patients. To compare the clinical course and prognosis, we matched each patient with rectal sparing UC 1:3 with controls by age, sex, and disease extent.

RESULTS

Of 619 UC patients, 24 (3.9%) showed rectal sparing at diagnosis. During the follow-up period (median 8 years), in two (8.3%) of the 24 patients, rectal sparing remained through follow-up inspections; but for the other 22 (91.7%) patients, obvious rectal inflammation was found at follow-up endoscopy. Of the 24 patients, 8 (33.3%) were initially misdiagnosed with infectious colitis. No diagnosis was changed to Crohn's disease. The uses of corticosteroid or biologic agents, hospitalisation rate, and colectomy rates were not different between the rectal sparing UC group and typical UC group.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement.

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CONCLUSION
Some patients with UC can reveal atypical patterns of disease distribution, such as rectal sparing in its initial stage; but despite this, the clinical course and prognosis may not differ from those of typical UC patients.

Key Words: Ulcerative colitis; Rectal sparing; Clinical characteristics; Prognosis; At diagnosis; Adult

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Core Tip: Ulcerative colitis (UC) is characterised by mucosal inflammation from the rectum to its proximal area in a symmetric and continuous fashion. However, the atypical distribution of UC, such as skip inflammation or rectal sparing can be encountered at initial stage, making diagnosis difficult in usual practice although it is uncommon. As a matter of fact, some studies concerning pediatric UC patients were reported, but its clinical significance and incidence is not known well in adult UC patients. Our study is the only study that evaluated the clinical characteristics and prognosis of adult rectal sparing-typed UC compared with typical UC.

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INTRODUCTION

Ulcerative colitis (UC) is an idiopathic inflammatory bowel disease that is characterised by mucosal inflammation in a continuous and symmetrical fashion from rectum to colon. Recently, however, together with the easy availability and technical advance of colonoscopy, some reports have demonstrated atypical disease distribution of UC, such as skipped lesion, rectal sparing, and upper gastrointestinal tract involvement of ulcerative colitis[1-6]. Moreover, early and increasing diagnosis of UC may also raise the possibility of this diagnostic perplexity, and make it more difficult to differentiate UC from other colitis that can show similar endoscopic findings, such as infectious colitis (*i.e.*, bacterial, amoebic, tuberculous, *etc.*), ischemic colitis, radiation-induced colitis, drug-induced colitis, eosinophilic colitis, lymphoma, and solitary rectal ulcer syndrome[7].

Atypical distribution of UC, such as rectal sparing, can be encountered in patients with UC during treatment, when the mucosal healing of ulcerative proctitis is achieved by topical treatment with mesalamine or corticorsteroids[8]. This condition can also be found more frequently in paediatric UC patients[9-11]. Nevertheless, although uncommon, it can be noted even in adult patients, even at the initial UC diagnosis. In fact, challenging cases of UC with rectal sparing can be encountered at initial diagnosis, which may lead to misdiagnosis.

The clinical characteristics and significance of rectal sparing UC are not known well. Some previous reports have suggested that rectal sparing UC was associated with primary sclerosing cholangitis[12,13]. However, the clinical study concerning its clinical courses and prognosis is still insufficient, although some Japanese studies reported that rectal sparing type UC was related to poor prognosis[14,15]. The aim of the present study was to evaluate the clinical characteristics and clinical course for rectal sparing UC, compared to typical UC.

MATERIALS AND METHODS

Patients' inclusion

We looked at the records of 905 patients [median age: 39 years; range: (16-81) years]

who were newly diagnosed with UC at Daehang Hospital, Seoul, Korea, from January 2004 to December 2015; all UC patients were initially diagnosed and regularly followed for at least 5 years in our clinic.

We then retrospectively investigated a number of baseline patient demographics, which included sex and age, time of diagnosis, symptom duration, perinuclear antineutrophil cytoplasmic antibody status, white cell count, erythrocyte sedimentation rate, C-reactive protein levels, initial disease extent, endoscopic findings (new development of rectal inflammation on follow-up endoscopy as well as initial findings), clinical courses including hospitalisation or colectomy, and medication history.

Study design and definitions

To compare the clinical course and prognosis, we matched each patient with rectal sparing UC (n = 24) 1:3 with controls who had typical continuous and symmetric pattern of UC without rectal sparing (n = 72) to reduce bias; we matched the controls with the cases by age, gender, and disease extent. Primary study outcomes were the cumulative use of corticosteroid. Secondary outcomes were the use of biologic agents (including infliximab, adalimumab, golimumab, vedolizumab, or tofacitinib), hospitalisation of patients, and colectomy in patients with UC with and without rectal sparing at diagnosis. We collected and retrospectively analysed all data through December 31, 2015, or until loss to follow-up. The UC patients who were not on follow-up for less than 5 years were excluded from the analysis. The study was approved by the ethics committee of Daehang Hospital.

UC was definitively diagnosed in those who met the following criteria: (1) Typical history of diarrhea, blood and pus in the stool, or both, for longer than four weeks; (2) Typical sigmoidoscopic or colonoscopic picture with loss of vascularity, friability, granularity, and/or ulcerations of the colorectal mucosa in a continuous and circumferential pattern in the rectum; and (3) Characteristic histopathologic signs of inflammation on biopsy, such as chronic inflammation or distortion of crypt architecture, inflammation of crypts, crypt abscesses, increased chronic inflammatory cells in the lamina propria, erosions, and/or ulcers[16]. Proctitis was categorised when disease extent was limited to the rectum (E1), left-sided colitis when disease extent was limited to the proportion of the colon distal to the splenic flexure (E2), and extensive disease when the disease extended proximal to the splenic flexure, including pancolitis (E3) [17,18]. In the case of UC with rectal sparing, left-sided colitis (E2) and pancolitis (E3) were defined as the same without rectal involvement. We defined rectal sparing as no evidence of mucosal inflammation of the rectal mucosa by colonoscopy, such as normal transparent mucosa with visible capillary vasculature. Endoscopic findings were reviewed by two experienced endoscopists in random order (Kim JK and Choi YS).

Statistical analysis

We used the χ^2 test to compare the categorical variables, and the independent t test to compare the continuous variables. We calculated the cumulative rates of corticosteroids use using the Kaplan-Meier method, and we used the log-rank test to compare the categorical variables. We considered $P < 0.05$ to be statistically significant, and conducted all calculations using SPSS version 15.0 statistical software package (SPSS Inc., Chicago, IL, United States).

RESULTS

Clinical characteristics at diagnosis

Of 619 UC patients, 24 (3.9%) showed rectal sparing by colonoscopy at initial diagnosis (Figures 1 and 2). Of the 24 patients, 16 (66.7%) had a disease extent beyond splenic flexure (E3), while 8 (33.3%) of the 24 patients were limited before splenic flexure (E2) with rectal sparing. During the follow-up period [median 9 years, range (5-15) years], in two (8.3%) of the 24 patients, rectal sparing remained through follow-up inspections; but for the other 22 (91.7%) patients, obvious rectal inflammation was found at follow-up endoscopy. Of the 24 patients, 8 (33.3%) were initially misdiagnosed with infectious colitis, and empirical antibiotics were administered. No diagnosis was changed from ulcerative colitis to Crohn's disease (Table 1).

Table 1 Clinical characteristics of rectal sparing ulcerative colitis at diagnosis

	Rectal spring UC at diagnosis (*n* = 24)
Age (yr)	35.8 ± 11.0
Sex (male:female)	19:5
Disease distribution	
Extensive colitis (E3) with rectal sparing	16 (66.7%)
Left-sided colon (E2) with rectal sparing	8 (33.3%)
Initial Diagnosis	
IBD-U	8 (33.3%)
Infectious colitis	7 (29.2%)
UC	7 (29.2%)
Nonspecific	2 (8.3%)
Symptom duration	2 mo (2 wk to 60 mo)
Laboratory findings	
WBC (count/mm^3)	6475.9 ± 2273.4
ESR (mm/h)	17.4 ± 13.9
CRP (mg/dL)	0.4 ± 0.7
p-ANCA positive	4 (16.7%)
Follow-up endoscopy (follow-up period median 9 yr, 5-15 yr)	
Persistence of rectal sparing	2 (8.3%)
Appearance of proctitis	22 (91.7%)

UC: Ulcerative colitis; IBD: Inflammatory bowel disease; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; ANCA: Anti-neutrophil cytoplasmic antibodies; WBC: White blood cell.

Clinical courses and prognosis

During the follow-up period [median: 115 mo; range: (60-194) mo], in the UC with rectal sparing group, 11 of 24 patients (45.8%) were treated with systemic corticosteroid therapy; in the control group, 38 of 72 patients (52.8%) were treated with systemic corticosteroid. The median time to use corticosteroids were 91 mo in rectal sparing group and 87 mo in control group, respectively. The cumulative rates of ever use of corticosteroid in rectal sparing group and in the control were 35.3%, 46.0% and 53.8% *vs* 34.7%, 41.8% and 61.1% at 3, 5 and 10 years, respectively (log rank: $P = 0.77$) (Figure 3).

In the UC with rectal sparing group, 4 patients (16.7%) were treated with biologic agents; in the control group, 10 patients (13.9%) with biologic agent, which did not significantly differ (Table 2). In the UC with rectal sparing group, 4 patients (16.7%) received hospital treatment, and 2 patients (8.3%) underwent total colectomy at maximal follow-up; in the control group, 16 patients (22.2%) were hospitalised, and 2 patients were colectomised, which also did not significantly differ (Table 3).

DISCUSSION

Although "rectal involvement" and "continuous and symmetric fashion" are known well as typical colonoscopic findings of ulcerative colitis, rectal sparing or non-continuous distribution of mucosal inflammation can be found by colonoscopy in usual practice. For example, it is common in patients with UC who receive local therapy, such as suppository, enema, or foam type of mesalamine, or corticosteroid enema. However, unfortunately, if it is at the moment of initial diagnosis, it is a challenge to an endoscopist, although clinical or pathologic correlation is necessary for the definitive diagnosis of UC. In any event, is it possible to encounter rectal sparing in a newly diagnosed UC patient? If so, how often? Is the prognosis of this case different

Table 2 Summarized clinical history of ulcerative colitis patients who used biologics in both study and control group

No.	Age at diagnosis	Sex	Initial endoscopic finding	No. of systemic steroid use	Indication for biologics	History of biologics	Colectomy
1	21	F	RS	4	Steroid dependent	infliximab	-
2	30	F	RS	2	Steroid refractory	Infliximab (failed)	+
3	31	F	RS	9	Steroid dependent	golimumab	-
4	35	M	RS	2	Steroid refractory	Infliximab (failed)	+
5	15	F	RI	3	Steroid refractory	golimumab	
6	22	F	RI	1	Steroid refractory	Infliximab (failed)	+
7	20	F	RI	7	Steroid dependent	golimumab topacitinib	-
8	33	M	RI	4	Steroid refractory	infliximab	-
9	34	M	RI	2	Steroid refractory	Infliximab (failed)	+
10	35	M	RI	4	Steroid refractory	golimumab	-
11	39	M	RI	3	Steroid refractory	golimumab	-
12	41	F	RI	4	Steroid dependent	golimumab	-
13	44	M	RI	5	Steroid refractory	golimumab	-
14	48	M	RI	2	Steroid refractory	golimumab	-

RS: Rectal sparing; RI: Rectal involvement.

Table 3 Clinical prognosis of ulcerative colitis with rectal sparing versus without rectal sparing (control)

	Rectal sparing UC (*n* = 24)	Control (*n* = 72)	*P* value
Age	35.8 ± 11.0	36.6 ± 10.6	Matched
Sex (male:female)	19:5	57:15	Matched
Disease extent (E2/E3)	8/16	24/48	Matched
Follow-up period (mo)	103.4 ± 41.3	109.4 ± 41.6	0.5
Clinical outcomes			
Use of systemic corticosteroid			0.77
3-yr cumulative rate	35.3%	34.7%	
5-yr cumulative rate	46.0%	41.8%	
10-yr cumulative rate	53.8%	61.1%	
Use of biologics	4 (16.7%)	10 (13.9%)	0.74
Hospitalization	4 (16.7%)	16 (22.2%)	0.77
Colectomy	2 (8.3%)	2 (2.8%)	0.26

UC: Ulcerative colitis.

from a typical one?

To the best of our knowledge, our study is the only study that evaluated the clinical prognosis of adult UC patients who showed rectal sparing at the stage of initial diagnosis. In fact, the studies analysing the incidence of rectal sparing UC are very rare, because initial endoscopic data can be modified by prior treatment in tertiary or referred hospital, and differential diagnostic methods from infectious colitis, such as culture, serologic test, or PCR, have limitations in primary practice. In one Korean data, eight (3.3%) of the 240 patients had rectal sparing at initial colonoscopy[3]. They suggested that the atypically-distributed UC, including rectal sparing UC, seemed to be uncorrelated with poor prognosis, in terms of rates of remission, relapse, disease

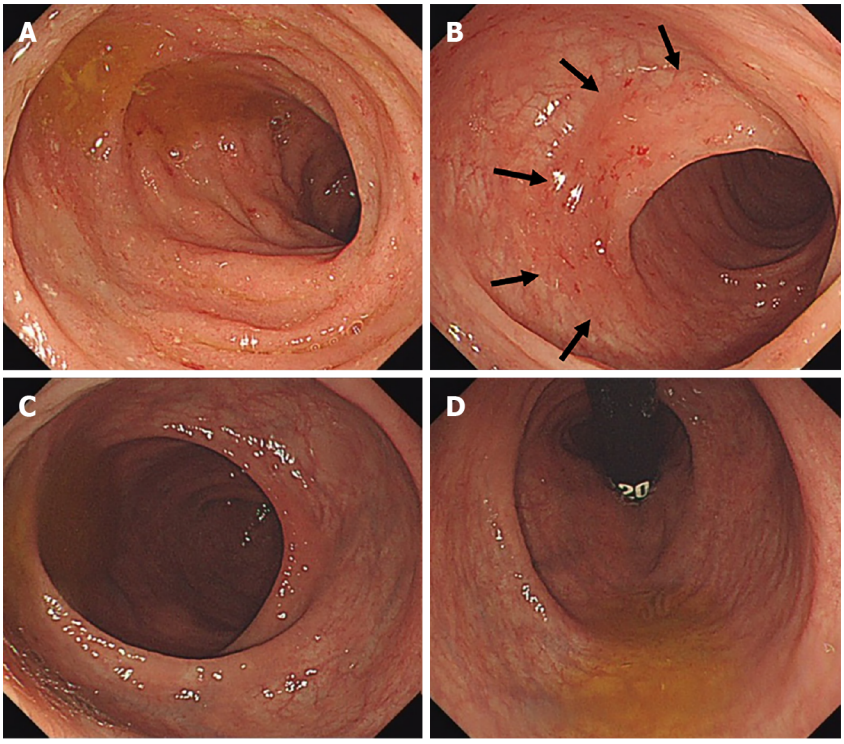

Figure 1 Colonoscopy at initial diagnosis. A: On descending and sigmoid colon, continuous and symmetric micro-erosive inflammation with friability was noted; B: At distal sigmoid colon, transitional zone was noted (arrow); C: On the rectum, normal transparent mucosa with visible vascularity was noted; D: At retroflexion view, there was no evidence of mucosal inflammation.

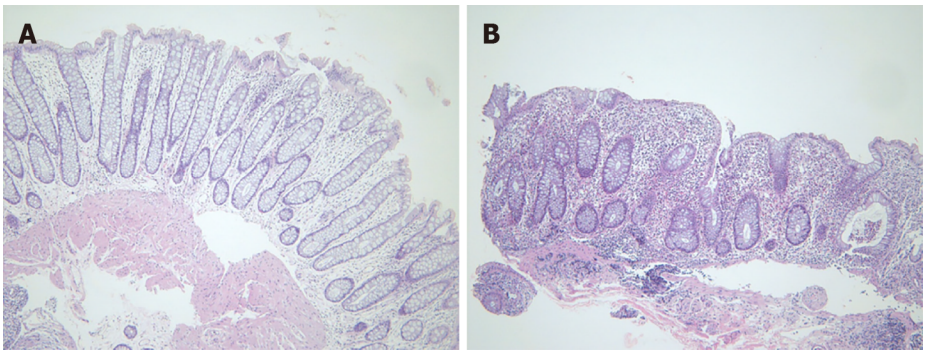

Figure 2 Hematoxylin and eosin stain. A: Rectum: No architectural distortion or neutrophilic inflammation; B: Sigmoid colon: Crypt abscess, crypt distortion, and lymphoplasmacytic infiltration in lamina propria (hematoxylin and eosin stain × 100).

extension, colectomy, and mortality. However, the prognosis of rectal sparing UC is still debatable, because in the previous study, the number of patients with rectal sparing was too small (n = 8), and follow-up data was insufficient, because of relatively short follow-up period [median 69 mo, range (2 to 238) mo].

In contrast to prior clinical studies suggesting the unfavourable prognosis of UC with rectal sparing, our result concluded that clinical course and prognosis were not different from those of typical UC patients. Oshitani *et al*[14] suggest that rectal sparing may be associated with intractability or a tendency to relapse; but that data included the patients with relapsing type of UC, which means that study demonstrated the clinical courses of moderate to severe UC patients with rectal sparing during or after medical treatment, and not the patients at the time of diagnosis. Horio *et al*[15] also reported that rectal sparing UC was an independent risk factor for surgery in the analysis of colectomy specimens of 46 surgically treated patients with UC. However, the subjects of that study were not selected by their initial colonoscopic finding, but selected by pathologic review after colectomy.

In contrast to adult UC, paediatric UC patients seem to have different clinical patterns. Rajwal *et al*[19] reported that rectal sparing was more frequent, and found in

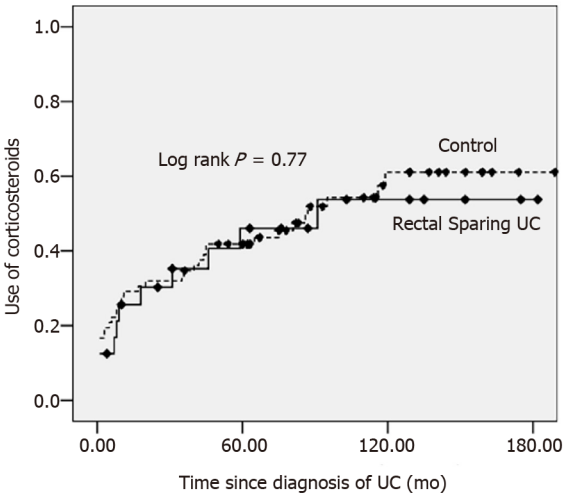

Figure 3 Cumulative rate of corticosteroids use in rectal sparing group (*n* = 24) *vs* control group (*n* = 72). UC: Ulcerative colitis.

23% of children with newly diagnosed and untreated UC; and that the presence of rectal sparing may be related to less responsiveness to conventional medical treatment. Glickman *et al*[11] reported that the endoscopic rectal sparing was found in 9% (6 of 73) and pathologic rectal sparing in 30% (absolute 3% *vs* relative 27%) of paediatric patients with newly diagnosed UC. Interestingly, according to their result, in the adult control group (*n* = 38), no patient showed endoscopic rectal sparing, but one patient revealed pathologic relative rectal sparing.

Already in the 1980s, one report demonstrated 12 cases of rectal sparing UC, in which double-contrast barium enema showed an apparently normal rectum but an abnormal colon; but in all cases, the author reported that rectal biopsy showed changes compatible with ulcerative colitis[20]. Although the study subjects were different from ours, because those cases included the patients after and during medical treatment, their study suggested that rectal sparing of UC had been challenging diagnostically. As early detection of ulcerative colitis is possible thanks to the easy availability of colonoscopy and advanced imaging techniques, we can hypothesise that atypical pattern of colonoscopic findings in a patient with ulcerative colitis can be observed more frequently. In fact, in our data, most of the UC patients with rectal sparing showed rectal lesion during the follow-up examination, which means that the atypical distribution of mucosal inflammation may be found temporarily at an early stage. In one of our cases (Figure 2), a biopsy obtained at rectal sparing area demonstrated normal pathologic finding, although it is not certain whether normal-looking mucosa by colonoscopy is really pathologically intact, because pathologic evaluation at skipped lesion was not performed in all cases.

We should think outside the box, and reconsider the stereotype of ulcerative colitis, such as rectal involvement with continuity, and symmetricity in colonoscopy. In the present study, a third of patients were initially diagnosed with infectious colitis, because the results of stool and pathologic examination were nonspecific, and so proper management was delayed. However, there was no case of diagnostic change to Crohn's disease in our data. In two of 24 cases, rectal sparing has persisted for more than 10 years; one 30-year-old male has mucosal inflammation on cecum and ascending colon, while a 46-year-old female showed mucosal inflammation on ascending, transverse, and descending colon in a homogenous, symmetric, and continuous fashion. In cases like this, definitive diagnosis of ulcerative colitis is still not easy. Both are being kept stable on mesalamine therapy during the follow-up period.

There are some limitations to this study. First, the definition of rectal sparing was ambiguous. For example, in this study, it is based only on endoscopical findings, and additional pathologic correlation was insufficient. However, at initial diagnosis, biopsies tend to be obtained only at grossly inflamed mucosa, because the extent of UC is generally classified according to endoscopic features, rather than histologic features. To define the rectal sparing more with more confidence, prospective designed study is needed. Second, the number of patients with rectal sparing UC was relatively small, so survival analysis in comparison with the control group was impossible. Long-term survival analysis is required to draw a more reliable conclusion. To minimise this

limitation inevitably caused by retrospective analysis, we included the patients who could be followed up for more than five years [medium follow-up period was 115 mo; range (60 to 194) mo], and matched each UC patient with rectal sparing with controls.

CONCLUSION

In conclusion, adult patients with UC can reveal atypical patterns of disease distribution, such as rectal sparing; and the incidence at initial diagnosis was rare, but existed in 3.9%. The clinical course and prognosis that we can assume through the need for advanced treatment, hospitalisation, and colectomy did not differ from that of typical UC patients. We trust that this information can be useful in making an accurate diagnosis, and understanding the various disease phenotypes of UC.

ARTICLE HIGHLIGHTS

Research background

In practice, atypical pattern of ulcerative colitis (UC) such as rectal sparing UC is a challenge to endoscopist in timely diagnosis of UC, therefore we retrospectively reviewed the data of our clinic to study the clinical feature of these atypical pattern of UC, and their prognosis as well.

Research motivation

As early diagnosis and progression of diagnostic tools such as endoscopic, imaging techniques become possible, the detection of atypical pattern of inflammatory bowel disease seems to be possible. If we clarify the clinical characteristics, it will be helpful to understand the pathophysiology of inflammatory bowel disease.

Research objectives

The main object of this study is to predict the clinical course of these atypical pattern of UC. There are very rare report concerning this subject. A few reports demonstrated the poorer prognosis, but our experiences were out of accord.

Research methods

As atypical pattern of UC is very rare and difficult to define in the early stage of UC, prospectively-designed study seems to be impossible, therefore, we (three different inflammatory bowel disease experts) inevitably analyzed the chart, pathologic report and mainly endoscopic images, and reached agreement.

Research results

Some reports suggested that the atypical pattern of UC may have a poor clinical outcome such as higher rate of colectomy, but we demonstrated the different results because the patient selection was not similar to the previous studies. Advanced treatment, hopitalization and colectomy rates did not different between rectal sparing UC and typical UC patients.

Research conclusions

According to a few previous reports, the prognosis of UC showing atypical pattern is debatable. Our data propose that various form of UC phenotype can be possible and their prognosis seems to be similar to the typical one. Further study is needed to predict the prognosis of UC.

Research perspectives

In the future, further prospective studies to clarify the pathophysicology as well as prognosis of other various atypical patterns of UC is warranted.

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ORIGINAL ARTICLE

Observational Study

COVID-19 in the endoscopy unit: How likely is transmission of infection? Results from an international, multicenter study

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Abstract

BACKGROUND

Coronavirus disease 2019 (COVID-19) significantly affected endoscopy practice, as gastrointestinal endoscopy is considered a risky procedure for transmission of infection to patients and personnel of endoscopy units (PEU).

AIM

To assess the impact of COVID-19 on endoscopy during the first European lockdown (March-May 2020).

METHODS

Patients undergoing endoscopy in nine endoscopy units across six European countries during the period of the first European lockdown for COVID-19 (March-May 2020) were included. Prior to the endoscopy procedure, participants were stratified as low- or high- risk for potential COVID-19 infection according to the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) joint statement, and contacted 7-14 d later to assess COVID-19 infection status. PEU were questioned regarding COVID-19 symptoms and/or infection *via* questionnaire, while information regarding hospitalizations, intensive care unit-admissions and COVID-19-related deaths were collected. The number of weekly endoscopies at each center during the lockdown period was also recorded.

RESULTS

A total of 1267 endoscopies were performed in 1222 individuals across nine European endoscopy departments in six countries. Eighty-seven (7%) were excluded because of initial positive testing. Of the 1135 pre-endoscopy low risk or polymerase chain reaction negative for COVID-19, 254 (22.4%) were tested post endoscopy and 8 were eventually found positive, resulting in an infection rate of 0.7% [(95%CI: 0.2-0.12]. The majority (6 of the 8 patients, 75%) had undergone esophagogastroduodenoscopy. Of the 163 PEU, 5 [3%; (95%CI: 0.4-5.7)] tested positive during the study period. A decrease of 68.7% (95%CI: 64.8-72.7) in the number of weekly endoscopies was recorded in all centers after March 2020. All centers implemented appropriate personal protective measures (PPM) from the initial phases of the lockdown.

CONCLUSION

COVID-19 transmission in endoscopy units is highly unlikely in a lockdown setting, provided endoscopies are restricted to emergency cases and PPM are implemented.

Key Words: COVID-19; SARS-CoV-2; Gastrointestinal endoscopy; Personal protection measures; Transmission; Lockdown

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Core Tip: The Coronavirus disease 2019 (COVID-19) pandemic outbreak caused an unprecedented disruption in everyday endoscopy practice worldwide, with recent guidelines advocating suspension of nonemergency endoscopies, implementation of strict personal protection measures (PPM) and post-endoscopy evaluation of patient COVID-19 status. This was an international multicenter study seeking to evaluate the impact of COVID-19 on endoscopy during the first European lockdown (March-May 2020). COVID-19 transmission across endoscopic units proved to be highly unlikely in lockdown circumstances as long as endoscopy performance was restricted to emergency cases and sufficient PPM are available.

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic has spread throughout the world in a short period of time, rapidly affecting medical practice. Although the disease usually manifests with respiratory symptoms, gastrointestinal (GI) symptoms are not rare and, in some cases, constitute the basic clinical manifestations[1,2]. GI endoscopy is considered a risky procedure for transmission of the infection. During endoscopy, close contact of the endoscopist with the patient takes place, respiratory droplets and aerosols are generated, and contact with contaminated material, body fluids, and feces is likely to occur. Moreover, endoscopy also involves the assisting personnel of the unit (PEU). The PEU include not only the endoscopist, but also nurses and paramedical staff. In light of these considerations, specific protective measures and disinfection procedures have been recommended by scientific societies and recognized experts[3-5]. Endoscopic societies such as the European Society of Gastrointestinal Endoscopy (ESGE) and the European Society of Gastroenterology and Endoscopy Nurses and Associates (ESGENA) recently published a joint position statement for GI endoscopy during the COVID-19 pandemic regarding safe endoscopies for patients and PEU[3]. The statement suggests minimizing nonemergency endoscopies, implementation of personal protection measures (PPM), and post-endoscopy calls to patients 7 d and 14 d after the endoscopy to check their COVID-19 status. In a study from the heavily affected north of Italy, the number of post-endoscopy COVID-19 infections was negligible and the number of infected PEU was very small[6]. The aim of this European multicenter study was to evaluate the impact of endoscopic procedures on the risk of transmission for patients and PEU using the telephone as contact tool as suggested by ESGE and ESGENA.

MATERIALS AND METHODS

Study design

This was an international, multicenter study conducted during the period of the first European lockdown for COVID-19 (March-May 2020) in nine high-volume endoscopy departments across six European countries: Athens, Greece (two centers), Foggia/Verona, Italy (two centers), Brussels, Belgium, Skopje, Republic of North Macedonia, Zagreb/Rijeka, Croatia (two centers), and Belgrade, Serbia. The centers were included based on their high volume of endoscopic procedures prior to the COVID-19 outbreak and because they represented regions with a high prevalence of the disease on one side of the spectrum (Verona and Brussels) as well as regions with a lower prevalence of COVID-19 in southern Europe. This was an analysis of retrospectively collected data within a prospectively built database.

Inclusion criteria

All consecutive patients undergoing any endoscopic procedure, including upper and lower GI endoscopy (colonoscopy or rectosigmoidoscopy), endoscopic retrograde cholangiopancreatography (ERCP), or endoscopic ultrasonography (EUS) during the aforementioned period and involving each of the abovementioned PEU were considered eligible for inclusion.

Study population

Patients undergoing endoscopy: Following the triage protocol at each center, on the day of the endoscopy or the day before, all patients were questioned by the predetermined local study coordinator for symptoms and contacts that could be linked to COVID-19 and then stratified as low- or high-risk of potential COVID-19 infection, according to the ESGE/ESGENA joint statement[3]. Demographic data and procedural information regarding the endoscopy performed as well as previous performance of

testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) were also recorded. Following the ESGE/ESGENA joint statement recommendation regarding post-procedure risk management[3], local study coordinators contacted the patients by telephone on day 7 and day 14 after the endoscopy to inquire about any new COVID-19 diagnosis, or development of COVID-19 symptoms. The calls were carried out using a structured questionnaire that was identical across all centers (Supplementary Table 1) and filled out for each patient. Polymerase chain reaction (PCR) testing *a posteriori* was possible at physician's discretion after the endoscopic procedure on a case-by-case basis, taking into account each patient's clinical status. For those who tested positive after the endoscopic procedure, additional information regarding need for hospitalization, intensive care unit (ICU) admission for COVID-19 and COVID-19-related deaths were also collected.

PEU: The PEU were questioned regarding potential COVID-19 symptoms and/or SARS-CoV-2 infection with the use of a structured questionnaire (Supplementary Table 2). PEU included not only medical and nursing staff, but also assisting staff working in the unit who could contact patients or material potentially infected by SARS-CoV-2, *i.e.* cleaning personnel, transporters, and secretarial staff. For those positive for SARS-CoV-2, information regarding hospitalization, ICU admission and COVID-19-related deaths were collected. Additionally, the final part of the questionnaire recorded the total number of endoscopies conducted pre-, during and post-implementation of COVID-19-transmission preventative measures.

Study endpoints

The primary endpoint of the study was the incidence of infection among patients who underwent endoscopy during the established time period. Secondary endpoints were: (1) Incidence and outcome of hospitalization, ICU admission for COVID-19, and COVID-19-related deaths among patients who tested positive; (2) Prevalence of COVID-19 symptoms and/or positive SARS-CoV-2 testing among PEU; (3) Incidence and outcome of hospitalization, ICU admission for COVID-19, and COVID-19-related deaths among PEU who tested positive; and (4) Percentage decrease in the overall number of endoscopies before and after implementation of lockdown measures and implementation of PPM in the study centers. For the purposes of this study, only PCR testing was deemed adequately accurate for confirmation of infection. Rapid tests, when performed, needed to be confirmed by PCR.

Statistical analysis

Categorical data were reported as numbers and percentages (%) with their 95%CIs. The distribution of quantitative data was evaluated for normality by the Kolmogorov–Smirnov statistic and reported as means ± SD or means and interquartile range (IQR) depending to their distribution. A P value < 0.05 was considered significant. A statistical review of the study was performed by a biomedical statistician (IP).

Ethical approval

The protocol of this study was reviewed and approved by the local institutional review board (ΒΠΠΚ ΕΒΔ 320/10-6-20). The study was conducted in accordance with the ethical principles of the Declaration of Helsinki and in compliance with good clinical practice.

RESULTS

Overall, 1267 endoscopies were performed in 1222 patients during the study time period. Of those, 87 (7%) were excluded because of initial positive testing. The remaining 1135 patients were enrolled in the study (Figure 1). Baseline patient baseline characteristics and recruitment at center are presented in Table 1.

Primary endpoint

Among the 1135 enrolled patients, 254 (22.4%) were retested the days following endoscopy because of the onset of new symptoms that could indicate a potential COVID-19 infection. Eight (n = 8) were eventually found positive. The incidence of infection among patients undergoing endoscopy was thus 0.7% (95%CI: 0.2-0.12). Of those eight patients, the majority had undergone upper GI endoscopy (n = 6/8, 75%). A negative pre-endoscopy PCR test was available in only 1 case. A detailed overview

Table 1 Baseline characteristics of patients

Patients characteristics	
Male/female	678 (59.7)/457 (40.3)
Age (mean ± SD), yr	63.4 ± 14.5
Inpatient	506 (44.6)
Outpatient	598 (52.7)
Referral	31 (2.7)
Recruitment per center	
"Attikon" Hospital, Athens, Greece	236 (20.8)
Aretaieio Hospital, Athens, Greece	42 (3.7)
Foggia, Italy	215 (18.9)
Verona, Italy	235 (20.7)
Belgrade, Serbia	19 (1.7)
Brussels, Belgium	143 (12.6)
Skopje, Republic of North Macedonia	149 (13.1)
Zagreb/Rijeka, Croatia	96 (8.5)
Type of endoscopy[1]	
Upper GI-endoscopies	587 (46.3)
Colonoscopies/rectosigmoidoscopies	444 (35.1)
ERCP	178 (14.1)
EUS	57 (4.5)

Data are n (%) unless noted otherwise.
[1]A total of 1266 endoscopies. ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasonography; GI: Gastrointestinal; SD: Standard deviation.

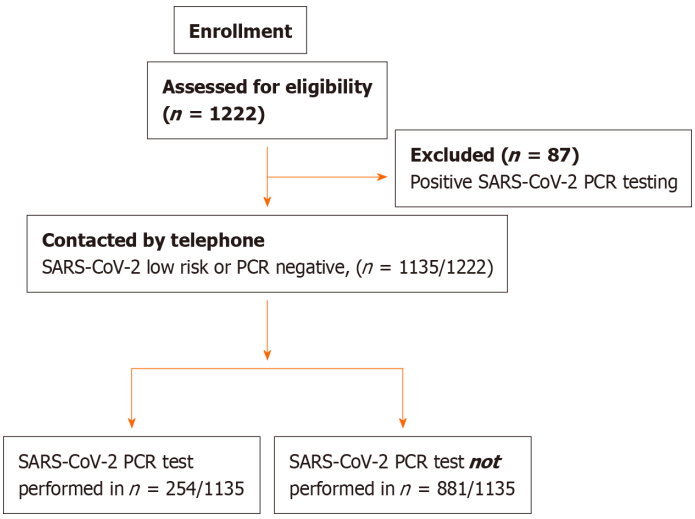

Figure 1 Study flowchart. PCR: Polymerase chain reaction; SARS-CoV2: Severe acute respiratory syndrome coronavirus 2.

of the infected characteristics of the patients is presented in Table 2.

Secondary endpoints

Of the 8 SARS-CoV-2-positive cases, 2 (25%) presented with a very mild illness and did not require hospitalization at all; the other 6 (75%) were hospitalized at some point, with 2 of them (33.3%) ultimately dying of COVID-19. Another 2 patients

Table 2 Baseline characteristics and outcomes of patients positive for severe acute respiratory syndrome coronavirus 2 after endoscopy

Case	Patient, age	Endoscopy	Date of endoscopy	COVID PCR test before endoscopy	Contact of suspected or confirmed COVID 19 case after endoscopy	Symptoms	COVID PCR test after endoscopy	Outcome of those hospitalized	Case related to endoscopy
1	Female, 66 yr	Upper GI	March 12, 2020	No	No	Fever and cough	Tested positive March 18, 2020	Death/deceased due to COVID-19	Cannot reasonably exclude
2	Male, 81 yr	Upper GI	April 8, 2020	No	No	Fever, cough and sore throat since April 17 for 42 d	Hospital admission April 12, 2020, tested positive and had Pneumonia	Death May 4/deceased due to COVID-19	Cannot reasonably exclude
3	Male, 66 yr, head/neck cancer and arterial disease	Upper GI	March 18, 2020	No	Yes with suspected case	Fever and Diarrhea since March 27, 2020	Tested positive March 28, 2020	Death May 7 due to cancer	Cannot reasonably exclude
4	Male, 55 yr, cancer esophagus	Upper GI	March 18, 2020	No	Yes with suspected case	Cough since March 16, 2020	Tested positive March 24, 2020	Discharge	No
5	Male, 76 yr, cancer stomach, 2, COPD	EUS	March 24, 2020	No	Yes with suspected case	Cough since March 19, 2020	Tested positive Apirl 23, 2020	Became negative/remained at nursing home	No
6	Female, 66 yr, AML	Lower GI	Apirl 1, 2020	Yes March 30, 2020negative	Yes with suspected case	Fever since April 3, 2020 for 6 d	Tested positive Apirl 10, 2020	Death May 4 due to cancer/at home	Cannot reasonably exclude
7	Male, 48 yr	Upper GI	March 27, 2020	No	No	Fever and cough since April 8, 2020 for 4 d	Tested positive Apirl 12, 2020	Not hospitalized	No
8	Male, 63 yr, diabetes, lung disease, IBD	Upper GI	March 30, 2020	No	Yes with suspected case	Fever and cough since April 22, 2020 for 2 d	Tested positive Apirl 22, 2020	Not hospitalized	No

AML: Acute myeloid leukemia; Chronic obstructive pulmonary disease; COPD; EUS: Endoscopic ultrasonography; GI: Gastrointestinal; IBD: Inflammatory bowel disease; PCR: Polymerase chain reaction.

(33.3%) died, but the cause of death was considered to be their underlying cancer. The remaining 2 (33.3%) were discharged to home and to a nursing residency.

Overall, the data included the COVID-19 infection status of 163 PEU from all 9 PEU. Eighty-four of the 163 (51.5%) were physicians (attendings as well as trainees), 62/163 (38%) were nurses and 17/163 (10.4%) were assisting staff working exclusively (or mostly) in the PEU (*i.e.* cleaning personnel, transporters, and secretarial staff of the units). Overall, 5/163 of the total PEU tested positive during the study period (2 physicians and 3 nurses), giving a 3% (95%CI: 0.4-5.7) incidence of infection. The majority of the infections (n = 4, 80%) were considered to be associated with the work environment. Those cases represent 2.3% (4/163) of the total PEU in our study and 7% and 16.6% of the PEU of their own units, respectively. None (0/5) of the infected PEU developed severe disease, none required hospitalization, and no COVID-19-related deaths occurred in the PEU who were included in our study.

PPM in accord with the ESGE/ESGENA position statement regarding reduction of cases to focus on emergency therapies, *i.e.* gowns, goggles, and masks, were implemented and adhered to in all participating centers during the initial phase of the study, which continued from 9 to 23 March, 2020. Overall, a significant reduction in the number of endoscopies was evident in all the participating centers after March 2020 (Figure 2). In detail, 1 wk before implementation of the ESGE/ESGENA position statement suggestions, the total number of endoscopies across all centers was 534 (246

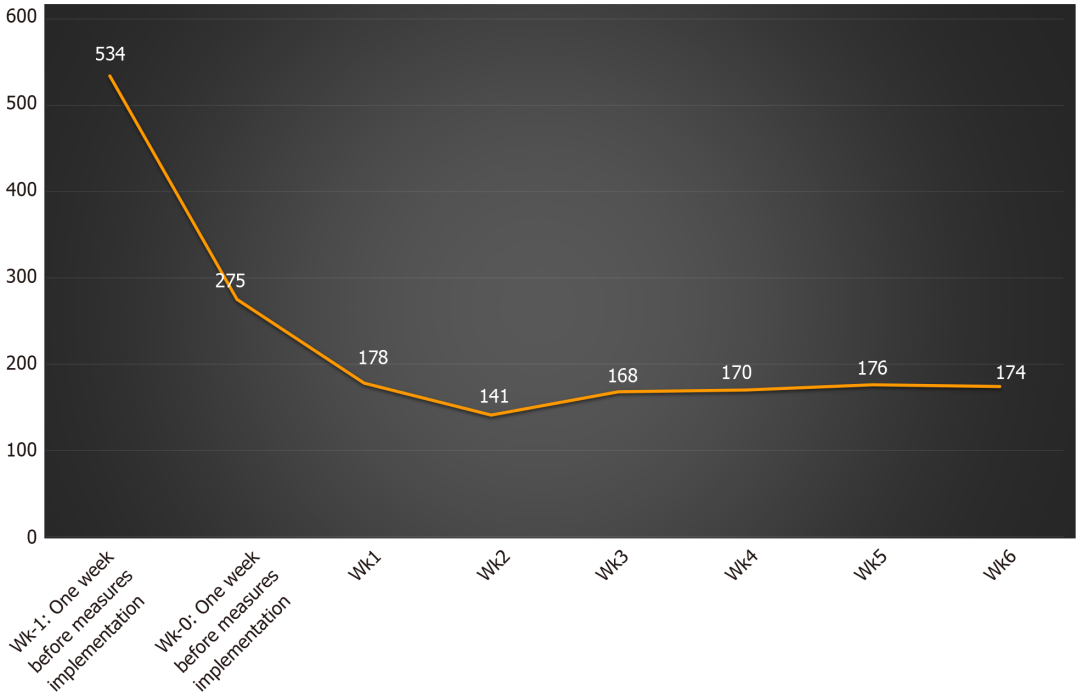

Figure 2 Overall endoscopies 1 wk before and in the weeks during lockdown.

upper GI-endoscopies, 209 colonoscopies/rectosigmoidoscopies, 56 ERCPs and 23 EUS). During the following 6 wk, the number gradually dropped, reaching a plateau with a mean of 167 ± 14 endoscopies per week, an estimated 68.7% (95%CI: 64.8-72.7) decrease in the performance of endoscopic procedures.

DISCUSSION

Endoscopic procedures were deemed as risky procedures for bidirectional COVID-19 infection transmission[1,2,7,8]. In this analysis of retrospectively collected data within a prospectively built database conducted across nine European endoscopic facilities, we showed that the risk of COVID-19 infection for patients undergoing GI endoscopy was extremely low in a lockdown setting. The results underline the value of following ESGE/ESGENA recommendations to address the danger of COVID-19 infection in everyday, real-world clinical practice.

Although COVID-19 infection and its potential implications have been at the focal point of ongoing research worldwide, evidence regarding this risk of healthcare professional and patient infection after endoscopy remain scarce[9]. In one of the few studies, Repici *et al*[6] retrospectively analyzed data from 802 patients and 968 PEU in 41 hospitals in northern Italy. Their results suggested that the number of post-endoscopy patient infections was negligible, *i.e.* 1 infection in 802 patients for a confirmed infection rate of 0.12%. Similarly in a much smaller multicenter, retrospective study that evaluated patients who underwent stent placement for upper GI obstruction[10]; only 1 of 29 patients (3.4%) tested positive for SARS-CoV-2 after the procedure. All the medical staff involved in the stenting procedures remained COVID-19 free 14 d later. The results of our multicenter study are also in line with those, as only 8 of the 1135 patients who were deemed pre-endoscopy SARS-CoV-2 low risk or negative, became positive. The results are further corroborated by the findings of a recent cross-sectional study. In a high-volume Japanese endoscopic facility, not a single positive result was detected among 783 PCR-analyzed saliva samples from patients undergoing endoscopic procedures[11].

Regarding PEU infection after endoscopy, our study is consistent with that of Repici *et al*[6], who found a very low risk of PEU contamination. Indeed, the Italian study reported a very small number of infected PEU (42 cases, or only 4.3% of the PEU population in their study), with 85.7% of the infections occurring before PPM were introduced. Even for the PEU who were infected, fewer than 1% needed hospitalization and none required admission in ICU or died[6]. Outside Europe, the risk of

COVID-19 infection of PEU may be higher, up to 23.9%, especially in endoscopy technicians[12]. Our study had even more impressive results, with only 5 PEU testing positive during the study period, representing a 3% of the total PEU involved in the endoscopies that were performed in the study. In only 4 of the total PEU, 1 physician and 3 nurses, was the infection considered to be linked to their work. As in the Italian study, none of the infected PEU in our study developed severe disease, required hospitalization, or died, compared with 2 COVID-19-related deaths that occurred in the 8 patients who became positive post endoscopy. Whether that was merely a random association or a result of the younger age and better health status of the PEU compared with that of our patient population, who were severely ill individuals undergoing emergency endoscopies, remains unclear. Published data suggest that PEU, when affected, experience relatively mild disease, but as the numbers were extremely small, we cannot provide further insights[5,6]. Notably, a case-by-case analysis revealed a clustering of infections, as all PEU found positive worked in a unit performing almost exclusively ERCPs. A possible explanation could be based on the longer duration of those particular examinations compared with standard upper GI-endoscopies, resulting in increased risk for transmission.

Pre-endoscopic testing for COVID-19 was available only for one-fourth of the patients of our study (326/1222, 26.7%). One might consider that to be a low percentage; however, it should be noted that this policy is in accordance with the ESGE/ESGENA recommendations that do not advocate SARS-CoV-2 tests as a prerequisite for GI endoscopy. On the contrary, they put a spotlight on appropriate triaging of nonemergency endoscopies and PPM. Our low post-endoscopy infection rates of both patients and PEU seem to justify those suggestions.

The finding that the COVID-19 pandemic led to a significant reduction in the volume of endoscopic procedures is not novel. Beyond patient stratification as low- or high-risk of COVID-19 infection, the position ESGE/ESGENA statement for GI endoscopy during the COVID-19 pandemic also clearly lists which endoscopic procedures should be definitely performed and which can be postponed. That policy was uniformly applied at all the participating centers of our study. Thus, all the endoscopies performed in our series, if not emergency, were nevertheless completely necessary; none were purely elective. Still, the optimal policy, when resumption of endoscopy services comes into question, remains to be elucidated. In that regard, a stepwise approach that takes: (1) The regional prevalence of COVID-19 with stricter guidelines in endoscopy and use of PPE in high-prevalence (> 2%) areas[13]; (2) Patient stratification for procedures that should be performed immediately or postponed, as well as low- or high-risk of infection[3]; and (3) Modifications in PEU working schedules to prevent hospital-based transmission into account seems the most appropriate[14,15].

A number of study strengths should be cited. First, this iteration is one of the few studies addressing the question of the safety of endoscopy during the COVID-19 pandemic. Second, we enrolled patients in different countries, giving a more representative overview of the impact of COVID-19 outbreak on endoscopy units. Third, our questionnaire content was guided by the ESGE/ESGENA position statement. Finally, our population was homogenous, including patients who underwent endoscopic procedures involving both the upper and lower GI tract as well as the respective participating PEU.

On the other hand, there are also limitations that merit attention. The lack of SARS-CoV-2 testing of patients presenting for endoscopy without COVID-19 symptoms and heterogeneity of PEU testing can initially be seen as such; but that practice was in accord with endoscopy society recommendations including those of the ESGE/ESGENA). The practice should therefore be considered unavoidable, but it undoubtedly had an impact on our epidemiological data, as the percentage of asymptomatic patients in our group remains unknown and hinders the complete tracking of the infection. Another shortcoming is the possibility of recall bias, given that the study data was acquired by asking patients to recall their symptoms. Again, that was unavoidable, as it complied with the ESGE/ESGENA directive stating that patients should be contacted 7 d and 14 d post endoscopy. Finally, the small number of positive cases and study design prevent a definitive causal relationship to be established. However, aim of the study was not to address issues related to potential routes of infection, but rather to investigate the actual possibility of COVID-19 transmission in endoscopy units when established guidelines are implemented.

CONCLUSION

In conclusion, COVID-19 transmission in endoscopy units is a highly unlikely event for both patients and PEU in a lockdown setting, provided endoscopies are effectively restricted to emergency cases and appropriate, stringent PPM are implemented. In the extremely rare cases of PEU infection in our series, the disease was relatively mild, with no hospitalizations or COVID-19-related deaths.

ARTICLE HIGHLIGHTS

Research background

The coronavirus disease 2019 (COVID-19) outbreak significantly affected endoscopic practice, as gastrointestinal endoscopy is considered as a risky procedure for transmission of infection. The ESGE and ESGENA published a position statement for endoscopy during the COVID-19 pandemic regarding the safety of endoscopies for patients and the personnel of endoscopy units (PEU). However, the incidence and outcome of infection among patients undergoing endoscopy and PEU remains to be determined.

Research motivation

Currently, there is insufficient data regarding the incidence and outcomes of COVID-19 infection among patients undergoing endoscopy and in PEU.

Research objectives

We aimed to evaluate the impact of endoscopic procedures on the risk of transmission to patients and PEU in a European multicenter study, using telephone contact as a tool as suggested by the ESGE and ESGENA.

Research methods

Patients undergoing endoscopy in nine endoscopy departments across six European countries during the period of the first European lockdown for COVID-19 (March-May 2020) were included. Participants were stratified as low- or high-risk for potential COVID-19 infection according to the ESGE/ESGENA joint statement were contacted 7 d and 14 d later to assess COVID-19 infection status. PEU were questioned regarding COVID-19 symptoms and/or infection by questionnaire. Information on hospitalizations, ICU-admissions, and COVID-19-related deaths were collected. The number of weekly endoscopies during the lockdown period was also recorded.

Research results

A total of 1267 endoscopies were performed in 1222 individuals; 87 (7%) were excluded following initial positive PCR testing. The remaining 1135 individuals were at low risk or PCR negative for COVID-19 before endoscopy, and of 254 (22.4%) who were tested post endoscopy, eight were eventually found positive, resulting in an infection rate of 0.7% (95%CI: 0.2-0.12). The majority, (6/8, 75%) had undergone esophagogastroduodenoscopy. Data were available for 163 PEU, and 5 (3%; 95%CI: 0.4-5.7) tested positive during the study period. In 4 of the 5, or 2% of the total, the infection was deemed relevant to their work environment. A decrease of 68.7% (95%CI: 64.8-72.7) in the number of endoscopies was recorded.

Research conclusions

This study showed that COVID-19 transmission in endoscopic units was highly unlikely during a lockdown setting, provided endoscopies were restricted to emergency cases and PPM were implemented.

Research perspectives

More robust data are definitely warranted to identify various clinical factors that contribute to an increased risk of endoscopy-related COVID-19 infection.

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ORIGINAL ARTICLE

Observational Study

Enlarged folds on endoscopic gastritis as a predictor for submucosal invasion of gastric cancers

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Author contributions: Toyoshima O designed the study, recruited patients, analyzed the data, and wrote the manuscript; Nishizawa T designed the study, recruited patients, edited, and revised the manuscript; Yoshida S recruited patients and revised the manuscript; Toyoshima A, Matsuno T, Yamada T, Matsuo T, Nakagawa H, and Koike K revised the manuscript; Sakitani K reviewed endoscopic images and revised the manuscript.

Institutional review board statement: This retrospective study was approved by Certificated Review Board, Hattori Clinic on September 4, 2020 (approval No. S2009-U04).

Informed consent statement: Patients were not required to give

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Abstract

BACKGROUND

Accurate diagnosis of the depth of gastric cancer invasion is crucial in clinical practice. The diagnosis of gastric cancer depth is often made using endoscopic characteristics of the tumor and its margins; however, evaluating invasion depth based on endoscopic background gastritis remains unclear.

AIM

To investigate predicting submucosal invasion using the endoscopy-based Kyoto classification of gastritis.

METHODS

Patients with gastric cancer detected on esophagogastroduodenoscopy at

Toyoshima Endoscopy Clinic were enrolled. We analyzed the effects of patient and tumor characteristics, including age, sex, body mass index, surveillance endoscopy within 2 years, current *Helicobacter pylori* infection, the Kyoto classification, and Lauren's tumor type, on submucosal tumor invasion and curative endoscopic resection. The Kyoto classification included atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. Atrophy was characterized by non-reddish and low mucosa. Intestinal metaplasia was detected as patchy whitish or grayish-white flat elevations, forming an irregular uneven surface. An enlarged fold referred to a fold width ≥ 5 mm in the greater curvature of the corpus. Nodularity was characterized by goosebump-like multiple nodules in the antrum. Diffuse redness was characterized by uniform reddish non-atrophic mucosa in the greater curvature of the corpus.

RESULTS

A total of 266 gastric cancer patients (mean age, 66.7 years; male sex, 58.6%; mean body mass index, 22.8 kg/m^2) were enrolled. Ninety-three patients underwent esophagogastroduodenoscopy for surveillance within 2 years, and 140 had current *Helicobacter pylori* infection. The mean Kyoto score was 4.54. Fifty-eight cancers were diffuse-type, and 87 cancers had invaded the submucosa. Multivariate analysis revealed that low body mass index (odds ratio 0.88, P = 0.02), no surveillance esophagogastroduodenoscopy within 2 years (odds ratio 0.15, P < 0.001), endoscopic enlarged folds of gastritis (odds ratio 3.39, P = 0.001), and Lauren's diffuse-type (odds ratio 5.09, P < 0.001) were independently associated with submucosal invasion. Similar results were obtained with curative endoscopic resection. Among cancer patients with enlarged folds, severely enlarged folds (width ≥ 10 mm) were more related to submucosal invasion than mildly enlarged folds (width 5-9 mm, P < 0.001).

CONCLUSION

Enlarged folds of gastritis were associated with submucosal invasion. Endoscopic observation of background gastritis as well as the lesion itself may help diagnose the depth of cancer invasion.

Key Words: Gastric cancer; Gastritis; Enlarged fold; Endoscopy; Kyoto classification

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Core Tip: We investigated predicting submucosal invasion using the endoscopy-based Kyoto classification of gastritis. We analyzed the effects of patient and tumor characteristics, including the Kyoto classification, on submucosal tumor invasion. Two hundred sixty-six gastric cancer patients were enrolled. Multivariate analysis revealed that low body mass index, no surveillance esophagogastroduodenoscopy within 2 years, endoscopic enlarged folds of gastritis, and Lauren's diffuse-type were independently associated with submucosal invasion. Among cancer patients with enlarged folds, severely enlarged folds (width ≥ 10 mm) were more related to submucosal invasion than mildly enlarged folds (width 5-9 mm). Enlarged folds of gastritis were associated with submucosal invasion.

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informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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INTRODUCTION

Gastric cancer is the third most common cause of cancer mortality worldwide, making

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it an important disease[1,2]. The depth of gastric cancer invasion is associated with lymph node metastasis[3,4], recurrence[5], and survival[6,7] and has a great influence on therapeutic strategy[8-10]. This means that the diagnosis of invasion depth is crucial.

At present, the diagnosis of gastric cancer depth is often made using the endoscopic characteristics of the tumor and its margins. For example, an irregular surface, marked marginal elevation, and clubbing/abrupt cutting/fusion of converting folds are useful for the diagnosis of submucosal invasion[11]. Similarly, using nodular mucosal changes, deep depression, and fold convergence for the diagnosis of signet ring cell carcinoma with submucosal invasion[12], and the non-extension sign[13], size > 30 mm, margin elevation, uneven surface[14], remarkable redness[14,15], and abrupt cutting converging folds[15] for the diagnosis of deeper submucosal invasion (SM2: ≥ 500 μm in depth) have also been reported. For the last decade, the depth of gastric cancer has been predicted using magnifying narrow-band imaging, which is an image-enhanced endoscopy, in addition to conventional white-light imaging[16]. Findings such as non-structure, scattering, or multi-caliber vessels[17], D-vessels[18], and the vessel plus surface classification[19] were found to be useful for depth diagnosis. Furthermore, various modalities, including endoscopic ultrasonography[20] and computed tomography[21], have been found to assist in depth diagnosis. Thus, research on the depth of invasion is being vigorously conducted.

On the other hand, artificial intelligence is now overwhelming human intelligence. Artificial intelligence defeated the world champion in chess in 1997 and in the East Asian game of go in 2017. The style of play used by artificial intelligence was of a different dimension unimaginable to humans. Recently, artificial intelligence has been used for endoscopic diagnosis[22]. In the future, artificial intelligence may be used to diagnose the depth of invasion based not only on the tumor itself but also on background gastritis. However, there are few reports on the evaluation of invasion depth based on endoscopic background gastritis. Therefore, we decided to investigate predictions for submucosal invasion using the endoscopy-based Kyoto classification of gastritis, for which evidence has been accumulated recently[23-25].

MATERIALS AND METHODS

Patients and overview

This study involved those patients who underwent esophagogastroduodenoscopy (EGD) between January 2008 and August 2020 at Toyoshima Endoscopy Clinic, in whom gastric cancers were detected. Exclusion criteria were cancer located in the esophagogastric junction or in the residual stomach after surgery, or unavailable EGD images. We also excluded patients with unavailable *Helicobacter pylori* (*H. pylori*) status. In this study, curative endoscopic resection of gastric cancer was performed according to the guidelines of the Japanese Gastric Cancer Association[26].

This retrospective study was approved by the Certificated Review Board, Hattori Clinic on September 4, 2020 (approval No. S2009-U04). Written informed consent was obtained from all participants. All clinical evaluations were conducted in accordance with the ethical guidelines of the Declaration of Helsinki. This study had no financial support.

Endoscopy

The Japan Gastroenterological Endoscopy Society advocated the endoscopy-based Kyoto classification of gastritis in 2013 with the aim of matching endoscopic findings and pathology. The Kyoto classification of gastritis comprises atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness. Endoscopic atrophy is characterized by non-reddish and low mucosa, identified by an atrophic border, according to the Kimura-Takemoto classification[27]. Endoscopic intestinal metaplasia is detected as patchy whitish or grayish-white flat elevations, forming an irregular uneven surface[28]. An enlarged fold refers to a fold with width ≥ 5 mm in the greater curvature of the corpus, which is not flattened or only partially flattened by stomach insufflation. Endoscopic nodularity is characterized by goosebump-like multiple nodules that appear mainly in the antrum and represent a collection of lymphoid follicles. Diffuse redness is characterized by uniform reddish non-atrophic mucosa located mainly in the greater curvature of the corpus and representing superficial gastritis.

The Kyoto score is the sum of the following five parameters: atrophy, intestinal metaplasia, enlarged folds, nodularity, and diffuse redness score and ranges from 0 to 8. Kimura-Takemoto classification gradings of C0 and CI are defined as an atrophy score of 0, CII and CIII have an atrophy score of 1, and OI to OIII have an atrophy score of 2. Absence of intestinal metaplasia was defined as an intestinal metaplasia score of 0, intestinal metaplasia limited to the antrum was given 1, and intestinal metaplasia extending into the corpus received an intestinal metaplasia score of 2. The absence and presence of enlarged folds were defined as enlarged fold scores of 0 and 1, respectively. The absence and presence of nodularity were defined as nodularity scores of 0 and 1, respectively. Diffuse redness scores were defined as 0, 1, and 2 for no diffuse redness, mild redness, and severe redness, respectively. The Kyoto score has been proven to be associated with the presence of gastric cancer[23], the risk of gastric cancer[25], and *H. pylori* infection[24].

In this study, enlarged folds were divided into two groups: severely enlarged folds with widths ≥ 10 mm and mildly enlarged folds with widths of 5-9 mm[29,30]. Fold width was measured by placing a closed or opened forceps, which has a width of 2 mm or 7mm, against enlarged folds.

One expert endoscopist retrospectively reviewed the EGD images and evaluated the Kyoto score. Surveillance EGD was defined as such only if the patients had undergone a previous EGD at our institution within the last 2 years[31].

Pathology

The depth of the tumor was diagnosed using the resected specimen or if unresectable, from computed tomography images. Tumor type was evaluated according to the Lauren classification (diffuse- or intestinal-type)[32].

H. pylori status

We divided the *H. pylori* infection status into two groups: current infection and negative for current infection. The current infection group included patients in whom *H. pylori* eradication therapy had failed. The group of negative for current infection included *H. pylori*-uninfected patients and *H. pylori*-past infected patients who had undergone successful eradication therapy or in whom *H. pylori* had spontaneously disappeared[33].

Data collection and outcomes

The T-File System (STS-Medic Inc., Tokyo, Japan) was used to file the endoscopic images and for documentation of the endoscopic findings. We collected data on age, sex, interval from previous EGD, and endoscopic images from the T-File System, and data on body mass index (BMI), *H. pylori* status, treatment for the cancer, and Lauren type of the tumor from electronic medical records.

Statistical analysis

Univariate and multivariate analyses for the effect on submucosal invasion and curative endoscopic resection were performed using a binomial logistic regression model. Variables with a P value < 0.1 in the univariate analysis were entered into the multivariate analysis and calculated using the all-possible-regressions procedure. We used a complete analysis for missing data. We evaluated the frequency of submucosal invasion among patients with negatively enlarged folds and mildly and severely enlarged folds using the Cochran-Armitage trend test.

Statistical significance was indicated by a P value of < 0.05. Calculations were performed using the statistical software Ekuseru-Toukei 2015 (Social Survey Research Information Co., Ltd., Tokyo, Japan).

RESULTS

Patient enrollment

A total of 300 patients with gastric adenocarcinomas were observed at the Toyoshima Endoscopy Clinic during the study period. We excluded nine cancers located at the esophagogastric junction, seven cancers located in the residual stomach after surgery, nine cancers with unavailable EGD images, and nine cancers with unavailable *H. pylori* status. Finally, 266 gastric cancers were enrolled. Figure 1 presents the patient flowchart of this study.

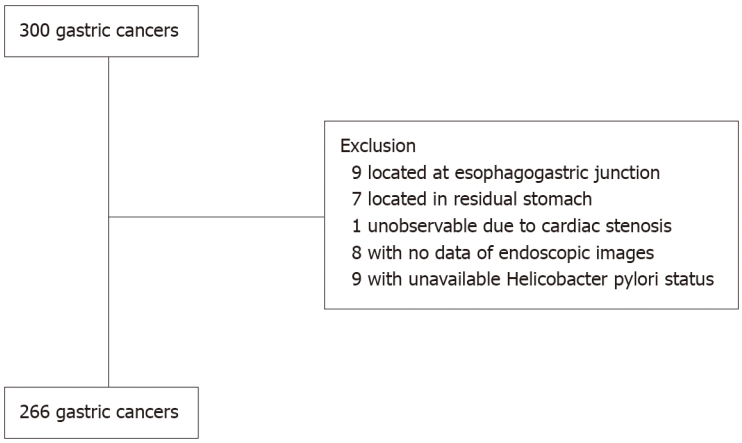

Figure 1 Patient flowchart.

Patient characteristics

Table 1 shows the patient characteristics of the study. The mean age was 66.7 (range, 37-89) years. Of the patients, 58.6% were male. The mean BMI was 22.8 kg/m^2. Ninety-three patients (35.0%) underwent EGD for surveillance within 2 years. Current *H. pylori* infection was identified in 52.6% (including 129 patients without past eradication therapy and 11 patients with failed eradication therapy) of the study patients. Cases negative for current *H. pylori* infection included 13 uninfected and 113 past-infected patients. The mean Kyoto score was 4.54 (atrophy score, 1.75; intestinal metaplasia, 1.32; enlarged folds, 0.24; nodularity, 0.08; diffuse redness score, 1.15). The proportion of diffuse-type adenocarcinoma on the Lauren classification was 21.8%. With respect to the depth of gastric cancer, 179 (67.3%) were in the mucosa, 51 (19.2%) were in the submucosa, and 36 (13.5%) were in the muscularis propria or deeper.

Effects on submucosal invasion of gastric cancer

We analyzed the effects on submucosal invasion of gastric cancer using univariate and multivariate analyses (Table 2). Multivariate analysis showed that low BMI (odds ratio 0.88, $P = 0.02$), non-surveillance EGD (odds ratio 0.15, $P < 0.001$), enlarged folds (odds ratio 3.39, $P = 0.001$), and Lauren's diffuse-type adenocarcinoma (odds ratio 5.09, $P < 0.001$) were associated with submucosal invasion.

Next, we analyzed the effects on patients who underwent curative treatment with endoscopic resection without surgery. In addition to the mucosal depth of gastric cancer, patients who underwent curative endoscopic resection were associated with high BMI, surveillance EGD, no enlarged folds, and Lauren's intestinal-type adenocarcinoma (Supplementary Table 1).

Sub-analysis of patients with enlarged folds

We divided gastric cancer patients with enlarged folds into two categories: mildly and severely enlarged folds. Submucosal invasion was observed in 49 of 203 cancers without enlarged folds, 14 of 30 cancers with mildly enlarged folds, and 24 of 33 cancers with severely enlarged folds. Figure 2 shows the proportions of submucosal invasion based on the severity of the enlarged folds. The severity of the enlarged folds was related to the depth of the tumor ($P < 0.001$, Cochran-Armitage trend test).

Representative images of enlarged fold gastritis and coexisting gastric cancer are shown in Figure 3.

DISCUSSION

In this study, we found that the enlarged folds of background gastritis were related to submucosal invasion of gastric cancer. Furthermore, the severity of the enlarged folds was associated with the depth of the tumor. We showed that cancer invasion may be predicted based on background gastritis. The strength of this study is that background gastritis, under the new criterion of the Kyoto classification, is related to the depth of invasion and not limited to observation of the lesions themselves. However, comprehensive endoscopic diagnosis is required in clinical practice because of advances in

Table 1 Patient characteristics of this study

Patient characteristics	
n	266
Age, mean (SD), yr	66.7 (12.1)
Male sex	58.6%
Body mass index, mean (SD), kg/m^2	22.8 (3.3)
Surveillance endoscopy within 2 yr	35.0%
Current *Helicobacter pylori* infection	52.6%
Endoscopic findings	
Atrophy score, mean (SD)	1.75 (0.54)
Intestinal metaplasia score, mean (SD)	1.32 (0.84)
Enlarged folds score, mean (SD)	0.24 (0.43)
Nodularity score, mean (SD)	0.08 (0.27)
Diffuse redness score, mean (SD)	1.15 (0.92)
Kyoto score, mean (SD)	4.54 (1.84)
Lauren's diffuse-type	21.8%
Depth of gastric cancer, M/SM/MP or deeper, *n*	179/51/36

M: Mucosa; MP: Muscularis propria; SD: Standard deviation; SM: Submucosa.

Table 2 Effect on submucosal invasion of gastric cancer

	Univariate analysis		Multivariate analysis		
	Odds ratio	*P* value	Regression coefficient	Odds ratio (95% confidence interval)	*P* value
Age	0.96	< 0.001	0.003	1.00 (0.97-1.03)	0.82
Male sex	1.17	0.56			
Body mass index	0.85	< 0.001	-0.130	0.88 (0.79-0.98)	0.02
Surveillance endoscopy within 2 yr	0.12	< 0.001	-1.913	0.15 (0.06-0.38)	< 0.001
Current *Helicobacter pylori* infection	2.55	< 0.001	-0.387	0.68 (0.21-2.24)	0.52
Endoscopic findings					
Atrophy score	0.58	0.11			
Intestinal metaplasia score	0.71	0.03	-0.014	0.99 (0.65-1.49)	0.95
Enlarged folds score	4.76	< 0.001	1.222	3.39 (1.61-7.14)	0.001
Nodularity score	1.57	0.33			
Diffuse redness score	1.48	0.01	-0.020	0.98 (0.54-1.78)	0.95
Kyoto score	1.14	0.08			
Lauren's diffuse-type	7.61	< 0.001	1.627	5.09 (2.22-11.64)	< 0.001

P values were calculated using binomial logistic regression analysis.

technology such as artificial intelligence.

Enlarged folds have been well studied for their biological characteristics. Enlarged folds have been shown to be associated with the tumor necrosis factor-alpha gene polymorphism as a genetic predisposition[34]. Genome wide hypomethylation and regional hypermethylation have been shown to occur in enlarged folds[35,36]. The production of interleukin 1 beta and hepatocyte growth factor caused by *H. pylori* infection reportedly contributes to fold enlargement in the stomach by stimulating

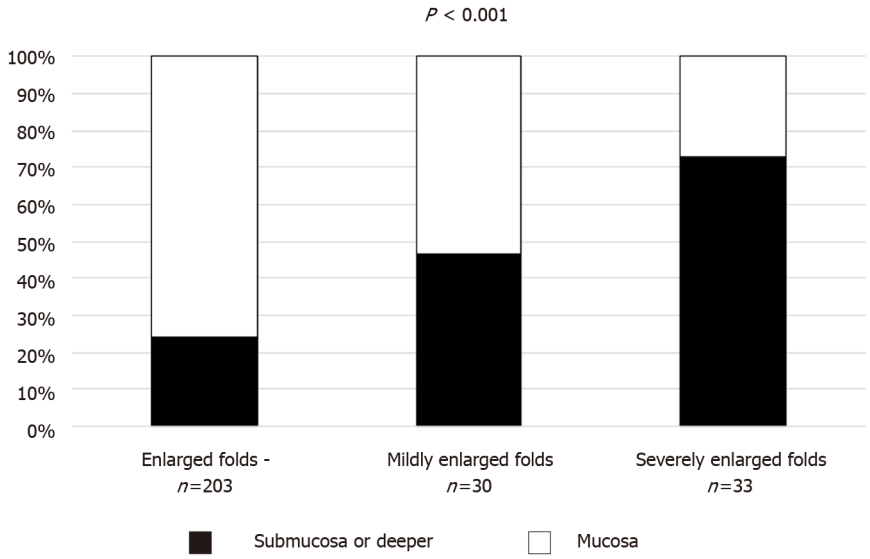

Figure 2 Proportion of submucosal invasion based on severity of enlarged folds. The *P* value was calculated using the Cochran-Armitage trend test.

epithelial cell proliferation and inhibiting acid secretion[37,38]. Morphological changes in parietal cells associated with *H. pylori* infection have been reported to be functionally related to the inhibition of acid secretion seen in patients with enlarged folds[39]. In addition, enlarged folds are strongly associated with *H. pylori* infection and have been shown to improve with eradication[24,29,34]. Enlarged folds are considered to be at high risk of gastric cancer, especially diffuse cancer, which is closely related to highly active inflammation[36,40]. These biological behaviors of the enlarged folds may be attributed to the depth of the cancer.

Yasunaga *et al*[29] divided enlarged folds into two categories (severe and mild) and found that severely enlarged folds suppressed acid secretion and had higher serum gastrin, pepsinogen I, and pepsinogen II levels compared to mildly enlarged folds[30]. Such differences may contribute to active inflammation of the mucosa and depth of cancer.

Invasion depth has already been reported to be associated with Lauren's histological type[41], surveillance endoscopy[31], and BMI[42]. Consistent with these previous reports, the multivariate analysis of the present study demonstrated that submucosal invasion was associated with pathology, surveillance, and BMI.

This study has some limitations. First, this was a single-institute retrospective study. However, the quality of the data was well-controlled. In the future, a prospective, multicenter design is needed. Second, because the number of events was small, the variables that could be entered into multivariate analysis were limited. It is desirable to increase the number of events and investigate factors such as family history, drinking and smoking history, and aspirin use. Third, we did not endoscopically evaluate the tumor itself. Comprehensive analyses of the tumor itself and background gastritis are warranted.

CONCLUSION

Endoscopy-based enlarged folds of gastritis were associated with submucosal invasion of the tumor. Endoscopic observation of background gastritis as well as the lesion itself may help diagnose the depth of cancer invasion in clinical practice. Therefore, further comprehensive investigations are required.

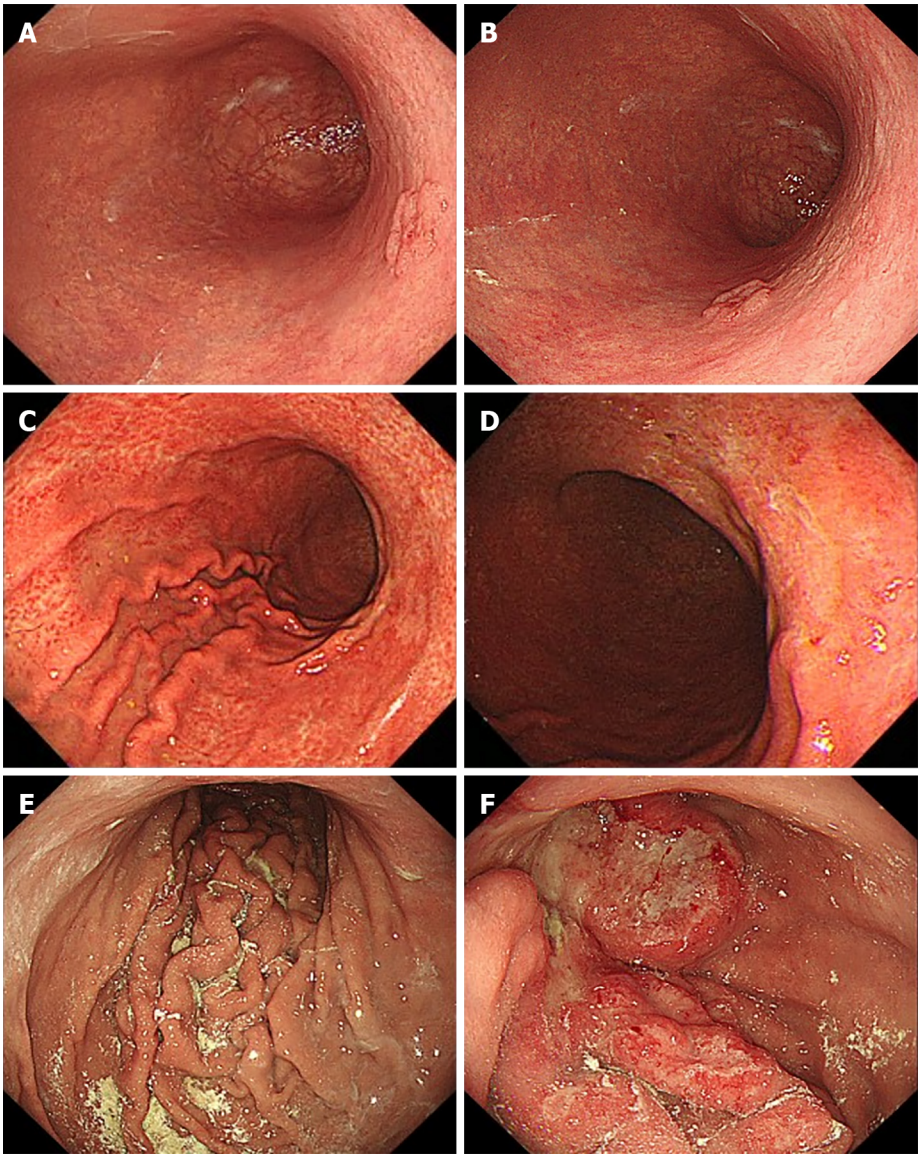

Figure 3 Representative images of enlarged folds and coexisting gastric cancer. A and B: Enlarged fold-negative; 74-year-old man with current *Helicobacter pylori* (*H. pylori*) infection. The cancer was limited to the mucosa and was intestinal-type; C and D: Mildly enlarged folds; 40-year-old woman with current *H. pylori* infection. The cancer invaded the submucosa and was diffuse-type; E and F: Severely enlarged folds; 60-year-old man with current *H. pylori* infection. The cancer invaded the serosa and was diffuse-type. A, C and E: Greater curvature of the body; B, D and F: Gastric cancer.

ARTICLE HIGHLIGHTS

Research background

The diagnosis of gastric cancer depth is often made using endoscopic characteristics of the tumor and its margins.

Research motivation

In the future, artificial intelligence may be used to diagnose the depth of invasion based not only on the tumor itself but also on background gastritis.

Research objectives

We investigated predicting submucosal invasion based on endoscopic background gastritis.

Research methods

Patients with gastric cancer detected on esophagogastroduodenoscopy were enrolled. We analyzed the effects of patient and tumor characteristics including the Kyoto classification.

Research results

Endoscopic enlarged folds of gastritis (odds ratio 3.39, $P = 0.001$) was independently associated with submucosal invasion. Among cancer patients with enlarged folds, severely enlarged folds (width ≥ 10 mm) were more related to submucosal invasion than mildly enlarged folds (width 5-9 mm, $P < 0.001$).

Research conclusions

Enlarged folds of gastritis were associated with submucosal invasion.

Research perspectives

Endoscopic observation of background gastritis as well as the lesion itself may help diagnose the depth of cancer invasion.

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CASE REPORT

Ectopic pancreas at the ampulla of Vater diagnosed with endoscopic snare papillectomy: A case report and review of literature

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Abstract

BACKGROUND

Ectopic pancreas is a rare developmental anomaly that results in a variety of clinical presentations. Patients with ectopic pancreas are mostly asymptomatic, and if symptomatic, symptoms are usually nonspecific and determined by the location of the lesion and the various complications arising from it. Ectopic pancreas at the ampulla of Vater (EPAV) is rare and typically diagnosed after highly morbid surgical procedures such as pancreaticoduodenectomy or ampullectomy. To our knowledge, we report the first case of confirmed EPAV with a minimally invasive intervention.

CASE SUMMARY

A 71-year-old male with coronary artery disease, presented to us with new-onset dyspepsia with imaging studies revealing a 'double duct sign' secondary to a small subepithelial ampullary lesion. His hematological and biochemical investigations were normal. His age, comorbidity, poor diagnostic accuracy of endoscopy, biopsies and imaging techniques for subepithelial ampullary lesions, and suspicion of malignancy made us acquire histological diagnosis before morbid surgical intervention. We performed balloon-catheter-assisted endoscopic snare papillectomy which aided us to achieve *en bloc* resection of the ampulla for histopathological diagnosis and staging. The patient's post-procedure recovery was uneventful. The *en bloc* resected specimen revealed ectopic pancreatic tissue in the ampullary region. Thus, the benign histopathology avoided morbid surgical intervention in our patient. At 15 mo follow-up, the patient is asymptomatic.

CONCLUSION

EPAV is rare and remains challenging to diagnose. This rare entity should be included in the differential diagnosis of subepithelial ampullary lesions.

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Endoscopic *en bloc* resection of the papilla may play a vital role as a diagnostic and therapeutic option for preoperative histological diagnosis and staging to avoid morbid surgical procedures.

Key Words: Ectopic pancreas; Heterotopic pancreas; Ampulla of Vater; Endoscopic snare papillectomy; Ampullary tumors; Case report

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Core Tip: Ectopic pancreas at the ampulla of Vater (EPAV) is an extremely rare condition, usually mimicking malignancy and presents as abdominal pain and obstructive jaundice. This rare entity should be included in the differential diagnosis of subepithelial ampullary lesions. The diagnosis of EPAV remains very challenging despite several endoscopic and radiological advances. The diagnosis is usually based on morbid surgical interventions such as pancreaticoduodenectomy/ampullectomy or autopsy. Endoscopic *en bloc* resection of the papilla with endoscopic snare papillectomy may play a vital role as a diagnostic and therapeutic option for preoperative histological diagnosis and staging to avoid morbid surgical procedures.

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INTRODUCTION

Ectopic or heterotopic pancreas is a rare developmental anomaly with an estimated frequency of 0.6% to 13.7% at autopsy. It is mostly an incidental finding in the upper gastrointestinal tract, the most typical sites being the stomach (25%-38%), duodenum (17%-36%), and jejunum (15%-21.7%). It has been noted occasionally in the esophagus, gallbladder, common bile duct (CBD), spleen, mesentery, mediastinum and fallopian tubes[1,2]. The clinical manifestations of ectopic pancreas are usually nonspecific and are determined by the location of the lesion and the various complications arising from it.

Ectopic pancreas at the ampulla of Vater (EPAV) is extremely rare and usually presents as obstructive jaundice or abdominal pain, and hence, mimicking ampullary malignancy. Despite several advances in endoscopic and radiological techniques, the diagnosis of EPAV remains challenging and is mostly identified post-surgery or at autopsy.

Endoscopic snare papillectomy (ESP) is a minimally invasive technique that helps to achieve *en bloc* resection of the ampulla for preoperative histopathological diagnosis and staging, and thus avoids morbid surgical intervention. To our knowledge, we report the first case of this rare and challenging entity diagnosed by *en bloc* resection of the ampulla with ESP.

CASE PRESENTATION

Chief complaints

A 71-year old male presented in the outpatient department in August 2019 with the chief complaint of epigastric pain of 3 mo duration.

History of present illness

The epigastric pain was mild to moderate, localized, continuous, with no relation to meals. There was no relief with proton pump inhibitors. There was no history of jaundice, pruritus, clay-colored stools, anorexia, weight loss, dysphagia, gastrointestinal bleeding or vomiting.

History of past illness

The patient had undergone coronary angioplasty for coronary artery disease in 2010 and was on dual antiplatelet drugs.

Personal and family history

He had no addictions, and his family history was non-contributory.

Physical examination

The patient was conscious and oriented. His pulse rate was 80 bpm and regular, and blood pressure was 110/70 mmHg. There was no pallor, icterus, or lymphadenopathy. Abdominal examination and other systemic examinations did not reveal any abnormalities.

Laboratory examinations

His blood investigations were as follows: Hb 13.9 g/ dL, white blood cell count 4600/μL, platelet count 166000/μL, prothrombin time 16.5 s, serum bilirubin 0.42 mg/dL, ALT 18 U/L, AST 17 U/L, ALP 83 U/L (< 129 U/L), gamma glutamyl transferase - 33 U/L (< 71 U/L), and serum creatinine 1.22 mg/dL (< 1.4 mg/dL).

Imaging examinations

At the local medical center, he had undergone ultrasonography of the abdomen that revealed dilatation of the CBD (15 mm) and pancreatic duct (PD) (5 mm). He was referred to our center for further management. Abdominal magnetic resonance imaging and magnetic resonance cholangiopancreatography (MRCP) showed dilated CBD (15 mm) and PD (6 mm) with abrupt cut-off at the level of the ampulla. No other abnormalities were noted (Figure 1). Endoscopic ultrasonography (EUS) revealed a subepithelial, hypoechoic mass lesion at the ampulla 7 mm in size, causing upstream dilation of the CBD and PD. The lesion was free from duodenal muscularis propria. There was no regional lymphadenopathy.

Diagnostic and therapeutic intervention

The age and comorbidity of the patient, the limitations and diagnostic accuracy of endoscopy, biopsies and imaging for ampullary lesions, and suspicion of malignancy made us acquire the histological diagnosis of ampullary lesion before a highly morbid surgical intervention. EUS-guided biopsy was not possible due to technical difficulties of the tiny mobile lesion. Hence, ESP was considered a diagnostic and therapeutic intervention for the subepithelial ampullary lesion. ESP aids in achieving *en bloc* resection of the ampulla for histopathological diagnosis and staging. Thus, *en bloc* ESP was performed with a balloon-catheter-assisted technique as described by Aiura *et al* [3]. ESP was carried out with a therapeutic duodenoscope (TJF Q 180V, Olympus Medical Systems Corp., Tokyo, Japan) with a 4.2 mm diameter accessory channel. Selective CBD cannulation was achieved with a 0.035" guidewire using a sphincterotome. The linked stone extraction balloon catheter (Fusion Quattro Extraction Balloon, Wilson Cook Medical Inc., Winston-Salem NC, USA) and a 5 Fr snare were inserted over the guidewire through the accessory channel side by side. The balloon catheter alone was advanced into the bile duct, and then the balloon was expanded with distilled water mixed with contrast. The balloon was pulled back gently towards the duodenal lumen, at which point the snare was opened so that it grasped the base of the papilla next to the inflated balloon. Pulling the balloon catheter toward the duodenal lumen made it easier to snare the papillary lesion entirely by lifting the papilla from the duodenal wall and towards the lumen[3]. *En bloc* papillectomy was performed with a monopolar electrosurgical current (ERBE Vio3, Endocut Q mode). A 5 Fr X 7 cm single pigtail pancreatic plastic stent was placed prophylactically, and a 10 Fr X 10 cm biliary plastic stent was placed after biliary sphincterotomy (Figure 2).

FINAL DIAGNOSIS

Histopathological examination of the retrieved specimen showed ampullary-type mucosa with the central area of erosion associated with mild acute on chronic inflammation in the lamina propria. There was a lobular arrangement of normal looking exocrine pancreatic tissue on the deeper aspect of the lamina propria consistent with the ectopic pancreatic tissue (Gasper Fuentes Classification - Type III) (Figure 3). Thus, the final diagnosis in the presented case was EPAV.

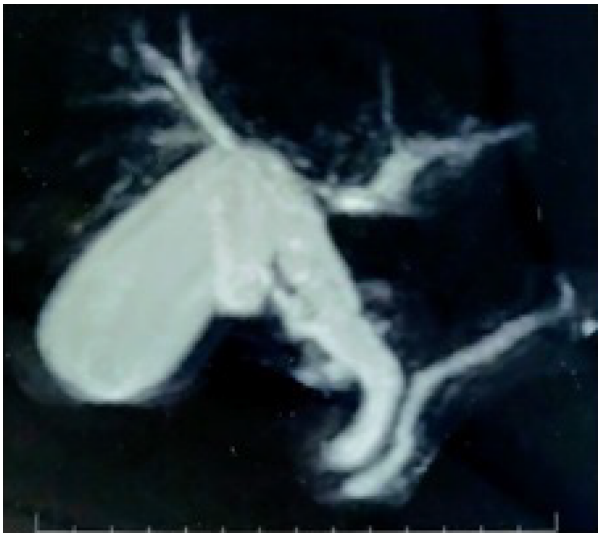

Figure 1 Magnetic resonance cholangiopancreatography showing the dilated common bile duct and pancreatic duct with abrupt cut-off at the ampulla.

TREATMENT

ESP (as described in section 'Diagnostic and Therapeutic intervention') played a vital role as a diagnostic and therapeutic modality in this case.

OUTCOME AND FOLLOW-UP

Post-procedure recovery was uneventful. Both stents were removed after ten days. The patient was asymptomatic at the 15 mo follow-up.

DISCUSSION

Ectopic pancreas is an uncommon developmental anomaly where pancreatic tissue has grown outside its usual location and shows no vascular or anatomical connections to the pancreas. The prevalence of ectopic pancreas is estimated to range from 0.6% to 13.7% of autopsies. It is mostly identified as an incidental finding within the upper gastrointestinal tract, the most typical sites being the stomach (25%-38%), duodenum (17%-36%), and jejunum (15%-21.7%)[1]. Ectopic pancreas is found in all age groups, with most cases in the 4th to 6th decade of life with a male preponderance (male:female ratio is 3:1).

In 1909, Heinrich described the first histological classification system for ectopic pancreas that Gasper Fuentes subsequently modified in 1973[4,5] (Table 1).

The exact incidence of EPAV is unknown. The autopsy series by Dolzhikov *et al*[6] found 48 cases (14.7%) of ectopic pancreatic tissue in 327 routine autopsies of the ampulla of Vater. Notably, the ectopic pancreatic tissue was detected macroscopically in one case only (2.1%) where it was suspected as a tumor of the ampulla of Vater. All other 47 cases had no macroscopic changes. The ectopic pancreatic tissue was positioned in the medial wall of the major duodenal papilla (37.5%), interductular septum (37.5%), lateral wall (16.7%) and the parapapillary area of the duodenum (8.3%). The autopsy findings further stated that the most common site of EPAV was in the walls of the ampulla of Vater and the base of the interductular septum (39.6%) followed by mucosa and the muscular glandular layer of the ampulla of Vater (27.1%). The exocrine variety of ectopic pancreas was the most typical variant (72.9%)[6].

EPAV is an infrequent entity presenting with clinical symptoms in the form of jaundice or abdominal pain. We found only 43 cases of EPAV (excluding bile duct ectopic pancreatic tissue) after an extensive literature search (Table 2)[7-31]. The most extensive series was fourteen cases by Vankemmel and Houcke[12] in 1977. They found these cases after undertaking a systematic study with multiple sections of the region of the ampulla of Vater in a total of 50 pancreaticoduodenectomies (49 – chronic

Table 1 Histological classification of ectopic pancreas

Heinrich classification (1909)
Type I - Contains acini, ducts and islands of Langerhans
Type II - Contains acini and ducts, but lacks endocrine elements
Type III Comprises proliferating ducts, exhibiting neither acini nor endocrine elements
Gasper Fuentes Classification (1973)
Type I - typical pancreatic tissue with acini, ducts, and islet cells similar to the normal pancreas.
Type II (canalicular variety) - pancreatic ducts only.
Type III (exocrine pancreas) - acinar tissue only.
Type IV (endocrine pancreas) - islet cells only.

pancreatitis; 1 – benign ampullary tumor). The age of the 43 cases of EPAV ranged from 32 years to 72 years with almost equal sex distribution. The most common symptoms were jaundice and abdominal pain. Eighty-two percent of cases revealed some degree of biliary dilatation, but it was shown that jaundice did not correlate with the size of the lesion. The size of the tumor ranged from 1 mm to 40 mm. The precise mechanism of CBD obstruction by ectopic pancreas is not known but may be due to mechanical obstruction (pressure by ectopic pancreatic tissue or surrounding tissue edema) or functional obstruction (spasm due to irritative secretions).

The important differential diagnoses for an ampullary lesion in addition to adenomatous lesions are neuroendocrine tumors, adenomyomas, gangliocytic paraganglioma, duodenal duplication cyst, inflammatory pseudotumor and infrequently ectopic pancreas[32-34]. Despite several advances in endoscopic and radiological techniques, the diagnosis of EPAV remains challenging. The unique finding of central umbilication on endoscopy is seldom seen at the ampulla of Vater. An endoscopic biopsy is unhelpful due to the subepithelial nature of the lesion. Radiological techniques such as CT scan and MRCP do not appear to be useful for preoperative diagnosis. Although very few cases had been subjected to EUS according to the previously reported cases, EUS appears to assist in determining the dimensions, layer of origin, adherence to the muscularis propria of the ampullary lesion and any regional lymphadenopathy. EUS-guided fine needle aspiration may help to clarify the diagnosis[35].

Thus, almost all the reported cases of EPAV in the literature are diagnosed after surgical intervention (95%), either in the form of pancreaticoduodenectomy (80%) or transduodenal ampullectomy (10%) or other interventions (10%). This appears to be due to in preoperative diagnosis and suspicion of malignancy. Similar findings were reported in the literature review by Biswas *et al*[26] in 2007. Surgical intervention carries a high rate of morbidity (pancreaticoduodenectomy – 25%-50% and transduodenal ampullectomy – 20%-30%) and mortality (pancreaticoduodenectomy 3-9% and transduodenal ampullectomy – 0%-6%)[36].

ESP is a minimally invasive technique that helps achieve *en bloc* resection of the ampulla for accurate preoperative histology and thus avoids morbid surgical procedures. ESP is a safe procedure that has low morbidity and mortality rates (9.7%–20% and 0.09%–0.3%, respectively)[36]. Lesions less than 5 cm, with no evidence of intraductal growth and no evidence of malignancy on endoscopic appearance (spontaneous bleeding, ulceration) are considered suitable for ESP. However, with advances in endoscopic techniques and armamentarium, the indications are expanding[37]. ESP can provide accurate histology and grading, tumor and lymphovascular invasion staging in cases of malignancy. There are plenty of debatable issues such as the use of submucosal injection, cautery current settings, and the use of prophylactic pancreatic stents *etc.*, in ESP. However, ESP seems to be a feasible and safe modality to achieve *en bloc* resection of ampullary lesions for accurate histology after pre-procedure work up in expert hands.

Our patient presented with new-onset dyspepsia with a ‘double duct sign’ on imaging, giving rise to the suspicion of ampullary malignancy. The age and comorbidity of the patient, the limitations and diagnostic accuracy of endoscopy, biopsies and imaging for ampullary lesions, and suspicion of malignancy made us acquire the histological diagnosis of ampullary lesion before considering a highly morbid surgical intervention. Hence, we carried out endoscopic *en bloc* resection of the

Table 2 Summary of clinical features of patients with ectopic pancreas at the ampulla of Vater

Author	Number of cases	Age (yr)/sex	Symptoms	Tumor size (mm)	CBD dilation	Treatment
Hoelzer[7], 1940	1	54/F	Abdominal pain, jaundice	12	Yes	Inoperable
Mitchell and Augrist [8], 1943	1	68/F	N/A	5	No	N/A
Varay[9], 1946	1	44/F	Jaundice	3	Yes	Pancreaticoduodenectomy
Pearson[10], 1951	1	43/F	Abdominal pain, jaundice	25	Yes	Pancreaticoduodenectomy
Weber *et al*[11], 1968	1	46/F	Abdominal pain, jaundice	8	Yes	Pancreaticoduodenectomy
Vankemmel and Houcke[12], 1977	14	32-53/ NA	13 cases – chronic pancreatitis1 case – ampullary tumor	1-10 mm	NA	14 cases - Pancreaticoduodenectomy
Bill *et al*[13], 1982	1	64/M	Abdominal pain	40	Yes	Pancreaticoduodenectomy
O'Reilly *et al*[14], 1983	1	61/M	Jaundice	8	Yes	Pancreaticoduodenectomy
Laughlin *et al*[15], 1983	1	54/F	Abdominal pain	5	Yes	Ampullectomy
Xu[16], 1991[1]	6	35-60 /5M/1F	6 cases - Jaundice	NA	NA	6 cases - Pancreaticoduodenectomy
Kubota *et al*[17], 1996	1	71/M	Abdominal pain	NA	Yes	Pancreaticoduodenectomy
Hammarström and Nordgren[18], 1999	1	NA/F	Acute pancreatitis	4	No	ERCP, Sphincterotomy & biopsy
Molinari *et al*[19], 2000	1	42/M	Abdominal pain, jaundice, weight loss	4	Yes	Pancreaticoduodenectomy
Chen *et al*[20], 2001	1	59/F	Abdominal pain	12	Yes	Ampullectomy
Contini *et al*[21], 2003	1	72/F	Abdominal pain, jaundice	8	Yes	Ampullectomy
Obermaier *et al*[22], 2004	1	46/M	Jaundice	2	Yes	Pancreaticoduodenectomy
Wagle *et al*[23], 2005	1	70/F	Abdominal pain, jaundice	NA	Yes	Pancreaticoduodenectomy
Filippou *et al*[24], 2006	1	69/F	Jaundice, weight loss	NA	Yes	Ampullectomy
Karahan *et al*[25], 2006	1	67/M	Abdominal pain, jaundice	10	Yes	Laparotomy, biopsy, Choledochojejunostomy
Biswas *et al*[26], 2007	1	47/M	Abdominal pain, jaundice	15	Yes	Pancreaticoduodenectomy
Hsu *et al*[27], 2008	1	54/M	Abdominal pain, jaundice	NA	Yes	Pancreaticoduodenectomy
Rao *et al*[28], 2011	1	48/M	Jaundice	1.5	Yes	Pancreaticoduodenectomy
Ciesielski *et al*[29], 2015	1	54/M	Abdominal pain, jaundice	NA	No	Cholecystectomy with intraoperative CBD BX
Kang *et al*[30], 2016[2]	1	39/F	-	14	No	Endoscopic resection
Nari *et al*[31], 2019	1	49/M	Abdominal pain, Jaundice	NA	Yes	Cholecystectomy with CBD Exploration and Bx; Papillo - Sphincterotomy
Present case, 2021	1	71/M	Abdominal pain	8	Yes	Endoscopic snare papillectomy
Total no of cases	44					

[1]Article in Chinese language.
[2]Article in Korean language.
Ampullary gangliocytic paraganglioma along with ectopic pancreas. CBD: Common bile duct; N/A: Not applicable; NA: Not available.

subepithelial ampullary lesion using a balloon-catheter-assisted ESP. The benign histopathology of the resected specimen avoided morbid surgical intervention in our case.

To our knowledge, this is the first reported case of EPAV managed with minimally invasive ESP.

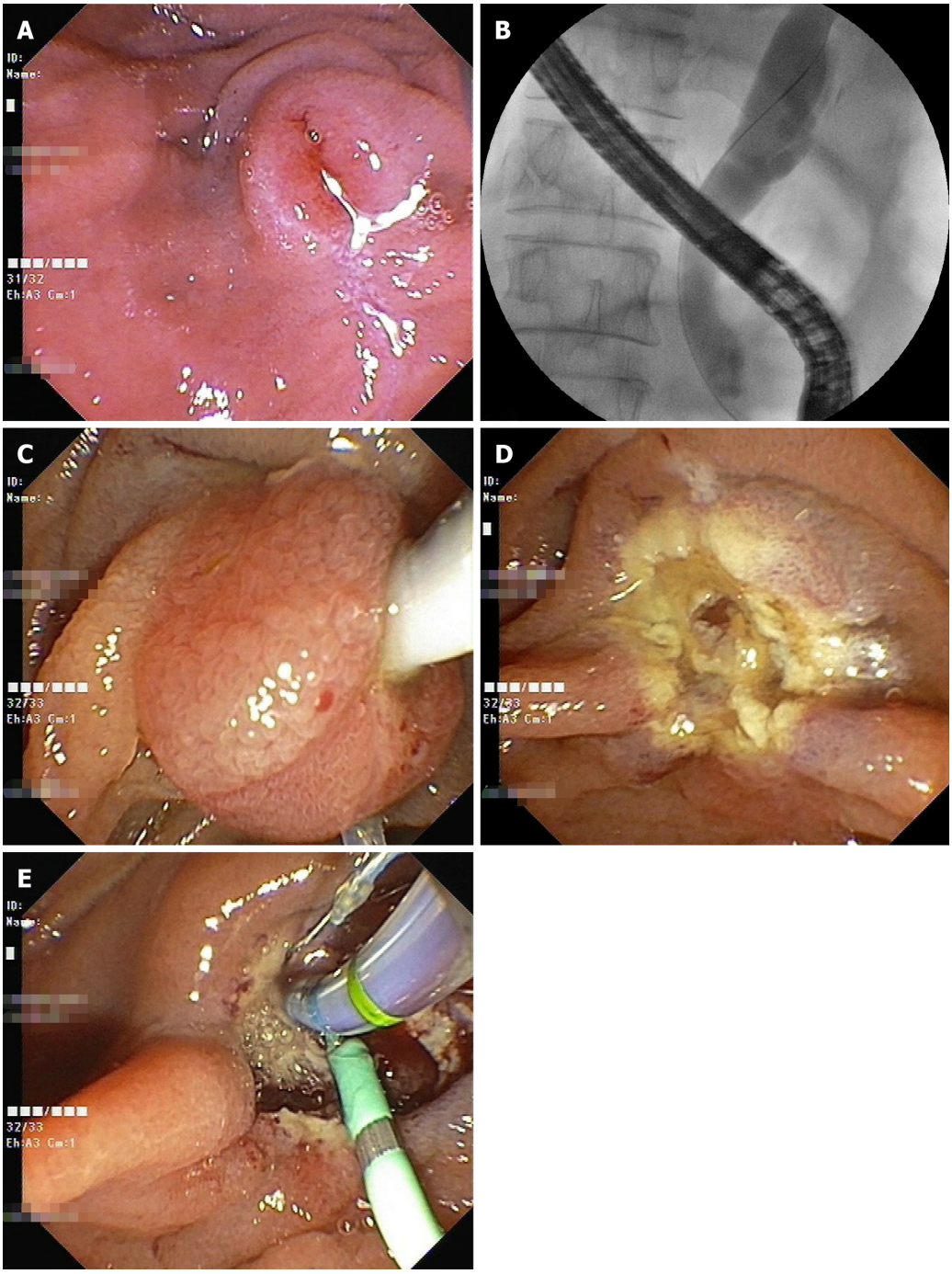

Figure 2 Endoscopic snare papillectomy. A: Endoscopic view of the sub-epithelial ampullary lesion; B: Cholangiogram showing terminal common bile duct (CBD) stricture with upstream dilated CBD after selective CBD cannulation; C: Endoscopic view showing snaring of the papilla while pulling back the expanded balloon within the CBD towards the duodenal lumen; D: Endoscopic view after endoscopic snare papillectomy; E: Endoscopic view of the biliary sphincterotomy and pancreatic stent in place.

CONCLUSION

EPAV mimicking malignancy with a 'double duct sign' is an extremely rare condition. The diagnosis remains challenging even with advances in endoscopic and radiological techniques. Hence, the diagnosis rests totally on morbid surgical interventions or autopsy. This rare entity should be included in the differential diagnosis of subepithelial ampullary lesions. ESP which helps to achieve *en bloc* resection of the ampulla may play a vital role as a diagnostic and therapeutic option for preoperative histological diagnosis and staging to avoid morbid surgical procedures.

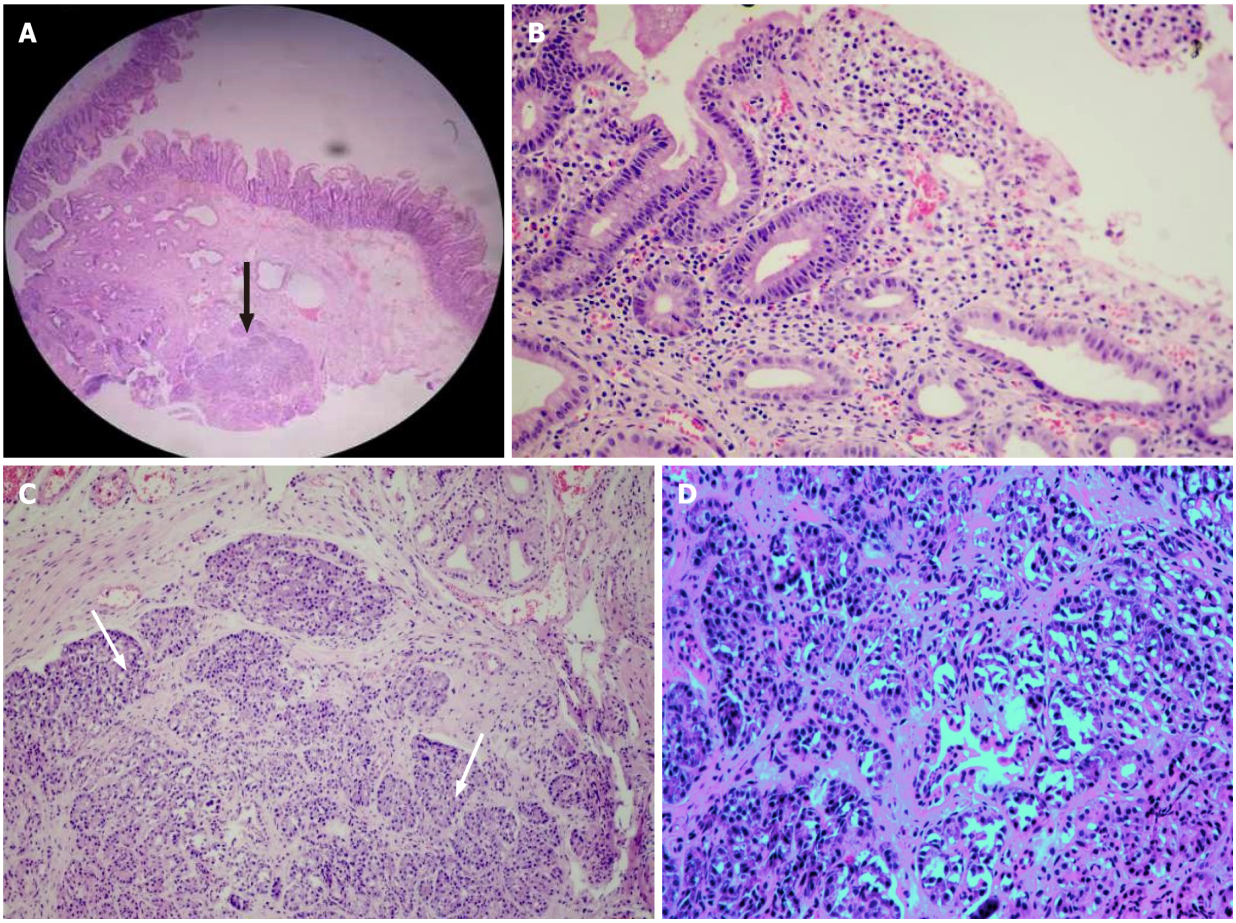

Figure 3 Ectopic pancreas at the ampulla of Vater–histopathology. A: Hematoxylin and eosin (HE) staining showing ampullary mucosa with ectopic pancreatic tissue (arrow) on low power view; B: Ampullary mucosa with inflammatory infiltrates in the lamina propria; C: HE staining showing ectopic exocrine pancreatic tissue (arrows) (20 ×); D: Pancreatic acini (40 ×).

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LETTER TO THE EDITOR

Ethical dilemma of colorectal screening: What age should a screening colonoscopy start and stop?

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Abstract

Many advanced age patients who are diagnosed with colorectal cancer are often not offered surgical treatment due to presumed high risks of the procedure. While there is data to support surgical treatment of colorectal cancer in advanced age patients, screening colonoscopy is not currently recommended for patients older than 85 years. Moreover, recent studies concluded that the incidence of colorectal cancer in patients 80 years and older is increasing. This raises the concern that the current guidelines are withholding screening colonoscopy for healthy elderly patients. Another concern contrary to this would be the new trend of growing incidence of advanced colorectal cancer in the younger patient population. Together they raise the ethical dilemma of how to best utilize colonoscopies as well as surgical intervention, as they are limited resources.

Key Words: Colonoscopy; Colorectal cancer; Screening; Advanced age patient; Screening colonoscopy

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Core Tip: Flynn *et al* collected data on surgery in colorectal cancer patients who are 85 years or older. They concluded that surgery in this patient population is safe, and that age alone is not a reason to withhold surgery. The incidence of colorectal cancer in patients 80 years and older is increasing. This raises the concern that the current

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guidelines are withholding screening colonoscopy for healthy elderly patients. On the other hand, a greater number of younger patients are being diagnosed with colorectal cancer. This raises an inevitable ethical dilemma of how to best utilize screening and treatment resources.

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TO THE EDITOR

Continuous development and new advances in medical treatment have extended the life expectancy of the average patient. As a result, the advanced age population is increasing worldwide, with the United States Census Bureau estimating that 16.5 percent of the population in the United States in 2019 is 65 years of age or older[1]. The prevalence of colorectal cancer is increasing alongside extended life expectancies[2,3]. The significance of this is that an increasing number of individuals over the age of 65 years have colorectal cancer and must be screened and treated appropriately. Colorectal cancer continues to be the fourth most common cancer and is the second leading cause of cancer-related deaths worldwide, with many cases diagnosed between 50 and 70 years old[4]. While there are many advanced age patients that are diagnosed with colorectal cancer[5], surgery is frequently withheld due to presumed high risks associated with it given scarce data on surgical treatment outcomes in this patient population. Given this gap in epidemiological data, Flynn *et al*[6] sought to evaluate the post-operative outcomes for patients 85 years or older following colorectal cancer resection as well as compare outcomes in patients who underwent laparoscopic procedures *vs* open abdominal procedures.

Flynn *et al*[6] performed a single institution, retrospective cohort study of patients at The Prince Charles Hospital who underwent resection of colorectal cancer from January 2010 to December 2018. A total of 533 patients were identified: 136 patients were between the ages of 75-85 years old, and 48 patients were 85 years of age at the time of the surgery. Short-term post-operative outcomes were assessed in patients over the age of 85 in terms of operative technique, that being laparoscopic *vs* open colorectal resection. They found that 30-d mortality was similar between the open surgery (9 percent) and laparoscopic intervention (0 percent) groups. They also found no significant difference between the two age groups regarding short-term surgical outcomes in terms of length of stay, grading of complications, and 30-d mortality. Flynn *et al*[6] concluded that resection of colorectal cancer in patients over the age of 85 is safe and effective, and that age alone is not a sufficient reason to withhold surgical treatment in this patient population.

The study had a long follow up period and is well powered with 533 patients. However, only 136 patients were of age 75-85 years old and only 48 patients were at least 85 years old, and therefore were included in the analysis. There were disproportionately more women in the age group 85 years and older, which may have affected the results of the study. The study included analysis on the most common surgical interventions for colorectal cancer, using t-tests, chi squared tests, and Fisher's exact tests with statistically significant results having $P < 0.05$. The study, however, was retrospective as well as a single institution study which may introduce some unknown geographical variables and therefore affect this study's external validity. Lastly, when comparing 30-d mortality between laparoscopic and open methods, it was not accounted for that many of the open cases were more likely to be emergent cases. While Flynn *et al*[6] proposed that surgical intervention is safe in the older patient population with colorectal cancer, this is yet to be confirmed by a larger scale prospective randomized controlled study.

Recent studies concluded that the incidence rate of colorectal cancer in patients who are 80 years or older is increasing[1,2]. Despite that, the American Gastroenterological Association (AGA) 2020 guidelines for colorectal cancer screening suggest that screening should be discontinued once a patient reaches 75 years of age or had less

than ten years of life expectancy, given they have been up to date with screening and have had negative results[7]. The screening remains optional for 75 to 85 years of age and depends on risk factors and comorbidities[7]. AGA also expressed concerns about increasing incidence of colorectal cancer in the younger patient population, and it is now recommended to do a thorough diagnostic evaluation for persons under 50 years of age with colorectal bleeding[7]. Mauri *et al*[8] also discussed how colorectal cancer incidence in individuals younger than 50 years has been increasing by two percent per year since 1994. As of this year, routine screening of the average risk individual should begin at 50 years old, except in African Americans, in whom limited evidence suggests screening at 45 years old[7]. Currently, only patients with significant family history are considered for colorectal cancer screening at 40 years old or earlier[7]. The United States Preventive Services Task Force supported AGA's guidelines to screen adults ages 50 years to 75 years[9]. They concluded with moderate certainty that screening for colorectal cancer in adults of 45 years to 49 years has moderate benefit and that screening of adults of 75 years to 85 years has a small net benefit[9].

It remains unclear how to best utilize colonoscopies, as they are a limited resource. Given the recent concerning trend of a growing number of younger patients being diagnosed with advanced colorectal cancer[10,11], the question is raised whether younger patients could benefit from earlier screening and whether resources should be diverted to a younger patient group. It is important to note that patients of 35 years or younger are more likely to be diagnosed with stage III or IV colorectal cancer[4]. Interestingly, the 5 and 10-year overall survival is also decreased in patients younger than 35 years old[4]. Overall, younger patients diagnosed with colorectal cancer have a worse prognosis because of a higher proportion of advanced stage tumors.

In conclusion, it is evident that elderly individuals are still suffering from colorectal cancer in spite of current screening guidelines. Flynn *et al*[6] emphasized how the elderly population beyond age 85 years are indeed good surgical candidates for resection of colorectal cancer and that age should not be considered when determining surgical risk. With this being said, we propose that screening should be continued in adults over 85 years old despite no available recommendations for screening. Additionally, there is a concerning trend in younger individuals being diagnosed with colorectal cancer prior to initiation of screening at 50 years of age. The increasing incidence of colorectal cancer in the elderly population beyond 75 years of age as well as the increasing incidence of advanced stage colorectal cancer in patients younger than 50 years of age raises an important concern of whether colorectal cancer screening is being done appropriately. If elderly patients do well undergoing surgery, should colorectal cancer screening be stopped and/or reduced at 75 years of age? Likewise, should colorectal cancer screening be initiated prior to age 50 years old? While Flynn *et al*[6] provided no data on long term outcomes and on increase in life expectancy, screening and treatment for the very elderly, or those who are 86 years and older, may not necessarily provide a large gain in additional life-years, especially in comparison to those who are 76-85 years of age. Long term outcomes and effects on the life expectancy is something that still needs to be investigated. We propose that colorectal cancer screening, with colonoscopies in particular, should be extended to both the younger population of 40 years of age as well as patients 75 years or older based on risk factors and patient profile rather than on age as a number alone. By creating a scale or grading system, patients over 75 years and under 45 years could be stratified into high risk *vs* low risk for development of colorectal cancer. This would allow for diverging of resources towards the population(s) that would have the most benefit from screening[12,13]. This idea remains to be proven with prospective large scale randomized controlled studies.

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OPINION REVIEW

Proposal of the term "gallstone cholangiopancreatitis" to specify gallstone pancreatitis that needs urgent endoscopic retrograde cholangiopancreatography

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Abstract

Opie's "pancreatic duct obstruction" and "common channel" theories are generally accepted as explanations of the mechanisms involved in gallstone acute pancreatitis (AP). Common channel elucidates the mechanism of necrotizing pancreatitis due to gallstones. For pancreatic duct obstruction, the clinical picture of most patients with ampullary stone impaction accompanied by biliopancreatic obstruction is dominated by life-threatening acute cholangitis rather than by AP, which clouds the understanding of the severity of gallstone AP. According to the revised Atlanta classification, it is difficult to consider these clinical features as indications of severe pancreatitis. Hence, the term "gallstone cholangiopancreatitis" is suggested to define severe disease complicated by acute cholangitis due to persistent ampullary stone impaction. It incorporates the terms "cholangitis" and "gallstone pancreatitis." "Cholangitis" refers to acute cholangitis due to cholangiovenous reflux through the foci of extensive hepatocyte necrosis reflexed by marked elevation in transaminase levels caused by persistent ampullary obstruction. "Gallstone pancreatitis" refers to elevated pancreatic enzyme levels consequent to pancreatic duct obstruction. This pancreatic lesion is characterized by minimal or mild inflammation. Gallstone cholangiopancreatitis may be valuable in clinical practice for specifying gallstone AP that needs urgent endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy.

Key Words: Gallstone pancreatitis; Gallstone hepatitis; Acute cholangitis; Necrotizing pancreatitis; Pathophysiology; Endoscopic retrograde cholangiopancreatography

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acute pancreatitis complicated by life-threatening acute cholangitis due to persistent ampullary stone impaction and needs urgent endoscopic retrograde cholangiopancreatography with endoscopic sphincterotomy. The term "gallstone cholangiopancreatitis" incorporates the terms "cholangitis" and "gallstone pancreatitis." "Cholangitis" refers to acute cholangitis due to cholangiovenous reflux through the foci of extensive hepatocyte necrosis reflexed by marked elevation in transaminase levels caused by persistent ampullary obstruction. "Gallstone pancreatitis" refers to elevated pancreatic enzyme levels consequent to pancreatic duct obstruction, the pancreatic lesion that is characterized by minimal or mild inflammation.

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INTRODUCTION

The presence of gallstones is an important etiologic factor for the development of acute pancreatitis (AP). Generally, obstruction of pancreatic outflow, which is frequently caused by transiently impacted stones at the ampulla of Vater, can cause gallstone AP [1]. Most patients with gallstone AP have a mild disease due to the eventual passage of stones, exhibiting rapid objective improvement. Nevertheless, the pathophysiology of severe disease in the remaining patients, refractory to conventional supportive therapy, remains controversial. In addition to the low incidence of gallstone AP in those with gallstones (3.4%[2], 7.7%[3]), the rapid disease course and the relative inaccessibility of pancreatic tissues for the examination of AP have hampered investigations of the mechanism of severe disease in gallstone AP[4]. Considering these issues, investigations in humans may rely on findings from either autopsies or emergency surgeries performed during the early disease course. Emergency surgeries were common until the 1980s; however, they are no longer a common practice. Based on autopsy findings, Eugene Opie proposed the "pancreatic duct obstruction" and "common channel" theories in 1901, which are generally accepted as explanations of the mechanisms involved in gallstone AP[4]. Opie's postulates can be summarized as follows: (1) Stones impacted at the terminal bile duct or the ampulla of Vater obstruct the bile and pancreatic ducts simultaneously. The obstructed pancreatic juice and bile may be forced backward into the pancreatic and hepatic parenchyma and penetrate their surrounding tissues, causing interstitial edematous pancreatitis and/or fat necrosis ("pancreatic duct obstruction" theory) and tissue stain with bile pigments and/or jaundice, respectively; and (2) Small stones about 3 mm in diameter that are large enough to lodge at the duodenal orifice mostly measured 2 mm to 2.5 mm but too small to obstruct the bile and pancreatic duct orifices, convert both ducts into a continuous closed channel. Contraction of the gallbladder overcomes any slight pressure difference between the bile and pancreatic ducts, which may lead to repeated bile reflux into the pancreatic duct, causing necrotizing pancreatitis (NP) ("common channel" theory).

Pancreatic duct obstruction theory stipulates that simultaneous obstruction of both ducts due to the large stone size and very short length of the common channel causes AP. However, severe disease caused by persistent ampullary stone impaction combined with biliopancreatic obstruction remains controversial. This is one of the main issues considered in this opinion review.

NP AND PASSED STONE

Common channel theory elucidates the cause of NP due to gallstones. Animal models have shown that protease activation is highly dependent on calcium release[5], with bile acids inducing calcium-releasing signals and contributing to pancreatic acinar cell damage[6]. However, questions on the evidence of bile reflux into the pancreatic duct

and the presence of impacted stones, which prevent wide acceptance of this postulate, have been raised. Recently, histological evidence of bile reflux into the pancreas as the cause of NP has been reported[7], and Opie's long-speculated "common channel" theory that NP represents the primary action of bile has been proven. In a case in the 1980s reported by Isogai *et al*[7], the operative cholangiogram did not demonstrate any bile duct stones. However, it revealed reflux of contrast material into the pancreatic duct, suggesting that an "anatomic" common channel was converted into a "functioning" common channel[8]. Kelly[9] noted that a functioning common channel is necessary for bile reflux and favors stone passage. Thus, regarding the presence of no impacted stones, virtually all small stones of a size that settle in the narrow duodenal orifice and allow bile reflux into the pancreatic duct may be evacuated and passed soon after triggering NP, thereby providing no evidence of their former impaction[7,10].

Long common channels[11], which allow for communication between the two ducts using impacted stones at the duodenal orifice, are not universally present in patients with gallstone AP. Hernández and Lerch[12] observed that the migration of gallstones through the biliary tract induces functional stenosis at the sphincter of Oddi, and a common channel between the pancreatic and bile ducts can arise. In 1909, Opie and Meakins[13] reported a case of NP with an anomalous duct of Santorini with a relatively wide orifice. They concluded that duodenal contents might have regurgitated into the pancreatic duct, causing NP; enterokinase, which is the most potent activator of pancreatic proteolytic enzymes, is present in these duodenal secretions. The passage of stones may cause a similar patulous sphincter, permitting duodenopancreatic reflux[14]. However, it may be difficult to prove histologically the reflux as the cause of NP since duodenal contents have no pigment to indicate their presence.

CONTROVERSIES RELATED TO BILIOPANCREATIC OBSTRUCTION

As Opie noted, pancreatic lesions caused by impacted ampullary stones may be interstitial edematous pancreatitis, of which clinical symptoms usually resolve within the first week[15]. It can also be fat necrosis, which is probably caused by lipase (one of the few pancreatic enzymes that require no activation), phagocytized by macrophages that may later be replaced with small foci of fibrotic tissues[16]. Acosta *et al*[17] noted that during the early stage of gallstone AP with persistent ampullary obstruction, a possible pancreatic complication is a pancreatic phlegmon, which includes a pancreatic inflammatory mass, peripancreatic fluid, and fat necrosis. Similarly, Oría *et al*[18] noted that biliopancreatic obstruction does not, by itself, contribute to persistent pancreatic inflammation or its worsening. Moreover, whether pancreatic duct obstruction without reflux causes NP in humans remains unknown[4]. Additionally, the clinical picture of most patients with ampullary stone impaction is often dominated by cholangitis and septicemia rather than by AP[14], which clouds the understanding of the severity of gallstone AP and leads to confusion and controversy regarding the management of patients with gallstone AP.

As noted previously, during the era of Opie, macroscopic findings of fat necrosis and/or interstitial edematous pancreatitis and those of jaundice and/or tissue stain with bile pigments were the indicators of persistent pancreatic duct and bile duct obstruction, respectively. The current availability of biochemical tests has shown that patients with gallstone AP have highly elevated liver and pancreatic enzyme levels during the early disease course. A histopathological study of liver biopsy specimens in gallstone AP patients with minimal or mild pancreatic inflammation (few patients with NP underwent liver biopsy) have shown that elevated serum transaminase levels reflect histopathological acute inflammatory hepatocyte necrosis (accumulation of neutrophils in and around the disappeared liver cell plate) and acute cholangitis (neutrophil infiltration in and around the bile duct lumen in the portal triad)[19]. Using electron microscopy, a disorganized liver cell plate, retained biliary material in the dilated canaliculi, and cytoplasm shedding into the Disse space have also been detected[19]. Thus, highly elevated liver enzyme levels during the early disease course in patients with gallstone AP reflect microscopic hepatocyte necrosis and cholangitis caused by the sudden blockage of the ampulla of Vater because of migrating bile duct stones[19]. Liver enzymes escape from degenerated and necrotic hepatocytes, causing marked hypertransaminemia. These hepatic histopathological simultaneous changes of cholestasis, acute cholangitis, and hepatocyte necrosis were consistent with those observed in patients with gallstone hepatitis[20], which will be discussed later. Based

on the hepatic histopathological changes in gallstone AP, Neoptolemos *et al*[21] concluded that there is a degree of obstruction in both bile and pancreatic ducts in gallstone AP. In contrast, the admission serum bilirubin reflects the degree of "persistent" bile duct obstruction due to the continued presence of bile duct stones. Thus, the elevation of serum transaminase is consistent with the concept of transient ampullary obstruction in gallstone AP and useful in establishing gallstone etiology. An elevated alanine transaminase (ALT) level is widely considered the most useful to identify the biliary etiology of AP, and a 1994 meta-analysis found that an ALT level of > 150 units/L has a positive predictive value for gallstone AP of 95%[22]. A prospective study conducted by Anderson *et al*[23] demonstrated that the higher the ALT, the more likely a biliary cause becomes; ALT levels of > 300 units/L and > 500 units/L have positive predictive values of 87% and 92%, respectively.

In 1991, Isogai *et al*[20] proposed the term "gallstone hepatitis" as a new clinical entity defined as a marked elevation in serum transaminase levels due to acute inflammatory liver cell degeneration and necrosis during the early stage of gallstone impaction in the bile duct. Marked elevation in transaminase levels alone may lead to a diagnosis of so-called hepatitis. However, the pathogenesis of gallstone hepatitis differs from ordinary hepatitis in that hepatocyte necrosis does occur as a consequence of cholestasis. Hepatocellular degeneration and necrosis have been histologically shown to be the acute inflammatory reactions to liver injury caused by acute bile duct obstruction, which is transient and reversible after its early resolution[20]. It is easily conceivable that if the bile duct is obstructed by impacted stones, it becomes a closed system filled with bile and that pathological changes in the bile duct such as bile stasis, increased pressure, or infection may affect the liver cells that bound the bile canaliculus and cause hepatocellular injury[20]. Mayer and McMahon[24] reported that transient ampullary obstruction causes a rapid rise in bile duct pressure and consequent liver cell damage. Animal models showed that a combination of bile stasis and inflammation causes a mechanical insufficiency of lymph circulation, leading to extensive liver cell necrosis[25]. In addition to a marked depression of the hepatic microcirculation, increased neutrophil infiltration in the liver represents a potential source of liver injury during acute biliary obstruction[26]. In about half of patients with gallstone hepatitis, the gross appearance of the gallbladder showed acute cholecystitis. However, acute cholecystitis was significantly more infrequent among patients with gallstone hepatitis than control patients, and acute inflammation of the gallbladder is thought to be secondary to bile duct obstruction[20]. Similarly, histological evidence of acute cholangitis is considered after bile duct obstruction and not the initial process responsible for transaminase elevation[20]. In 2016, Huh *et al*[27] proposed to exclude patients with acute cholangitis upon hospital admission from gallstone hepatitis. Marked elevation of serum transaminase levels is induced under conditions in which intrabile duct pressure dramatically surges[27].

These highly elevated liver test results (gallstone hepatitis) should heighten the clinician's awareness of coexisting acute biliary tract disease with gallstone AP. Hepatocytes with tight junctional complexes, which form a seal between the lumen of the bile canaliculus and the hepatic intercellular space, play a role in the creation of a canaliculi–sinusoidal barrier[28], and discontinuities in the junctional meshwork provide a direct pathway between the lumen of the bile canaliculus and the intercellular space[29]. Thus, elevated liver enzyme levels, a serological reflection of microscopic hepatocyte necrosis, indicate disruption to the barrier. It permits regurgitation of the bile into the circulating blood if the pressure in the bile canaliculus increases further due to persistent obstruction of the bile duct leading to acute ascending cholangitis.

Conventionally, clinicians have paid less attention to hepatobiliary diseases characterized by markedly elevated liver enzyme levels caused by impacted bile duct stones; this seems to be the Achilles heel in managing patients with gallstone AP. This may be unavoidable because the term "gallstone AP" refers to "pancreatitis" alone. The term "gallstone hepatopancreatitis" reflects elevated liver and pancreatic enzyme levels, which may better direct the clinician's attention to hepatobiliary pancreatic lesions occurring in both the liver and the pancreas caused by transiently impacted stones at the ampulla of Vater early in the gallstone AP course.

SUBDIVISION OF SEVERE DISEASE INTO TWO CATEGORIES

The revised Atlanta classification for AP defines moderately severe and severe AP as the presence of transient organ failure, local complications, or exacerbation of

comorbid diseases and as persistent organ failure, respectively[15]. Subsequently, a clinical dilemma arises: Are those patients with AP of gallstone etiology (*i.e.* gallstone AP) who have minimal or mild pancreatitis complicated with life-threatening acute cholangitis due to persistent ampullary stone impaction diagnosed with moderately severe or severe AP? It is difficult to consider these clinical features to be indicative of such severity of AP. To cope with the dilemma mentioned above, the author suggests the term "gallstone cholangiopancreatitis (CP)" to define severe disease with minimal or mild pancreatitis complicated with life-threatening acute cholangitis. The term "gallstone CP" incorporates the terms "cholangitis" and "gallstone pancreatitis." "Cholangitis" refers to acute ascending cholangitis due to cholangiovenous reflux through the foci of extensive hepatocyte necrosis reflexed by marked elevation in transaminase levels (gallstone hepatitis) caused by persistent ampullary obstruction. Conversely, "gallstone pancreatitis" refers to elevated pancreatic enzyme levels due to pancreatic duct obstruction, the pancreatic lesion that has minimal or mild inflammation (Figure 1A). It should be emphasized that in gallstone CP, the hepatobiliary pathology reflected by "cholangitis" outweighs the pancreatic lesion reflected by "gallstone pancreatitis." Currently, endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) is the widely accepted modality for gallstone AP with coexisting cholangitis and persistent biliary obstruction (*i.e.* gallstone CP)[10,30].

In contrast, NP resulting from the reflux of bile or duodenal contents into the pancreas uncomplicated with acute biliary tract disease due to the passage of stones is recommended to define "gallstone NP" (Figure 1B). This is because AP is generally an inflammation secondary to pancreatic tissue necrosis, irrespective of etiology, resulting from autodigestion by pancreatic enzymes[16]. Considering that stones responsible for NP generally pass into the duodenum early in the disease course or have already been evacuated and lost, ES may not be necessary for patients with gallstone NP. Additionally, a recent multicenter randomized controlled trial reported that compared with conservative treatment, urgent ERCP with ES (within 24 h after hospital presentation) did not reduce the composite endpoint of major complications or mortality in patients with predicted severe gallstone AP (Acute Physiology and Chronic Health Evaluation II score ≥ 8, Imrie score ≥ 3, or C-reactive protein level > 150 mg/L) and without cholangitis[31]. For future clinical trials on the role of urgent ERCP, American Gastroenterological Association has recommended that the timing of the ERCP interventions should be 24-48 h after diagnosis (24 h to allow spontaneous passage of the stone and 48 h to ensure that prolonged biliary obstruction does not occur)[10].

PERSPECTIVES ON GALLSTONE PANCREATITIS

In 2017, Campos *et al*[32] reported that pancreaticobiliary diseases are the most common cause of the marked increase in serum aminotransferase levels, considering the decrease in the prevalence of liver diseases (including viral infections) due to vaccination programs, social awareness campaigns, and an increased incidence of cholesterol calculi in developed countries, which was considered to be a new paradigm. The marked increase in serum aminotransferase levels in pancreaticobiliary diseases observed by Campos *et al*[32] was specifically in gallstone hepatitis or gallstone AP. Thus, gallstone AP is expected to be more often encountered. Gallstone AP is a disease diagnosed by the abnormal biochemical data of pancreatic and liver enzymes or may be missed if the blood tests are not performed. Once gallstone AP is diagnosed based on the acute onset of a severe epigastric pain accompanied by an elevation of pancreatic and liver enzyme levels and gallstones are demonstrated by image modalities, it should be properly managed based on the differences in clinical features and the mechanism by which gallstones initiate AP. The acute inflammatory hepatobiliary disease indicated by marked hypertransaminasemia (gallstone hepatitis) together with the pancreatic lesion reflected by a pancreatic enzyme elevation needs to be evaluated.

Within the first 72 h following its diagnosis, the key management strategy is to predict patients with gallstone CP who will benefit from ERCP with ES. It may be difficult to distinguish the inflammatory response caused by pancreatic injury from that due to biliary sepsis. Additionally, the diagnosis of coexisting acute cholangitis is not always straightforward, and the reliance on Charcot's triad criteria may be insufficient[18]. The sensitivity and specificity of endoscopic ultrasound in detecting common bile duct stones are superior to those of both transabdominal ultrasound and

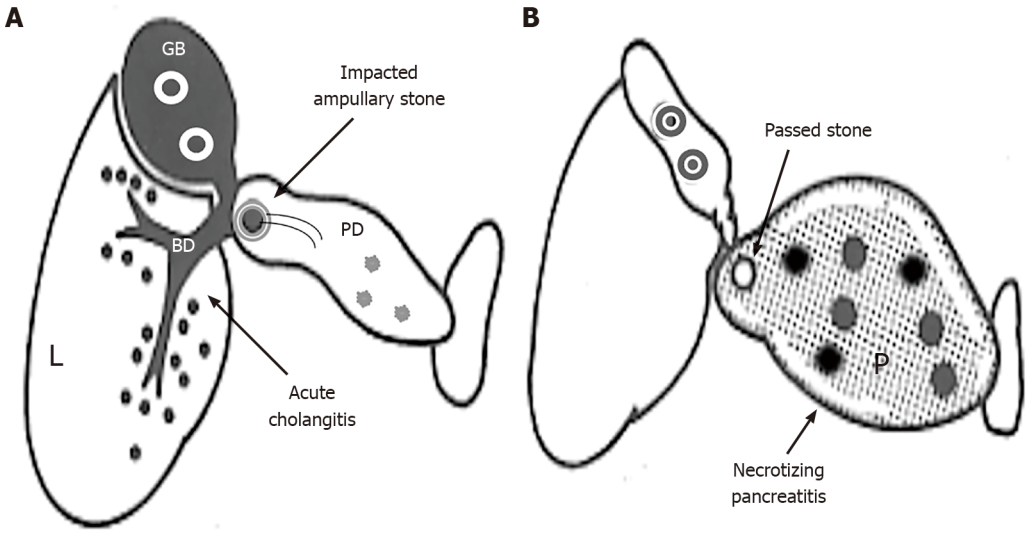

Figure 1 Subdivisions of gallstone pancreatitis with severe disease into gallstone cholangiopancreatitis and gallstone necrotizing pancreatitis. A: Gallstone cholangiopancreatitis with persistent ampullary stone impaction and ascending acute cholangitis complicated with minimal or mild pancreatic inflammation due to biliopancreatic obstruction; B: Gallstone necrotizing pancreatitis caused by the reflux of bile or duodenal contents into the pancreas (P), not complicated by acute biliary tract disease due to the passage of stones. L: Liver; BD: Bile duct; GB: Gallbladder; PD: Main pancreatic duct.

serum markers[33]. Hence, despite being invasive and not widely available, there is increasing use of endoscopic ultrasound to identify common bile duct stones in patients with gallstone AP. An endoscopic ultrasound-first strategy to establish the indication for ERCP with ES is expected[33].

If gallstone CP is ruled out and patients fail to improve after 5 to 7 d of initial treatment, contrast-enhanced computed tomography (CECT) is the most useful method for differentiating edematous pancreatitis from NP[34], and its findings are incorporated in the severity assessment of AP[35]. However, CECT should only be used when the value of the information obtained outweighs the disadvantages, such as impairment of renal function and allergic reaction[35]. Because an early CECT may underestimate the eventual extent of pancreatic and peripancreatic necrosis, a non-enhancing area of the pancreatic parenchyma identified using CECT should be considered as pancreatic parenchyma necrosis after the first week of the disease[15].

The algorithm for the diagnosis and initial treatment of gallstone AP is shown in Figure 2. The detailed management strategy for patients with gallstone NP has been suggested by a substantial evidence base[33], although this issue is beyond the scope of the present review.

CONCLUSION

Regarding gallstone AP, the disease severity caused by persistent ampullary stone impaction with biliopancreatic obstruction remains controversial. Based on the differences in clinical features and the mechanism by which gallstones initiate AP, the severe disease is subdivided into gallstone CP and gallstone NP. The term "gallstone CP" is suggested to define severe disease with minimal or mild pancreatitis complicated by life-threatening acute cholangitis due to persistent ampullary stone impaction. The term "gallstone CP" may be valuable in clinical practice for specifying gallstone AP that needs urgent ERCP with ES. Whereas severe disease with NP resulting from the reflux of bile or duodenal contents into the pancreas is defined as "gallstone NP," which is not complicated by acute biliary tract disease due to the passage of stones, and urgent ERCP may not be necessary.

Although elevation in serum transaminase levels in patients with gallstone CP reflects hepatic injury, which is inappropriate for use in multifactor prognostic systems of AP such as Ranson or Imrie score, the mechanism of transaminase elevation in patients with gallstone NP remains unclear without hepatic histopathological evidence, and further studies are needed.

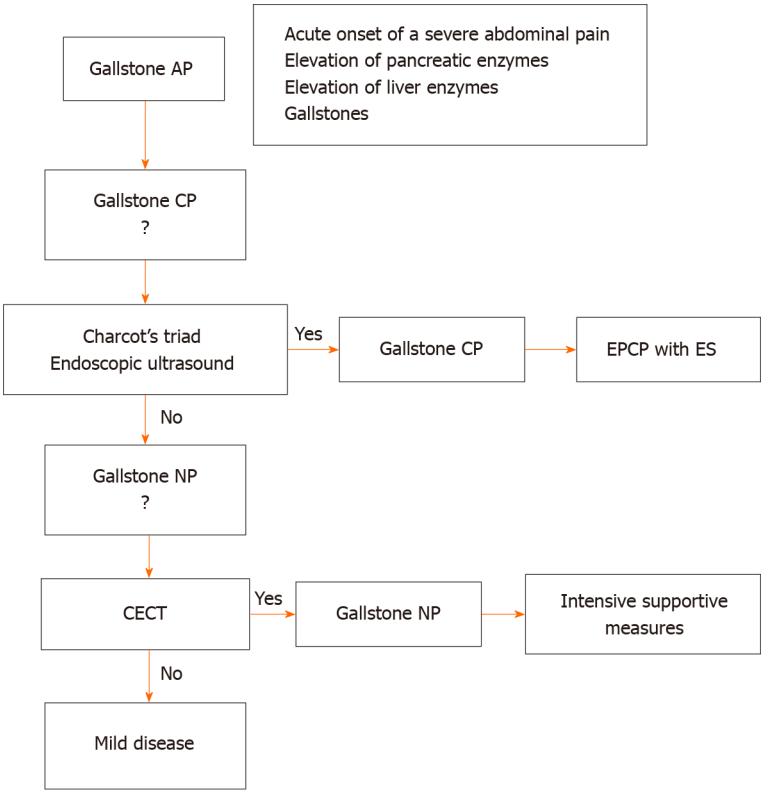

Figure 2 The algorithm for the diagnosis and initial treatment of gallstone pancreatitis. AP: Acute pancreatitis; CECT: Contrast-enhanced computed tomography; CP: Cholangiopancreatitis; ERCP: Endoscopic retrograde cholangiopancreatography; ES: Endoscopic sphincterotomy; NP: Necrotizing pancreatitis.

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MINIREVIEWS

Endoscopic ultrasonography-guided celiac plexus neurolysis in patients with unresectable pancreatic cancer: An update

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Abstract

Pancreatic cancer produces disabling abdominal pain, and the pain medical management for pancreatic cancer is often challenging because it mainly relies on the use of narcotics (major opioids). However, opioids often provide suboptimal pain relief, and the use of opioids can lead to patient tolerance and several side effects that considerably reduce the quality of life of pancreatic cancer patients. Endosonography-guided celiac plexus neurolysis (EUS-CPN) is an alternative for pain control in patients with nonsurgical pancreatic cancer; EUS-CPN consists of the injection of alcohol and a local anesthetic into the area of the celiac plexus to achieve chemical ablation of the nerve tissue. EUS-CPN *via* the transgastric approach is a safer and more accessible technique than the percutaneous approach. We have reviewed most of the studies that evaluate the efficacy of EUS-CPN and that have compared the different approaches that have been performed by endosonographers. The efficacy of EUS-CPN varies from 50% to 94% in the different studies, and EUS-CPN has a pain relief duration of 4–8 wk. Several factors are involved in its efficacy, such as the onset of pain, previous use of chemotherapy, presence of metastatic disease, EUS-CPN technique, type of needle or neurolytic agent used, *etc.* According to this review, injection into the ganglia may be the best technique, and a good visualization of the ganglia is the best predictor for a good EUS-CPN response, although more studies are needed. However, any of the 4 different techniques could be used to perform EUS-CPN effectively with no differences in terms of complications between the techniques,

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but more studies are needed. The effect of EUS-CPN on pain improvement, patient survival and patient quality of life should be evaluated in well-designed randomized clinical trials. Further research also needs to be performed to clarify the best time frame in performing a EUS-CPN.

Key Words: Pancreatic cancer; Endosonography; Celiac plexus neurolysis; Opioids; Echoendoscopy

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Core Tip: In this review, we analyzed the efficacy of the celiac plexus neurolysis through echoendoscopy (EUS-CPN) technique in patients with unresectable pancreatic cancer. The use of opioids for pain control are associated with numerous side effects that reduce the quality of life of pancreatic cancer patients, and the use of EUS-CPN is a safe and effective approach to pain management and allows for the reduction in the opioid doses used. There are different techniques to perform a EUS-CPN, all of which are described in this article. However, there are concerns about the efficacy of EUS-CPN (since it produces a reduction in pain for a short time), the ideal time to perform this technique is unknown, and it is also unknown whether this technique has any influence on patient survival and quality of life.

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INTRODUCTION

Pancreatic cancer is one of the solid tumors with the worst prognosis. Unfortunately, it is often diagnosed at an advanced stage of the disease, and only 12%–20% of cases are resectable at the time of diagnosis. Over 50% of patients with pancreatic cancer will not survive within the first year after diagnosis, and this disease has an overall five-year survival rate under 10%[1,2].

Chronic abdominal pain is a frequent symptom in patients with advanced pancreatic cancer due to the perineural invasion of tumor cells, and pain is present in 70%–90% of the patients at diagnosis and has very complex medical management[3,4].

Pain management in patients with pancreatic cancer usually begins with the administration of nonopioid analgesics followed by opioids in refractory cases. Opioids have many adverse effects, such as nausea, constipation, urinary retention, drowsiness, and patient tolerance or dependence.

Currently, many other therapeutic alternatives have been evaluated as complementary treatments, such as celiac plexus neurolysis (CPN) with various agents, which can be administered either percutaneously or transgastrically[5,6].

Pain originating in the intra-abdominal viscera, such as the pancreas, is transmitted by the afferent nerve fibers through the celiac plexus and finally reaching the central nervous system through the posterior root of the spinal cord at the level of T12-L2. The celiac plexus is a group of nerve fibers that converge into the celiac ganglia located in the retroperitoneum and is immediately adjacent to the anterolateral wall of the aorta at the origin of the celiac trunk. Traditionally, access to the celiac plexus has been percutaneous, and it is necessary to avoid the different structures located between the skin and the celiac plexus while performing a percutaneous access to the celiac plexus [5]. However, endosonography (EUS) allows the endosonographer to perform CPN close enough to the celiac plexus through the gastric wall, which could allow a safer and more effective access. EUS-CPN was first described by Wiersema *et al*[6] in 1996.

EUS-CPN is performed by the injection of a neurolytic agent directly into the celiac plexus, which causes an irreversible ablation. Pure ethanol is often used as the neurolytic agent in association with a local anesthetic agent, such as bupivacaine, and nociceptive afferent nerve fibers are blocked with these agents to achieve pain

reduction. EUS-CPN is performed to ameliorate pain and reduce the dose of analgesics in these patients, because the use of analgesics often causes a reduction in patient survival or quality of life.

In this review, we focused on patients with unresectable pancreatic cancer because pancreatic cancer is common and still affects a large number of cases. The options for pain management in these patients must be understood by all gastroenterologists and endoscopists. However, other pathologies, such as biliary tract tumors and patients with chronic pancreatitis, may require a CPN or celiac plexus block, respectively. Due to the large amount of evidence for the use of EUS-CPN in unresectable pancreatic cancer patients, we wanted to focus on this pathology to avoid performing such an extensive review and to focus on the management of chronic abdominal pain with this technique. We also wanted to further understand whether our interventions in this specific pathology have any impact on the survival and quality of life of patients.

INDICATIONS

EUS-CPN is performed in patients with chronic or uncontrolled abdominal pain associated with nonresectable pancreatic cancer; however, to ensure that EUS-CPN is effective, we must carefully select the patients who receive this technique. Current evidence does not precisely indicate when the best time is to perform an EUS-CPN[7].

EUS-CPN is useful in patients with uncontrolled pain or when the adverse effects of opioids reduce the patient's quality of life. Furthermore, other causes of pain must be investigated and ruled out prior to treatment, such as carcinomatosis, liver or bone metastases and peptic ulcers, because these conditions could lead to a partial or non-response to EUS-CPN.

CONTRAINDICATIONS

EUS-CPN should not be performed in patients with resectable pancreatic tumors because this technique may be difficult to perform, and it is mandatory to discuss borderline patients within a multidisciplinary team before performing a EUS-CPN. There are no absolute contraindications, but there are certain situations where a EUS-CPN should not be performed. The contraindications of EUS-CPN are shown in Table 1.

TECHNIQUE

Over the years, CPN has been performed *via* different techniques. It was initially described in 1914 as an intraoperative procedure[8], and since then, assistance with fluoroscopy, computed tomography or abdominal ultrasonography has been utilized [5]. In 1996, Wiersema described for the first time an endosonography-guided celiac plexus neurolysis (EUS-CPN) by a transgastric approach[6]. EUS-CPN allows for a more accurate and safer technique due to the use of color Doppler to avoid vessels that could be close to the needle path. It can be performed in an outpatient setting depending on the clinical status of the patient.

STEPS

Patient medical records must be reviewed to rule out previous surgeries or anatomical abnormalities and to evaluate the radiological images to study the location of the lesion, to evaluate for any possible infiltration of the celiac trunk and to determine if there is another pathology present.

The left decubitus position is the preferred position to perform a EUS-CPN. Deep sedation is also recommended for patients undergoing a EUS-CPN along with appropriately monitored anesthesia. The breathing rate, pulse oximetry, blood pressure and heart rate of the patients must be thoroughly monitored throughout the procedure.

The administration of at least 500 mL intravenous saline solution is needed before and after the procedure to minimize the risk of hypotension, as hypotension is one of the most common adverse effects after the procedure, only second to the hyperactivity

Table 1 Contraindications of endosonography-guided celiac plexus neurolysis

Absolute	Relative
Resectable pancreatic cancer	Esophagueal or gastric varices[21,26]
Coagulopathy (INR > 1.5)	Previous gastric surgery[2,14]
Low platelet count (< 50000 units)	Anomalies of celiac trunk[12]

of the parasympathetic nervous system[3,9-15].

The evidence is not clear regarding the administration of prophylactic antibiotics for EUS-CPN. Infectious complications due to EUS-CPN are rare, so most of the previous studies did not use prophylactic antibiotics[11-14].

An examination with radial echoendoscopy may be initially performed to explore the celiac trunk area. Then, a linear echoendoscope is introduced until reaching the origin of the celiac trunk, which is the first large vessel of the abdominal aorta just beneath the diaphragm. The diaphragm is a structure indirectly located by the visualization of the left diaphragmatic crus, 40–45 cm distal to the superior dental arch. Immediately under the celiac trunk is the origin of the superior mesenteric artery and the myenteric plexus (Figure 1).

The celiac plexus is located in the anterior wall of the aorta and is on both sides of the origin of the celiac trunk, and it is sometimes 1 mm above it or can sometimes be several millimeters below it (Figure 2). To locate this area, the echoendoscope should be rotated both clockwise and counterclockwise. The puncture area must be carefully selected, and before introducing the needle, it is recommended to use color Doppler in the target area of the puncture to make sure there are no vascular structures in the path of the needle.

TYPE OF NEEDLE

Any EUS needle may be used, as previous demonstrated in several studies, and these needles can range from small caliber needles, such as 25-gauge needles, to larger caliber needles, such as 19-gauge needles. Certainly, the use of a larger caliber needle will allow for an easier injection of substances.

One specific needle was designed for this technique: it is a 20-gauge needle with a dumpling pattern and conical tip [EchoTip® Ultra Celiac Plexus Neurolysis Needle, Cook Medical, Limerick (Ireland)], which allows the injection to be sprayed in a radial and uniform way and allows for adequate diffusion of the substance into the celiac plexus (Figure 3).

When the puncture area is selected, the needle must be primed with local anesthetic (usually bupivacaine or lidocaine) to avoid the injection of air into the puncture area.

Once the needle has been introduced, aspiration to confirm negative pressure must be performed to make sure that the needle was not placed into a vessel prior to injecting the substance, because the injection of these substances in a blood vessel wall or into the systemic circulation can be critical and life threatening.

NEUROLYTIC AGENT

Usually, the average injected volume of 0.25% bupivacaine is 10 to 20 mL, followed by 10 to 20 mL of 98% alcohol, although these quantities may vary slightly depending on the study. Optionally, some contrast agents can be used, even though the use of these is not clear. Ishiwatari *et al*[16] compared the use of phenol as compared to ethanol as a neurolytic agent and found no differences in pain control or complications.

TYPE OF APPROACHES

The different approaches for EUS-CPN are showed in Figure 4.

Bilateral approach/technique[6,17], once the celiac trunk has been located, the objective of this approach is to inject substances on both sides of it. It is recommended to make slow and rotatory clockwise movements without losing the longitudinal axis

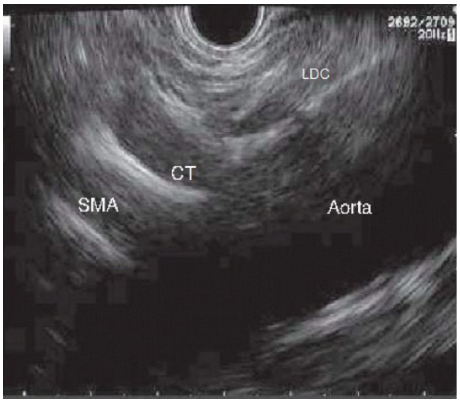

Figure 1 Sagittal plane of the aorta where we can see left diaphragmatic crus, celiac trunk and superior mesenteric artery emerging from Aorta. SMA: Superior mesenteric artery; LDC: Left diaphragmatic crus; CT: Celiac trunk.

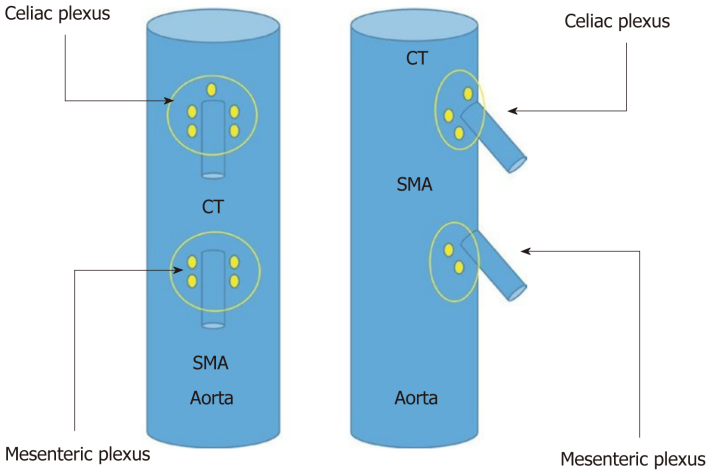

Figure 2 Schematic vision (frontal and lateral) of the situation of celiac and mesenteric plexus. SMA: Superior mesenteric artery; CT: Celiac trunk.

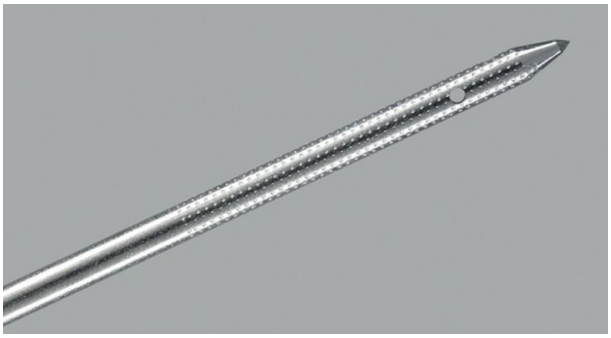

Figure 3 Specific needle designed for endosonography-guided celiac plexus neurolysis (Cook Medical, Limerick, Ireland).

of the aorta. With these movements, we are able to see the "injection windows", as shown in Figure 5.

Central approach/technique[9,10] is begun from the starting position at the origin of the celiac trunk and without losing the longitudinal axis of the aorta, the injection is performed in a cranial plane from the starting position, as shown in Figure 6.

Broad approach/technique was first described in 2010 by Sakamoto *et al*[18], and this approach is based on the injection of the substances above and on both sides of the origin of the superior mesenteric artery, without losing the longitudinal axis of the aorta, and by aiming for a broader diffusion of the neurolytic agent (Figure 5). In this technique, the needle reaches a greater depth; therefore, it is recommended to use a 25-

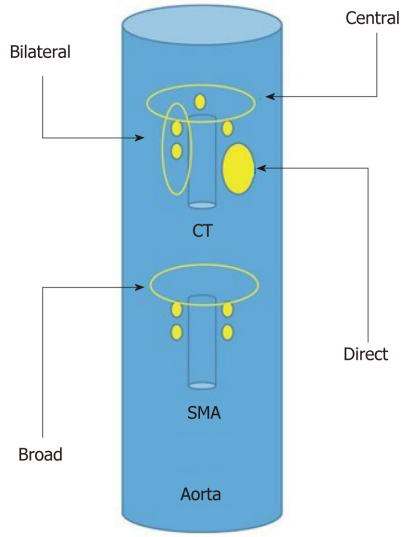

Figure 4 Schematic representation of the different endosonography-guided celiac plexus neurolysis approaches. SMA: Superior mesenteric artery; CT: Celiac trunk.

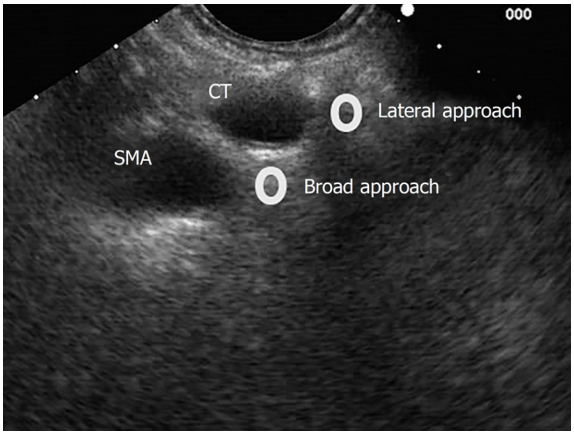

Figure 5 Lateral and broad approaches for endosonography-guided celiac plexus neurolysis. SMA: Superior mesenteric artery; CT: Celiac trunk.

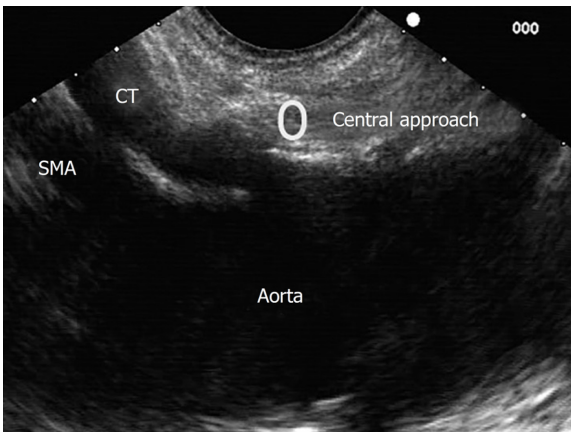

Figure 6 Central approach for endosonography-guided celiac plexus neurolysis. SMA: Superior mesenteric artery; CT: Celiac trunk.

gauge needle.

Direct approach/technique[11] is based on the direct injection of each celiac ganglia to distribute the alcohol and anesthetic doses. Celiac ganglia are sometimes visible as hypoechoic structures, which are almond shaped, are between 2 to 20 mm and are

usually located around the aorta at the origin of the celiac trunk. The right celiac ganglion is usually located 6 mm inferior to the origin of the celiac trunk, while the left celiac ganglion is located 9 mm below the origin of the celiac trunk. During the injection in the center of the ganglia, "ballonization" and an increase in volume will be seen. If this is not seen, the needle is probably misplaced.

AFTER THE PROCEDURE

Before extracting the needle, 3 mL of saline solution is injected to prevent the injection of ethanol into the path of the needle. If this injection of saline is not performed, it could result in the exacerbation of pain after the procedure. Patients should be monitored for at least two hours after the intervention, and the patient's blood pressure should be monitored.

RESULTS

The efficacy, study design, dose and type of neurolytic agent, follow-up and complications of EUS-CPN are summarized in Table 2[18-24].

EFFICACY OF CPN

Several studies have been performed to evaluate the efficacy of EUS-CPN. Globally, there has been a great variability shown in the efficacy of this technique for pain control associated with pancreatic cancer. The range of efficacy varies from 50% to 94% in the previous studies[6,7,9-11,13-19,23,24].

However, the available current literature has limitations due to the different quality of the studies (some of them are retrospective), and they differ in the injection technique, type and volume of neurolytic agent, number of patients and follow-up. In addition, the definitions for categorizing pain control vary in the different studies: improvement or resolution of pain, reduction of the Visual Analogue Scale (VAS) or Likert scale, reduction of the dose of opioids, *etc*.[6,7,9-11,13-19,23,24].

EUS-CPN was first performed by Wiersema *et al*[6] with an efficacy of 88% in 30 patients over 10 wk. In the first clinical trial, Wyse *et al*[7] randomized 96 patients with unresectable pancreatic cancer to either early treatment with EUS-CPN or a conventional medical treatment with analgesics and opioids. Clinical significance was observed with a reduction of 28% and 60% in the Likert scale at 4 and 10 wk of follow-up, respectively. A reduction in the dose of analgesics was also observed.

Momentary efficacy was observed in four systematic reviews and three meta-analyses. The studies demonstrated a reduction in pain in more than 50% of the patients during the 4–8 wk follow-up[15,25-27]. In addition, one of the systematic reviews concluded that pain control allowed for a reduction in the opioid dose with significantly fewer adverse effects in the treated group ($P < 0.0001$), but this was during the short term.

Based on this evidence, we can conclude that EUS-CPN significantly reduces the pain associated with pancreatic cancer (but does not make the pain disappear completely) and can reduce the dose of opioids[7,23,25,26]. The combination of an EUS-CPN plus analgesic opioids could be superior to opioid therapy alone[7]. However, this should be demonstrated in randomized clinical trials (RCTs) to further validate these findings[26,28].

IMPACT OF CPN ON QUALITY OF LIFE AND SURVIVAL

Current evidence supports the efficacy of CPN. However, the effect on the patient's quality of life is controversial, and there is no effect on survival. Changes in the quality of life were measured with different QOL scores Digestive Disease Questionnaire-15 [7].

On the one hand, Wyse *et al*[7] observed that the addition of EUS-CPN to the treatment regimen had no outcomes effect on the quality of life in patients. Lu *et al*[25] found in a their systematic review that EUS-CPN significantly reduced significantly the dose of opioids with a diminution of their adverse effects, but there wiwasth no

Table 2 Endosonography-guided celiac plexus neurolysis efficacy in current literature

Ref.	Design	*n*	Technique	Neurolytic agent	Pain control (follow up)	Complications
Wiersema *et al*[6]	Retrospective	30	Bilateral	3 mL bupivacaine (0.25%) + 10 mL ethanol (98%)	88% (10 wk)	Diarrhea 13.3%, Pain 3.3%
Gunaratnam *et al* [17]	Prospective	58	Bilateral	3-6 mL bupivacaine (0.25%) + 10 mL ethanol (98%)	78% (24 wk)	Pain 8.6%
Levy *et al*[11]	Retrospective	17	Direct	8 mL bupivacaine (0.25%) + 12 mL ethanol (99%)	94% (2-4 wk)	Hypotension 35%, pain 41% and diarrhea 16%
Sahai *et al*[9]	Prospective	160	Central *vs* Bilateral	10 mL bupivacaine (0.5%) + 20 mL ethanol	45.9% *vs* 70.5% (7 d). $P < 0.05$	Bleeding 0.7%
Sakamoto *et al* [18]	Retrospective	67	Broad *vs* bilateral	3 mL lidocaine (1%) + 9 mL ethanol (98%)	Mean VAS scores 3.9 *vs* 2.5 (7 d) and 4.8 *vs* a 3.4 (30 d) $P < 0.05$	None
Wyse *et al*[7]	RCT	48	Bilateral *vs* analgesia	10 mL bupivacaine (0.50%) + 20 mL ethanol	Likert scale reduction 28% (4 wk) + 60% (12 wk) $P < 0.05$	None
LeBlanc *et al*[10]	RCT	50	Central *vs* bilateral	20 mL lidocaine (0.75%) + 10 mL ethanol (98%)	69% *vs* 81% (61.9%)(14wk)	Hypotension 2% pain 36%
Iwata *et al*[19]	Retrospective	47	Central, direct or bilateral	2-3 mL bupivacaine + 20 mL ethanol	68% (7 wk)	Hypotension 17%, diarrhea 23% and inebriation 8%
Ascunce *et al*[20]	Retrospective	64	Bilateral	10 mL lidocaine (1%) + 20 mL ethanol (98%)	50% (1 wk). OR 15.61 of response if celiac ganglia was detected	Hypotension 2%, pain 2% and diarrhea 23%
Wiechowska-Kozłowska *et al* [12]	Retrospective	29	Central *vs* bilateral	2 mL lidocaine (2%) + 20 mL ethanol (98%)	86% (1-2 wk)	Hypotonia 3.4%, pain 6.9% and diarrhea 10.3%
Téllez-Ávila *et al* [21]	Retrospective	53	Central *vs* bilateral	10 mL lidocaine (1%) + 10-20 mL ethanol (98%)	48% *vs* 56% (4 wk)	Transitory pain 0% *vs* 3%
Seicean *et al*[22]	Retrospective	32	Central	10 mL lidocaine (1%) + 10-15 mL ethanol	75% (2 wk)	None
Doi *et al*[13]	RCT	68	Direct *vs* central	1-2 mL bupivacaine (0.25%-0.5%) + 10-20 mL ethanol	73.5% *vs* 45.5% (7 d) $P < 0.05$	Hypotension 2.9% *vs* 6%, pain 29.4% *vs* 21.2% and diarrhea 5.9% *vs* 9.1%. No diferences
Ishiwatari *et al* [16]	Retrospective	22	Direct or bilateral	1-2 mL bupivacaine (0.5%) + 40-60 mL ethanol or 20-25 mL fenol	83% (fenol) *vs* 69% (ethanol) (7 d)	Diarrhea 9%, hypotension 4.5%, pain 4.5% and inebriation 4.5%
Hao *et al*[23]	Retrospective	41	Central or direct	10 mL bupivacaine (2%) + 20 mL ethanol	Pain < 3 mo improve 84% (3 d), 96% (7 d) and 68% (90 d). Pain > 3 mo improve 75% (3 d), 81% (7 d) and 50% (90 d)	Hypotension 4.9%
Minaga *et al*[14]	Retrospective observational	112	Broad ± direct	3 mL lidocaine (1%) + 9 mL ethanol (98%)	Pain improvement 77. 7% (1 wk)+ 67.9% (4 wk)	Inebriation 8%, hypotension 4.5%, pain 3.6% and diarrhea 3.6%
Levy *et al*[24]	RCT	110	Direct *vs* bilateral	4 mL bupivacaine (0.25%) + 20 mL ethanol (99%)	Pain improvement 46.2% *vs* 40.4%. No changes on quality of life	Hypotension 11.7% *vs* 20%, diarrhea 10% *vs* 12.2%. Pain 8.3% *vs* 44.9% ($P < 0.05$)

VAS: Visual analogue scale. RCT: Randomized clinical trial.

differences in terms of quality of life.

On the other hand, Seicean *et al*[22] found little improvement in some factors associated with quality of life, such as the functional status or sleep quality, and there was no change in the acceptance of the disease and enjoyment of life.

Current evidence has not shown any clinical significance in terms of survival to recommend an EUS-CPN[7,26]. Although it has not been demonstrated that EUS-CPN significantly improves the quality of life of patients, the reduction of adverse effects associated with opioids could have some impact on the quality of life of these patients, which can be important[22,26].

PREDICTORS OF RESPONSE

CPN is usually performed as a palliative treatment in patients refractory to common analgesics. However, since Wiersema *et al*[6] performed the first EUS-CPN, they found that patients who had not received previous chemotherapy had significantly greater pain relief than patients who received chemotherapy.

It is known that chemotherapy improves the patient's pain and quality of life[7,24]. Patients who received chemotherapy before EUS-CPN could be impacted by the effect of the technique. In fact, as concluded by Wyse *et al*[7], pain improvement was seen earlier in patients who had not received previous chemotherapy than in patients who did receive chemotherapy.

In a different study, Hao *et al*[23] observed a significant improvement in the pain scales of the patients who had an onset of pain earlier than 3 mo, and an improvement of pain was then observed in both the short and long terms.

The best time to perform an EUS-CPN remains unclear[7]. It could be possible that a delay in performing an EUS-CPN or its application in patients who have received other treatments for pain control could decrease the efficacy of the EUS-CPN; however, there is not enough evidence to support this theory[7,17,21].

Few studies have also compared the different techniques of EUS-CPN[9,12,14,15,23,26]. Iwata *et al*[19] observed that the direct invasion of the celiac plexus and the distribution of ethanol on only the left side of the artery negatively influenced pain control [13].

A retrospective study by Ascunce *et al*[20] evaluated the efficacy of the bilateral technique. They concluded that the direct visualization of the celiac ganglia while performing a EUS-CPN (which needed to be referenced in the endoscopic report) was a good predictor of the response (OR 15.61).

BILATERAL *VS* CENTRAL TECHNIQUE

As mentioned above, there are several techniques for performing a EUS-CPN. We reviewed those studies that compared the different techniques to analyze which technique may be the most effective and that had fewer adverse effects[9,13,14,18,21,24].

On the one hand, bilateral and central techniques have shown comparative outcomes in a few studies[10,25,26], and the only exception was in a study performed by Sahai *et al*[9] in 2009. The bilateral approach improved the pain control compared to the central technique (70.5% *vs* 45.9%; $P < 0.05$), but the effect lasted only one week.

On the other hand, in a meta-analysis published in 2009, a subgroup analysis was performed that evaluated the different approaches that were performed. The bilateral approach was more effective than the central technique in terms of pain control (84.5% *vs* 45.9%; $P < 0.05$)[15].

Finally, one more recent meta-analysis of 437 patients concluded that comparable pain control was obtained with both approaches; however, the bilateral approach significantly reduced the dose of opioids compared to the central technique[25].

GANGLIA INJECTION

Direct injection of neurolytic agents into the ganglia has been demonstrated to be effective for pain relief associated with pancreatic cancer. The rate of effectiveness has varied from 65% to 94% in different studies,[11,13,14] and one of these studies was a clinical trial. Doi *et al*[13] demonstrated significant pain relief with the injection directly into the ganglia compared to the central approach, but the injections were only beneficial for one week (73.5% *vs* 45.5%).

Despite having good results in several studies, other studies have been published that have shown some concerns regarding this technique.

Levy *et al*[24] published a randomized double blind clinical trial comparing direct ganglia injection to central CPN, and no differences were found in pain control or in improving the quality of life with either technique. However, the median survival was significantly higher in patients treated with direct ganglia injection (10.5 mo *vs* 5.6 mo), particularly for patients with nonmetastatic disease.

Recently, Koulouris *et al*[28] performed a systematic review and meta-analysis on the efficacy of three EUS-CPN techniques on pain control: central, bilateral and ganglia injection. Pain control was achieved in 68% of the patients at week 2 and 53% of the

patients at 4 wk of follow-up. There was no difference between the techniques in terms of age, sex, tumor localization, stage or baseline pain before the intervention. Major bias could have been present in this review, because low-quality studies were included (not randomized studies), the measurement of treatment response was different, and the influence of other treatments (opioids or chemotherapy) was not evaluated in this study. However, no differences in the complications between the techniques were found.

CPN OVER THE MESENTERIC ARTERY (BROAD TECHNIQUE)

Few studies have evaluated the broad technique or have compared it to the other techniques. Sakamoto *et al*[18] compared the broad CPN technique against the bilateral technique, and this study showed that there was better pain control with the broad approach at 7 and 30 d of follow-up. There were no differences in the adverse events. Another study comparing the broad CPN technique against the broad CPN plus direct ganglia injection technique showed significantly better pain control with the combination of both techniques (OR 3.69 in the 1st week and OR 6.37 in the 1st month) [14]. Adequate pain management has been obtained by this approach of using both techniques, but more studies are needed to confirm these findings.

COMPLICATIONS

EUS-CPN is described as a safe procedure[6,7,9-11,13-19,23,24]. A total of 44% of complications have been reported, but most of them have been minor and transient. Diarrhea and interim hypotension are frequently observed due to the parasympathomimetic response. Pain exacerbation is another common adverse effect (8%) associated with ethanol injection. Transient inebriation was observed in three Japanese studies [13,14,16].

Major complications have been reported in less than 1% of patients; however, these patients frequently have fatal outcomes. Infection, bleeding, retroperitoneal abscesses, paraplegia and ischemia have been previously reported in the literature[29-34]. Usually, these complications are associated with an incorrect injection site of the neurolytic agent. EUS-CPN must be performed by expert endoscopists and at hospitals with a high volume of procedures.

NEW TECHNIQUES OF EUS-CPN

Recently, other techniques of EUS-CPN have been described with encouraging results. In 2012, Wang *et al*[35] achieved a EUS-CPN by the insertion of a radioactive seed, I^{125}, directly into the celiac ganglia. Twenty-three patients were included in this study, and there was a significant reduction in pain control and the dose of opioids.

In 2015, Facciorusso *et al*[36] suggested in a case report that the use of an EUS-CPN associated with the injection of ethanol directly into the tumor could enhance the effects of neurolysis; however, more studies of this approach are needed to confirm the results. Recently in 2019, Bang *et al*[37] published that an EUS-CPN could be performed with a radiofrequency ablation of the celiac ganglia. Twelve patients were included in this study, and they compared this technique against the traditional EUS-CPN. Radiofrequency ablation obtained better results not only regarding the pain associated with pancreatic cancer, but there was also an improvement in the quality of life scales. However, more studies are needed to validate these approaches.

CONCLUSION

EUS-CPN is a safe and effective therapeutic alternative for short-term pain control in unresectable pancreatic cancer patients. It can allow for a dose reduction of opioids, which are responsible for serious adverse effects that reduce the quality of life of these patients. However, an improvement in patient survival or quality of life after using an EUS-CPN has not been demonstrated in the current literature.

The strengths of our review are the large number of studies collected (many of them are clinical trials) with an acceptable number of patients, and many studies have demonstrated favorable results in the use of EUS-CPN in these patients, even though this technique has been performed by expert endoscopists in centers with a high volume of patients. We also present a scheme for performing this technique that shows a good applicability, and most of the complications of this technique are minor and preventable. There are several techniques for performing an EUS-CPN, all of which are valid, and the most commonly used technique is the central technique, which is known by all expert endoscopists in this field and is the technique we currently perform in our centers.

Therefore, we can conclude that the best predictor for a good response could be the celiac ganglia visualization during the EUS-CPN technique. However, any of the 4 different techniques could be offered to effectively perform an EUS-CPN with no differences in complications between the techniques based on this review.

According to this review, a universal pain reduction scale should be used to design further research and to prevent heterogeneity of the results among the studies. EUS-CPN must be performed by expert endosonographers to achieve the best approach and to have a good outcome from this technique as well as to avoid serious adverse events.

Further research is needed to clarify when to perform an EUS-CPN and whether it should be included as a first-line therapy in addition to traditional medical treatment, whether it should be performed as a prevention prior to chemotherapy or if it should be reserved for patients with uncontrolled pain that is refractory to major opioids. Well-designed RCTs are required to evaluate the improvement of pain, survival and quality of life in these patients.

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MINIREVIEWS

Tips and tricks for the diagnosis and management of biliary stenosis-state of the art review

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Abstract

Biliary stenosis may represent a diagnostic and therapeutic challenge resulting in a delay in diagnosis and initiation of therapy due to the frequent difficulty in distinguishing a benign from a malignant stricture. In such cases, the diagnostic flowchart includes the sequential execution of imaging techniques, such as magnetic resonance, magnetic resonance cholangiopancreatography, and endoscopic ultrasound, while endoscopic retrograde cholangiopancreatography is performed to collect tissue for histopathological/cytological diagnosis or to treat the stenosis by insertion of stent. The execution of percutaneous transhepatic drainage with subsequent biopsy has been shown to increase the possibility of tissue diagnosis after failure of the above techniques. Although the diagnostic yield of histopathology and imaging has increased with improvements in endoscopic ultrasound and peroral cholangioscopy, differential diagnosis between malignant and benign stenosis may not be easy in some patients, and strictures are classified as indeterminate. In these cases, a multidisciplinary workup including biochemical marker assays and advanced technologies available may speed up a diagnosis of malignancy or avoid unnecessary surgery in the event of a benign stricture. Here, we review recent advancements in the diagnosis and management of biliary strictures and describe tips and tricks to increase diagnostic yields in clinical routine.

Key Words: Biliary stenosis; Cholangioscopy; Metal stent; Endoscopic ultrasound; Endoscopic ultrasound-guided fine needle aspiration; Biliary stenosis treatment

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Core Tip: Biliary stenosis remains a diagnostic and therapeutic challenge due to the difficulty in obtaining a tissue diagnosis to differentiate a malignant from a benign stricture. The diagnostic and therapeutic workup of patients with a suspected malignant biliary stricture should be discussed at a multidisciplinary team meeting in a tertiary center. The use of all available diagnostic tools such as magnetic resonance cholangiopancreatography, endoscopic retrograde cholangiopancreatography, endoscopic ultrasound-fine needle aspiration, and cholangioscopy should be evaluated to avoid unnecessary surgery or a delay in diagnosis. Here, we focus on the most recently published findings regarding the diagnosis and therapy of biliary stricture.

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INTRODUCTION

A biliary stricture (BS) is a narrowing of the biliary tree caused by benign or malignant conditions. Differential diagnosis between the different forms of BS can be challenging, as the etiology may remain indeterminate even after carrying out complete laboratory, imaging, and tissue-based diagnostic investigations[1]. Despite improvements in endoscopic techniques and a greater knowledge of the underlying causes of the condition acquired over the last decade, about 15%-20% of patients with indeterminate BS undergoing surgery are found to have a benign disease, with high postoperative mortality (10%) reported in many Western referral centers[1-4]. Patients with indeterminate BS or a diagnosis of indeterminate dysplasia at histopathological evaluation require a multidisciplinary approach involving gastroenterologists, surgeons, radiologists, and oncologists for diagnosis and appropriate treatment.

ETIOLOGY

Most cases of BS are malignant BS (MBS) due to pancreatic adenocarcinoma, cholangiocarcinoma (CC), liver metastases, hepatocellular carcinoma, ampullary carcinoma, or gallbladder carcinoma. Rare causes of MBS are lymphoma and metastases to regional lymph node (RLN)s. Benign BS (BBS) accounts for up to 30% of all BS and may have a different etiology, although most are iatrogenic caused by biliary damage during surgery (*e.g.*, post-laparoscopic cholecystectomy) or after liver transplantation (stenosis of biliary anastomosis). Chronic pancreatitis and autoimmune pancreatic/biliary disease can also induce BBS[4] (Table 1).

DIAGNOSTIC WORKUP

The choice of the most appropriate diagnostic and therapeutic pathway is based on the localization of the stricture in the biliary tract. The commonly used Bismuth-Corlette classification[5] distinguishes five types of BS: type I – limited to the common hepatic duct, below the level of the confluence of the right and left hepatic ducts; type II – involving the confluence of the right and left hepatic ducts; type III – (1) Extending to the bifurcation of the right hepatic duct; or (2) Extending to the bifurcation of the left hepatic duct; type IV – extending to the bifurcations of both right and left hepatic ducts or with multifocal involvement; type V – a stricture at the junction of the common bile duct and cystic duct.

Table 1 Etiology of benign biliary stenosis

Iatrogenic	Post-cholecystectomy
	Post-liver transplantation (anastomotic, non-anastomotic)
	Hepaticojejunostomy anastomotic strictures
Autoimmune disease	Primary or secondary sclerosing cholangitis
	Autoimmune cholangitis (IgG4-related)
	Autoimmune pancreatitis
Chronic disease	Pancreatitis
	Choledocholithiasis
	Sarcoidosis
Infectious disease	Recurrent cholangitis, HIV cholangiopathy, tuberculosis
Ischemic disease	
Abdominal trauma	

HIV: Human immunodeficiency virus; IgG: Immunoglobulin G.

First step: Clinical presentation and biochemical parameters

Patients with BS are rarely asymptomatic; the most common clinical presentation is jaundice. Weight loss, fever, nausea, vomiting, pruritus, dark urine, discolored stool, and anorexia can also be present. Clinical history and symptoms are only in part useful for differential diagnosis as they may be similar in both benign and malignant forms of BS.

Biochemical parameters are not unequivocally indicative of the nature of BS, although increased levels of bilirubin, alkaline phosphatase, and alanine transaminase are considered strong predictors of malignancy[3,6]. Normal bilirubin associated with increased transaminases may also be suggestive of malignant disease, while normal bilirubin levels and normal liver function tests are unlikely to be indicative of primary biliopancreatic neoplasia[7]. Elevated levels of alkaline phosphatase, gamma glutamyl transpeptidase, carbohydrate antigen 19-9 (CA19-9), and carcinoembryonic antigen were associated with MBS in a multivariate analysis[8].

Among serum biomarkers, CA19-9 is the most common and validated tumor marker, showing high sensitivity and specificity for the diagnostic assessment of pancreatic cancer and seems to be useful in the early detection of this disease[9-11]. Diagnostic accuracy of CA19-9 in the diagnosis of pancreatic neoplasia is increased when associated with the assessment of CA242, which displays a high sensitivity (89%, 95% confidence interval (CI): 80%-95%) without impairing specificity (75%, 95%CI: 67%-82%)[10]. In CC, the sensitivity and specificity of CA19-9 are 72% and 84%, respectively[12]. CA19-9 showed variable diagnostic power among European, Asian, and American populations, possibly related to different genetic factors, cut-off value range, and assay method in the different studies[12]. However, it should be remembered that Lewis negative blood type patients (5%-10% of the Caucasian population), who cannot synthesize CA19-9, may have false-negative results[11]. False-positive cases may be due to other medical conditions, both benign and malignant, responsible for increased CA19-9 levels, such as acute diabetes, cholangitis, pancreatitis, obstructive jaundice, liver cirrhosis, and hepatocellular, ovarian, bronchial, colon, and gastric cancers[11].

New biomarkers, including glypican-1, microRNA, macrophage inhibitory cytokine 1, and osteopontin, have been studied for their diagnostic, predictive, and prognostic potential, but none have as yet been sufficiently validated for use in routine clinical settings[1,11,13].

Tips: Liquid biopsy

As a non-invasive molecular diagnostic tool, liquid biopsy has been attracting increasing attention for its promising application in cancer patients. This technique is based on the analysis of circulating free DNA, circulating tumor cells, circulating cell-free RNA, and circulating tumor DNA (ctDNA) and is expected to have a major impact on cancer diagnosis and management. Although available data regarding

circulating tumor DNA analysis in biliary tract tumors are limited, the evaluation of circulating tumor DNA may prove to have considerable application in diagnosis, monitoring of response to chemotherapy, and possible target therapy[14]. Liquid biopsy of bile is emerging as a promising option for the molecular diagnosis of MBS, as several bile biomarkers including proteins, metabolites, and microRNAs have been described. Selected reaction monitoring is a flexible high-throughput analytical approach based on targeted mass spectrometry used to quantify cancer biomarkers in human bile. The selected reaction monitoring assay was able to simultaneously quantify 31 peptides in human bile, indicating that the evaluation of cancer-related bile protein allows differentiation between MBS and BBS. The use of bile biomarkers in combination with serum CA19-9 was found to be highly accurate for the diagnosis of MBS and was proposed as an adjunctive technique in clinical practice[15].

Second step: Imaging and histopathological assessment

Cross-sectional imaging: Transabdominal ultrasound is a highly sensitive (> 90%) first-level technique able to detect indirect signs of BS, such as dilation of the distal tract and the intrahepatic branches. Transabdominal ultrasound is very useful as a screening test in the case of suspected biliary obstruction but has very low sensitivity in detecting strictures or masses[3,4,16].

Other non-invasive imaging techniques available to define the extension of and differentiate between BBS and MBS are multidetector computed tomography (MDCT), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), and positron emission tomography (PET). The diagnostic flowchart currently used in the differential diagnosis of BS includes MDCT and/or MRI plus MRCP, and occasionally PET as the standard imaging methods for preoperative assessment of suspected MBS. The choice of specific imaging techniques for evaluating and staging MBS depends on tumor localization (distal or intrahepatic biliary tract) and origin (primitive biliary or pancreatic). Since there is no single ideal imaging modality, a multimodality approach is frequently adopted in potential candidates for surgery[17-19] (Figure 1).

MDCT is a routine imaging investigation for the preoperative assessment of intrahepatic and extrahepatic stenosis. MDCT provides a comprehensive evaluation of the primary tumor and adjacent structures, such as hepatic artery or portal and superior mesenteric vein as well as of the whole abdomen, to exclude potential metastasis. Diagnostic accuracy in characterizing stricture extent is low, ranging from 75% to 90%. Recently, intraprocedural cone-beam computed tomography (CT) has proven to be effective in the three-dimensional characterization of BS. The pre-contrast phase is useful for detecting possible intraductal stones as cause of obstruction and in differentiating stones from tumors[16,18]. The arterial and venous post-contrast phase is able to identify the inflammatory/benign process of the suspected lesion and allows for an evaluation of the location and aspect of enhancement. In addition, delayed phases (usually 3-5 min after contrast medium injection) are helpful for the differential diagnosis of intrahepatic CC, which shows delayed phase enhancement due to its abundant fibrous stroma[18]. In a recent meta-analysis, MDCT demonstrated a pooled sensitivity of 89% and specificity of 92% for the detection of portal vein and hepatic artery involvement in perihilar CC[19]. The diagnostic accuracy of MDCT is 75%-92% for the longitudinal tumor extent of perihilar CC and 60%-88% for resectability due to underestimation of the proximal extent of the tumor. CT cholangiography imaging obtained with multiplanar reconstruction and minimum intensity projections was recently proposed as an alternative to MRCP for BS assessment, especially in patients with contraindication to MRI[20].

Due to the lack of associated ionizing radiation and the possibility of obtaining high-quality imaging of the biliary tract, MRI and MRCP are the techniques of choice in the diagnosis of BS, with high sensitivity in detecting the precise site and length of the stenosis but low sensitivity in differentiating malignant from benign strictures. The use of hepatocyte-specific MRI agents and diffusion-weighted imaging proved useful in tumor characterization[19]. MRI with MRCP is the method of choice in the case of suspected perihilar CC. MRCP has a high sensitivity in detecting BS (up to 98%), with a reported sensitivity and specificity in differentiating between malignant and benign forms ranging from 38% to 90% and from 70% to 85%, respectively. In addition, MRCP has high accuracy (88%-96%) in predicting the extent of bile duct involvement in MBS [4,16-19]. MRI can include two-dimensional and three-dimensional MRCP. Two-dimensional MRCP is performed in a single section of 4-8 cm thickness during breath holds and is less affected by motion artifacts, as it allows rapid acquisition. However, it may not reveal intraductal lesions due to the partial volume averaging artifact. In contrast, three- dimensional MRCP provides an excellent overall visualization of the

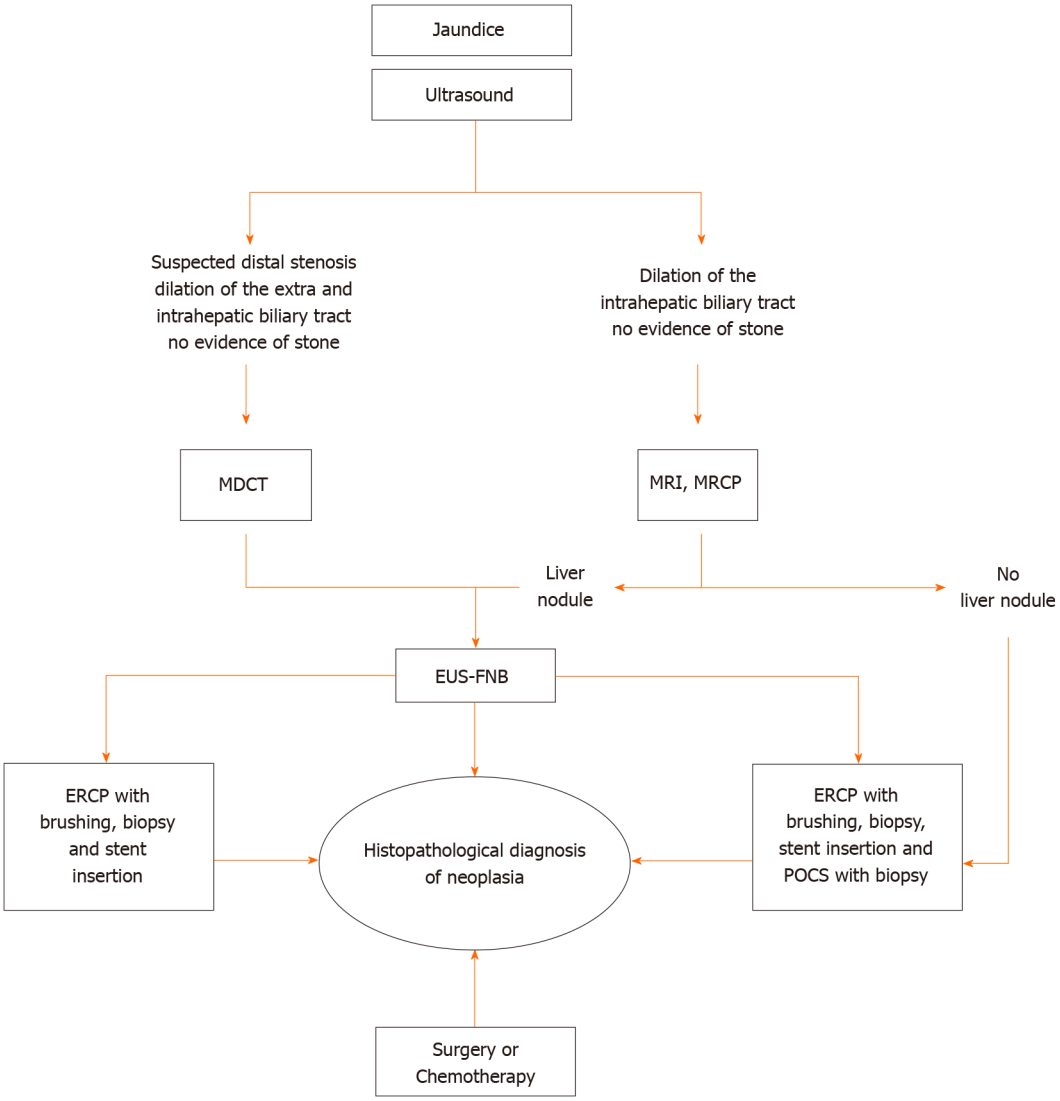

Figure 1 Algorithm of imaging investigations in biliary stenosis. MDCT: Multidetector computed tomography; MRI: Magnetic resonance imaging; MRCP: Magnetic resonance cholangiopancreatography; EUS-FNA: Endoscopic ultrasound-fine needle aspiration; ERCP: Endoscopic retrograde cholangiopancreatography; POCS: Peroral cholangioscopy.

biliary tree and an enhanced delineation of fine anatomical structures and small pathological features. Acquisition time is long, however, making it more susceptible to motion artifacts[19].

PET/CT is useful in the case of suspected distant metastasis or nodal metastases. In patients with resectable MBS, PET may help in the selection of candidates for surgery [19-21]. Dual-time-point fluorine-18 fludeoxyglucose integrated with PET/CT scan (18F- FDG PET/CT) was found to be effective in differentiating between BBS and MBS [20], although inflammation of the biliary tract or the presence of mucinous CC may cause false-positive and false-negative results[19]. The diagnostic power of 18F-FDG PET/CT for the diagnosis of primary tumor, lymph node invasion, and distant metastases was evaluated in a systematic review and meta-analysis of 2125 patients [22]. The study confirmed 18F-FDG PET/CT as a useful diagnostic tool in selected cases, as it provides valuable information in patients with indeterminate BS. 18F-FDG PET/CT changed the treatment plan in almost 20% of previously defined resectable MBS, avoiding unnecessary non-curative resection[22]. However, the routine use of 18F-FDG PET/CT as an imaging tool in tumor diagnosis remains controversial due to its low specificity (51%).

Tips: PET/MRI

Whole-body 18F-FDG-PET/MRI seems to hold great promise because of its ability to diagnose and stage potentially resectable MBS, providing in a single examination both MRI and PET information[19].

Tricks: Differential diagnosis using contrast-enhanced CT or MRI

The length of the involved biliary tract and contrast-enhanced morphological features are useful to differentiate BBS from MBS. Segmental involvement > 12 mm and thickening > 1.5 mm associated with luminal irregularity, asymmetry, and incremental enhancement may indicate the presence of MBS[18].

ENDOSCOPIC/RADIOLOGICAL IMAGING

Endoscopic retrograde cholangiopancreatography (ERCP) is the standard technique used to evaluate BS, as it combines the radiological imaging of cholangiography and the possibility of obtaining a histopathological diagnosis by multimodal sampling (guided brushing, biopsy, or bile aspiration). ERCP generates high-resolution fluoroscopic images that provide information regarding stricture site, length, and presence of irregularity of the biliary wall. Although fluoroscopic imaging has an accuracy of 80% in distinguishing a benign from a malignant stricture, tissue sampling by biliary brushing or endoluminal biopsy is required to histologically confirm the differential diagnosis.

Brush cytology is a simple tool with minimal adverse events but with very low sensitivity. Endoluminal forceps biopsy (Figure 2) requires sphincterotomy, which may be challenging to perform especially in the case of strictures above the bifurcation of the common bile duct. Standard ERCP with brushing has a 26%-73% sensitivity in the detection of malignancy[23]. The overall diagnostic yield of histopathological diagnosis ranges from 6% to 70%[24,25]. In a systematic review and meta-analysis, the pooled sensitivity reported for brush cytology and forceps biopsy was 45.0% and 48.1%, respectively; combining the two methods increased sensitivity up to 59.4%[23]. To improve the diagnostic accuracy of histological/cytological sampling during ERCP, Lee *et al*[24] evaluated aspiration cytology plus brush cytology or brush cytology plus biopsy or aspiration cytology plus biopsy. In terms of cancer type (CC *vs* non-CC), diagnostic sensitivity was higher for CC in the brush cytology plus biopsy or aspiration cytology plus biopsy group than in the aspiration cytology plus brush cytology group (100% *vs* 69.4%, respectively; $P < 0.001$) but not for non-CC (57.1% *vs* 57.1%, respectively)[24].

False-negative samples may be attributable to histopathological interpretation, tumor characteristics, and procedural factors. The combination of transpapillary tissue sampling followed by brushing and bile aspiration by nasobiliary drainage seems to increase sensitivity up to 72% in the diagnosis of MBS[26].

Pneumatic dilatation of the stenotic tract before tissue sampling with large biopsy forceps was found in a retrospective study to improve sensitivity from 40% to 71% and diagnostic accuracy from 55% to 87% compared to biopsy sampling without dilatation, with no difference in complication rate between the two procedures[27]. Fluorescence in situ hybridization (FISH) is used to analyze brush cytology specimens for chromosomal abnormalities in malignant cells. Although FISH is able to detect chromosomal changes in 80% of malignant biliary neoplasia, the combination of cytology and FISH revealed a sensitivity for malignancy of only 50%-60% in BS. A triple modality approach combining brush cytology, forceps biopsy, and FISH resulted in a marked increase in sensitivity for the diagnosis of CC compared with single modality testing and should be considered in the evaluation of indeterminate BS[26].

Tricks

Tube-assisted biopsy: Following biliary cannulation, a 10 Fr Soehendra biliary dilatation catheter is advanced over a guidewire in the stenosis in the left biliary tree. The tube is then placed as close as possible to the stricture area and the guidewire removed. Conventional endobiliary biopsy forceps are inserted through the tube into the area of the stricture for tissue collection[28].

Endoscopic transpapillary biopsy using the "tunnel" technique: This technique consists of the use of an 11.5 Fr biliary dilatation catheter as a tunnel for biopsy forceps after cutting the tapered tip. Following biliary cannulation, the catheter is advanced over a 0.035-inch guidewire and a 6 Fr catheter in the left biliary duct, where the previously identified stenosis is located. Next, the guidewire and 6 Fr catheter are removed, and 7 Fr biopsy forceps inserted in the 11.5 Fr catheter to collect tissue[29].

Endoscopic transpapillary biopsy using the "zipline" technique: A looped nylon thread is added to one cup of a pair of forceps with 2 mm-wide cups; the loop is then

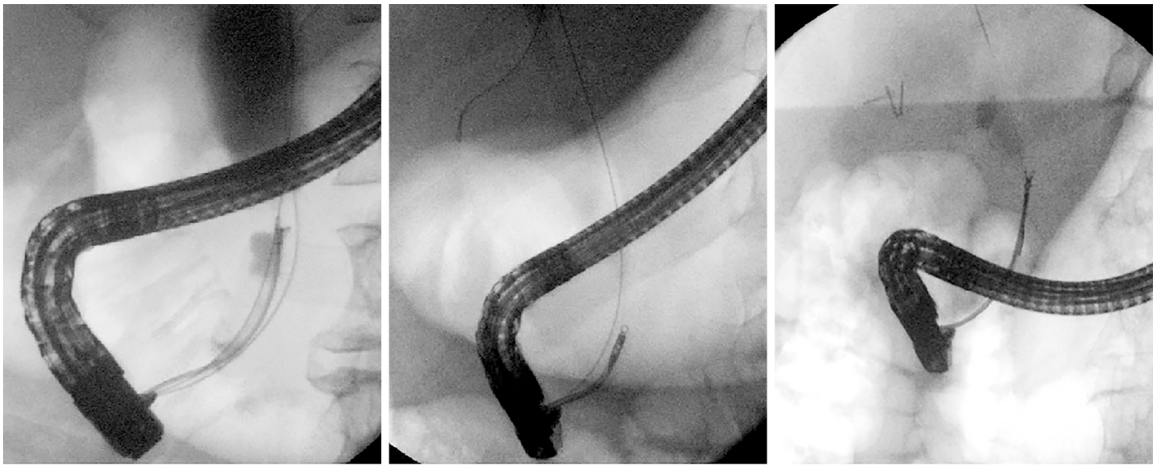

Figure 2 Three cases of patients with distal stenosis in which the diagnosis of cholangiocarcinoma was made by forceps biopsy during endoscopic retrograde cholangiopancreatography.

inserted over a guidewire and the forceps are advanced into the right bile duct[30].

Tips: How to improve ERCP histological results

Perform at least 10 brush passes under continuous fluoroscopy after meticulously preparing everything required for fixing the tissue sample in order to avoid contamination or air-drying artifacts. Combine different sampling methods and, if confident, perform brush and biopsy before and after stricture dilatation. Take at least four biopsy samples and work closely with the pathologist[31].

CHOLANGIOSCOPY

Direct visualization of the biliary tract by SpyGlass peroral cholangioscopy (POCS) system (Boston Scientific, Marlborough, Massachusetts) introduced in 2007[32] enhances

the diagnostic power of ERCP in patients with indeterminate BS by providing intraductal imaging of the stenotic duct or of the lesion suggestive of malignancy. Over the past two decades, three types of cholangioscopy platforms have become available. The most recently introduced is a digital single-operator cholangioscopy (D-SOC) ultra-slim endoscope inserted into the bile duct through the working channel of a duodenoscope and advanced into the papilla, providing excellent image quality achieved by image- enhanced endoscopy. Several studies demonstrated its high performance in the diagnosis of BS, with a > 70% sensitivity but < 50% specificity[33-35]. In a recent systematic review of published studies evaluating the diagnostic performance of any type of POCS, the sensitivity, specificity, and diagnostic accuracy of POCS for diagnosing MBS ranged from 38%-100%, 49%-100%, and 50%-100%, respectively, with a technical success rate of 82%-100%[34].

Although D-SOC allows viewing of the biliary tract from the inside, its use is limited by the high cost of the equipment and the lack of standardization in the interpretation of visual features of the biliary ducts. Endoscopic features defined as suggestive of MBS at cholangioscopy are nodular or papillary masses with irregular surface, fragile mucosa, and dilated and tortuous vessels (Figure 3). Kim *et al*[35] reported an association between the detection of tortuous vessels and malignancy with a sensitivity of 61% and specificity of 100%[35]. A recent meta-analysis on D-SOC in the visual interpretation of indeterminate BS reported a 94% sensitivity and 95% specificity, a diagnostic accuracy of 94%, a positive predictive value of 93%, and a negative predictive value of 98% in the diagnosis of MBS[36].

In a prospective study on 289 patients with indeterminate BS enrolled in 20 centers in Asia, the Middle East, and Africa, the use of two POCS systems (SpyGlass Legacy and SpyGlass DS digital system) was able to detect stricture/filling or bile duct defect in 98.6% of patients, providing a visual diagnostic impression in 87.2% and adequate biopsies in 92.9% of cases, with low rate of complication (1.7%)[37]. A limitation of this study was that it did not investigate patients with primary biliary disease. In two other

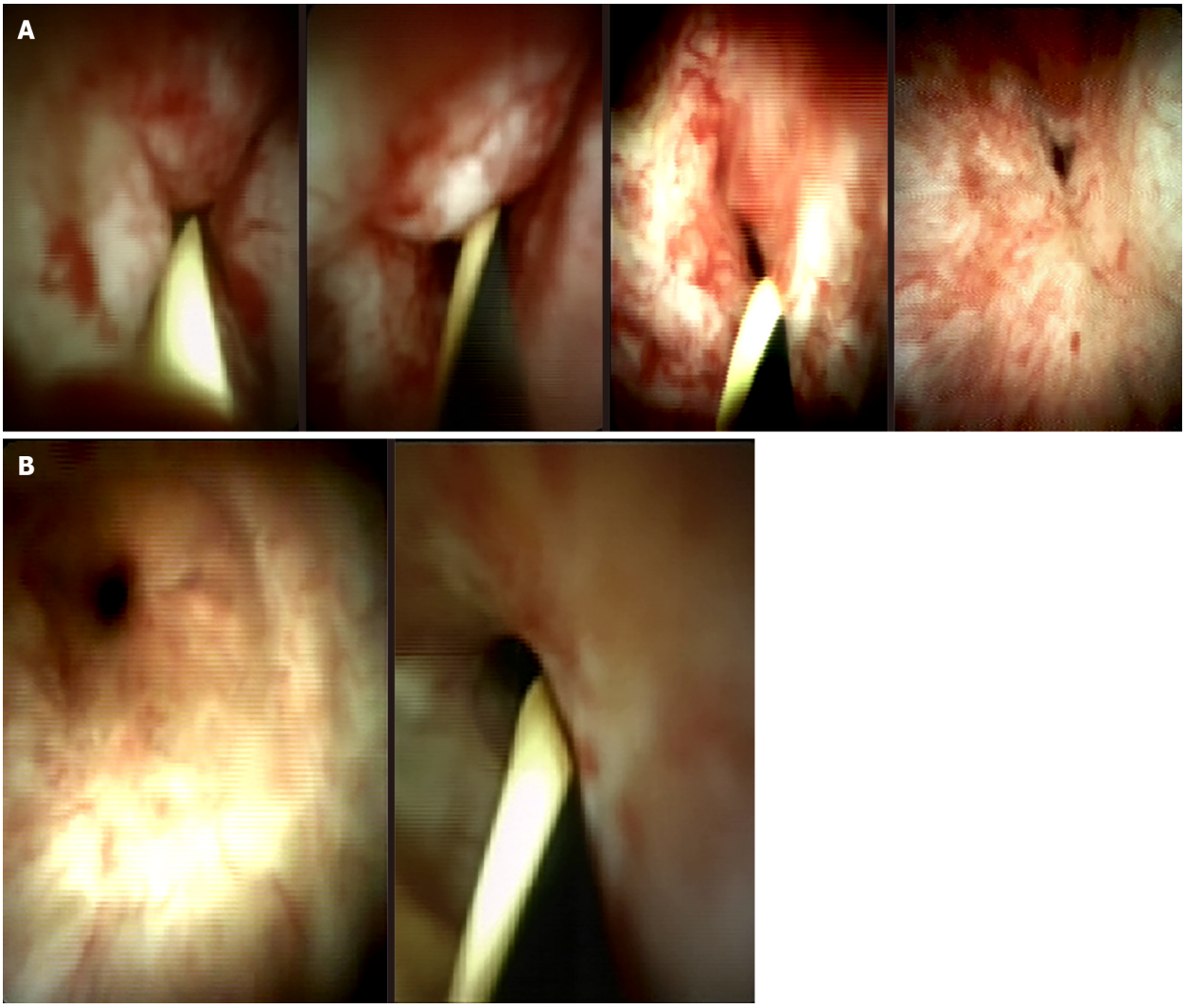

Figure 3 Digital (SpyGlass) cholangioscopy images. A: Cholangiocarcinoma; B: Benign stenosis.

recent studies from the United States and the Netherlands, which included patients with primary sclerosing cholangitis in their populations, POCS did not increase diagnostic sensitivity for CC over that of ERCP with brush cytology[38,39]. The lack of a standardized classification of image findings detected during cholangioscopy still causes problems of interpretation and may be responsible for unsatisfactory diagnostic accuracy[38,39].

To overcome this limit, Robles-Medranda *et al*[40] proposed in 2018 a classification system based on neoplastic and non-neoplastic findings including villous, polypoid, inflammatory, ulcerated, flat, or honeycomb patterns, which revealed an outstanding 96% sensitivity, 92% specificity, 96% negative predictive value, and an interobserver agreement up to 90%[40]. Similar results were found by Gerges *et al*[41], who reported a sensitivity of visualization of 95.5%[41]. In 2020, the Monaco classification was proposed for indeterminate BS based on eight visual criteria: presence of stricture, lesion (mass, nodule, or polypoid appearance), mucosal features, papillary projections, ulceration, abnormal vessels, scarring, and pronounced pit pattern. Final diagnostic accuracy based only on visual impression was 70%, with a high interobserver agreement for presumptive diagnosis (k = 0.31)[42].

The diagnostic accuracy of D-SOC is further improved by D-SOC-guided biopsy, which allows precise tissue sampling of the detected lesions. In a meta-analysis by Wen *et al*[43], SpyBite (Boston Scientific) biopsy showed a pooled sensitivity, specificity, positive likelihood ratio, negative likelihood ratio, and diagnostic odds ratio of 0.74 (95%CI: 0.67-0.80), 0.98 (95%CI: 0.95-1.00), 10.52 (95%CI: 5.45-20.32), 0.31 (95%CI: 0.23-0.41), and 65.18 (95%CI: 26.79-158.61), with a lower complication rate mainly ERCP-related. Acute cholangitis was the most common complication with a rate of 1.8%[43].

A point of great debate is the number of biopsies needed to obtain adequate tissue for a diagnostic histopathological assessment. Based on currently available studies, the number of biopsies is not defined with any certainty, but more than two biopsies are required to reach a sensitivity > 70%[23,43]. In a randomized multicenter investigation, an average of six biopsy specimens were taken during POCS, achieving a sensitivity of 68.2%, which increased up to 95.5% if visual impression at cholangioscopy was added to biopsy forceps performance[41].

The possible increase in diagnostic power using rapid on-site evaluation of D-SOC microbiopsy was recently assessed in a single-center prospective randomized trial among patients with indeterminate BS[44]. The authors concluded that there were no significant differences between the off-site and on-site groups in terms of diagnostic accuracy (90% *vs* 87.5%), sensitivity (76.9% *vs* 75%), and specificity (100% *vs* 100%). However, a greater number of biopsies was necessary to obtain a diagnosis in the off-site cohort (n = 3-4) than in the on-site cohort (n = 1)[44].

A precise evaluation of the extension of the neoplasia along the biliary wall in surgical candidate patients is of key importance in ensuring curative resection. D-SOC visualization of the biliary ducts allows the evaluation of intraductal cancer extension, not evident with diagnostic methods previously used and may guide the choice of surgical treatment, avoiding unnecessary surgery in the case of locally advanced neoplasia. In a retrospective study investigating the use of D-SOC for preoperative evaluation of extrahepatic biliary tumor, the visual impression accuracy of SpyGlass and SpyBite was 95.0% and 80.5%, respectively. D-SOC modified a previous classification of perihilar CC in 42% of patients and changed surgical management in 21% of cases[45]. Despite its high diagnostic accuracy, cholangioscopy is an expensive and difficult-to- handle technique that requires extensive experience in the performance of ERCP and adequate training in the interpretation of digital images and technique of execution. Several complications may occur during cholangioscopy, and the rate of serious adverse events ranges from 1% to 7%, with estimated rates of pancreatitis, cholangitis, and perforation of 2%, 4%, and 1%, respectively[46]. Cholangitis was reported in 8% of patients undergoing D-SOC; the administration of antibiotics during or immediately after the procedure seems to reduce the risk of this complication[47].

A cost-benefit analysis of D-SOC compared to conventional ERCP in the diagnosis of BS, based on data from two of the largest Belgian hospitals performing cholangioscopy, revealed that the adoption of D-SOC led to a 31% reduction in the number of procedures needed to obtain a diagnosis and saved about 5% of the allocated budget [48].

ENDOSCOPIC ULTRASOUND

Endoscopic ultrasound (EUS) is a diagnostic tool based on double endoscopic and ultrasonographic vision thanks to a high-frequency transducer placed on the tip of the endoscope. Due to the ease in identifying the biliary tract from the stomach and the duodenum, EUS may be considered a first-level procedure in identifying the cause of obstructive jaundice or in the diagnostic assessment of distal BS or unresectable intrahepatic CC (Figure 4).

The biliary examination usually starts from the stomach by identifying the biliary duct from the liver hilum and continues from the duodenal bulb to the second portion of the duodenum, studying the entire extrahepatic duct until the intrapancreatic portion. An endoscopic and ultrasonographic assessment of the ampulla and the gallbladder may also be performed to complete the investigation.

EUS has a diagnostic accuracy > 95% in identifying biliary thickening suggestive of malignancy compared to MRCP[48] (Figure 5). Given its high diagnostic accuracy in excluding a pathological thickening of the biliary wall, if performed at the beginning of the diagnostic process, EUS can avoid having to carry out an invasive procedure such as ERCP and any related complications[49].

The possibility of obtaining tissue from a clear mass by guided-EUS fine needle aspiration (EUS-FNA) increases the diagnostic power of EUS (Figures 6 and 7). EUS-FNA has a pooled sensitivity and specificity of 80% and 97%, respectively, in the diagnosis of malignancy in the biliary tract[50]. The advantage of performing EUS-FNA and ERCP in a single session should not be understated, as it reduces the duration of diagnostic workup in patients with BS and allows the selection of patients requiring therapeutic ERCP, thus avoiding an invasive procedure in absence of clear pathological thickening of the biliary tract (Figure 8). Zaheer *et al*[51] reported that EUS changed the diagnosis in 36% of patients from malignant to benign[51].

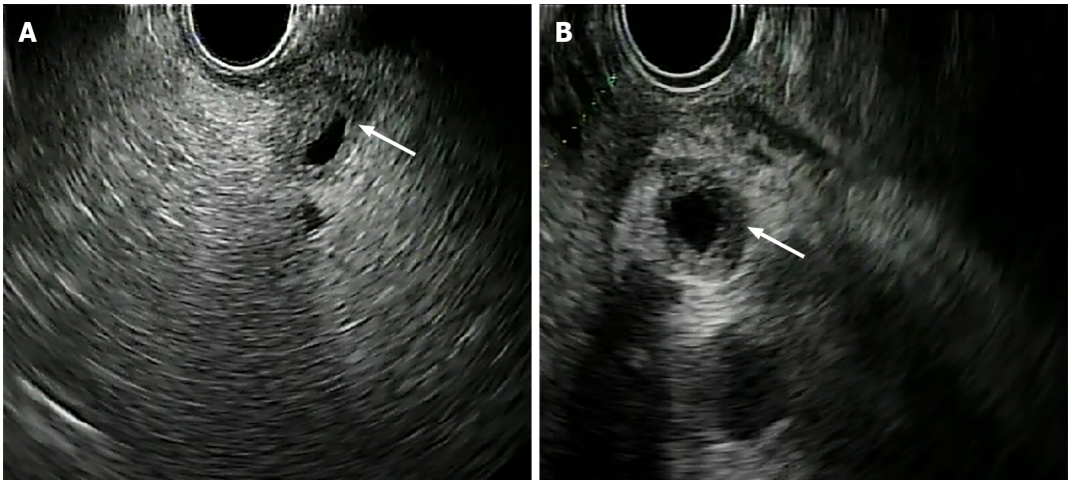

Figure 4 Two cases of cholangiocarcinoma evaluated with endoscopic ultrasound. A: Distal stenosis of the main biliary tract; B: Stenosis of the proximal-middle tract of the main biliary duct. Arrows indicate the stenotic tract.

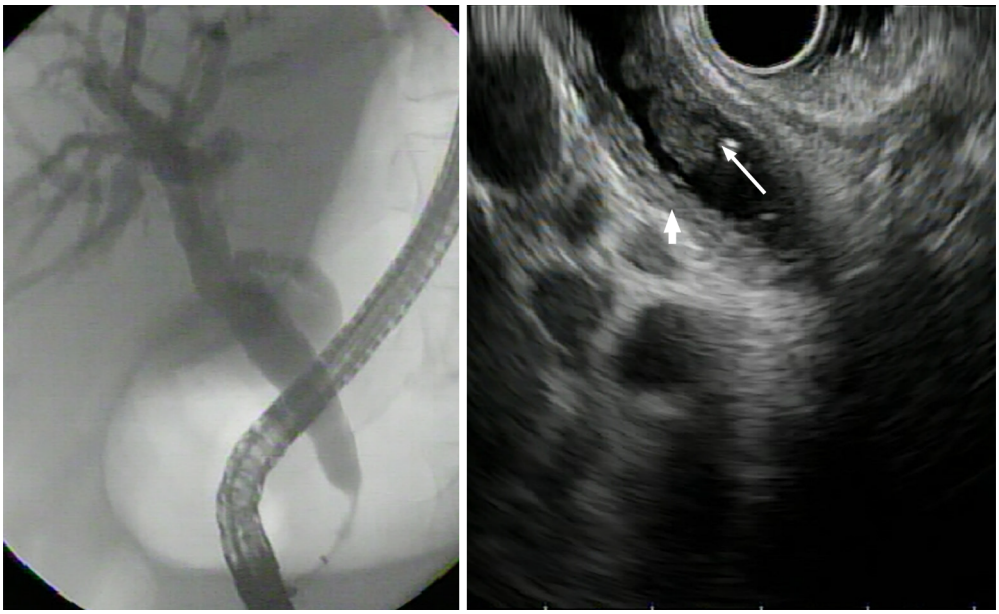

Figure 5 Endoscopic retrograde cholangiopancreatography and endoscopic ultrasound image of a stenotic tract of the distal biliary duct. In the endoscopic ultrasound image, the nodule inside the main biliary tract (large arrow) and thickening of the bile duct wall (small arrow) are visible.

The combination of EUS-FNA and ERCP-based tissue sampling in the same session has a diagnostic yield of up to 85%, whereas the overall accuracy of EUS-FNA tissue sampling is significantly higher than that of ERCP in the differential diagnosis of MBS (76% *vs* 58%)[52]. An additional advantage offered by EUS-FNA is the possibility of obtaining histological samples from an extraductal lesion not reachable by ERCP. In a retrospective multicenter study on 263 patients with suspected MBS, EUS, and ERCP were carried out in the same session and the diagnostic power of samples collected from BS by EUS-FNA and intraductal biopsy, cytology *via* nasobiliary drainage, or brushing by ERCP was compared[53]. This study found an overall sensitivity and diagnostic accuracy of 73.6% and 76.1% for EUS-FNA, 56.5% and 60.5% for ERCP-based tissue sampling, and 85.8% and 87.1% for the combination of both tissue-sampling methods[53].

As the therapeutic options for CC are surgical resection or liver transplantation, a precise definition of the tumor extension is crucial in guiding the treatment choice. RLN metastasis and margin status are the most important predictors of post-surgical outcome[54]. In this context, EUS-FNA proved to be the preferred technique in the identification and sampling of lymph nodes. In a retrospective study of consecutive patients with CC undergoing EUS staging with EUS-FNA of RLN, EUS identified

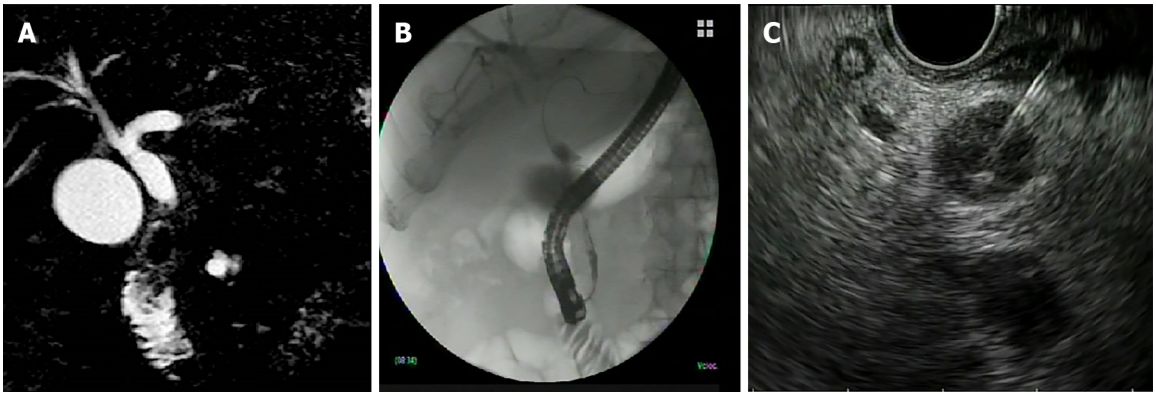

Figure 6 Adenocarcinoma of the main biliary tract. A: Magnetic resonance image of suspected neoplastic stenosis; B: Endoscopic retrograde cholangiopancreatography image confirming the stenosis; C: Endoscopic ultrasound-guided fine needle aspiration of the stenotic tract for tissue diagnosis.

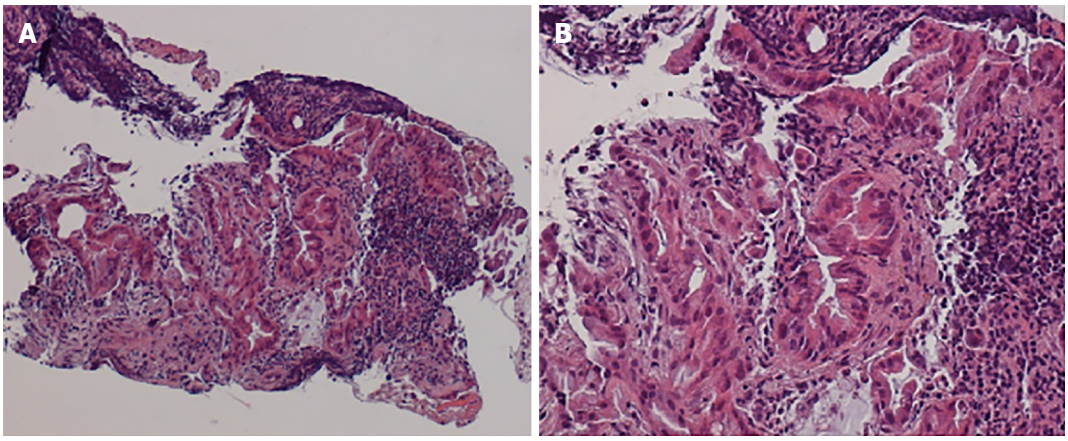

Figure 7 Histology of specimen collected by endoscopic ultrasound-fine needle aspiration from cholangiocarcinoma in a hepatic nodule. A: Hematoxylin and eosin staining, magnification × 40; B: Hematoxylin and eosin staining, magnification × 100.

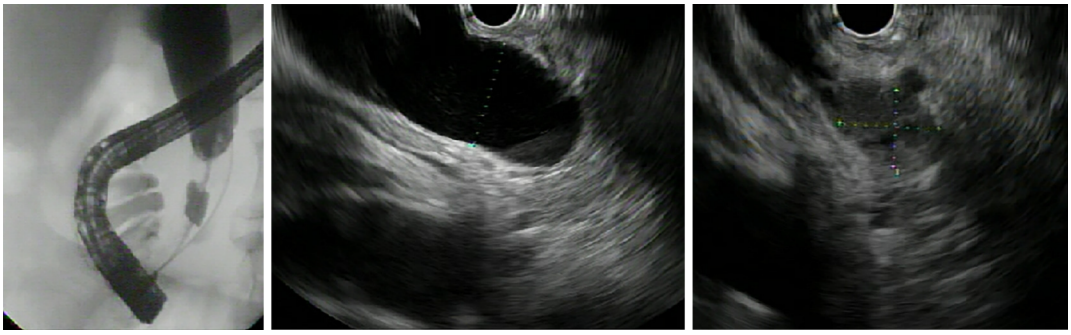

Figure 8 Diagnosis of cholangiocarcinoma of the distal tract of the main biliary duct, obtained in a single session by biopsy during endoscopic retrograde cholangiopancreatography and endoscopic ultrasound-guided fine needle aspiration. Endoscopic ultrasound images show dilation of the common bile duct and stenosis of the distal tract due to a neoplastic nodule.

positive RLN in 86% of patients and detected a higher percentage of positive RLN than cross-sectional imaging (83% *vs* 50%); EUS-FNA revealed metastatic RLN in 17% of patients[55]. According to the authors, preoperative staging with EUS and EUS-FNA of RLN should be considered in patients with any type of CC[56].

Tips

The choice of endoscopic technique to obtain a tissue-based differential diagnosis of BS should be tailored according to the stricture location. In patients where ERCP transpapillary forceps biopsy resulted non-diagnostic, POCS-guided forceps biopsy

should be preferred in proximal BS, whereas EUS-FNA biopsy may be more appropriate for distal BS[55].

INTRADUCTAL ULTRASOUND

Intraductal ultrasound (IDUS) involves a 2-mm high-frequency radial probe (12-20 MHz) introduced through the working channel of a duodenoscope. On IDUS visualization, the normal wall of the bile duct appears as three layers: an inner hyperechoic layer corresponding to mucosa, a middle hypoechoic layer corresponding to smooth muscle fibers, and an outer hyperechoic layer corresponding to connective tissue[57]. IDUS could be particularly effective in the assessment of CC, especially where no mass is detected, and may be used to distinguish BBS from MBS. Sonographic features associated with MBS are hypoechoic or heterogeneous echo-poor infiltrating tissue with irregular borders breaking the normal sonographic pattern of the bile duct wall, eccentric and irregular wall thickening, sessile mass, invasion of surrounding tissues, and presence of enlarged lymph nodes[58].

In a retrospective study by Chen *et al*[59], IDUS showed a sensitivity, specificity, positive predictive value, negative predictive value, and accuracy rate of 96.9%, 79.0%, 82.0%, 96.2%, and 88.0%, respectively, in distinguishing MBS from BBS. Combining IDUS and ERCP-guided tissue sampling improved the accuracy rate from 88.0% to 96.8% and specificity from 79.0% to 96.8%. A length > 20 mm and a wall thickness > 7 mm has a positive predictive value > 90% for malignancy[59]. A recent prospective study confirmed an > 80% accuracy of IDUS in detecting malignancy in patients with negative ERCP cytology and histology and corroborated its usefulness in targeting biopsy sampling with improvement in diagnostic accuracy[60]. However, this technique is not routinely performed, and its use is progressively decreasing in favor of D-SOC.

Third step: Endoscopic treatment of biliary stenosis

Endoscopic treatment of BS, both benign and malignant, is well documented and widely accepted. The European Society of Gastrointestinal Endoscopy guidelines defined the correct choice of stent according to the location and etiology of the stenosis [61]. In BS related to liver transplantation, chronic pancreatitis, or post-cholecystectomy strictures, the treatment of choice is temporary insertion of multiple plastic stents or a fully covered self-expandible metal stent (FC-SEMS) depending on the etiology and location of the stricture, diameter of the common bile duct, and operator expertise. With FC-SEMS insertion, the possibility of stent migration (9% of cases reported) with consequential failure of stricture resolution should be kept in mind[62]. A recent review by Larghi *et al*[63] described different strategies used to treat anastomotic BS after liver transplantation, comparing the advantages and disadvantages of plastic multi-stenting treatment *vs* placement of a metal stent reported in the literature, including four randomized controlled trials (Figure 9). The authors concluded that insufficient data are currently available to define which type of treatment is better than another, suggesting the need for a multicenter international randomized trial to draw definitive conclusions. Even less conclusive results are available for the treatment of refractory strictures, especially for hilar anastomotic strictures after liver transplants and hepaticojejunostomies. A recent single-center study aimed at evaluating the use of FC-SEMS for hilar BBS recently reported that temporary placement of an FC-SEMS is feasible and effective for refractory BBS, with a technical success rate of 100%, stricture resolution rate of 96.6%, and complication rate of 12.0%[64].

For MBS, the European Society of Gastrointestinal Endoscopy recommendations advise against routine preoperative biliary drainage in patients with surgical indication in absence of cholangitis, severe symptomatic jaundice, delayed surgery, or in the case of neoadjuvant therapy. A 10 mm-diameter SEMS is recommended for extrahepatic MBS before surgery. Palliative biliary drainage should be performed by ERCP with FC-SEMS or partially covered SEMS insertion. Surgical biliodigestive anastomosis and percutaneous biliary drainage should be indicated in selected cases where ERCP cannot be performed due to its high rate of complications and impact on the patient's quality of life[65,66].

Described for the first time in 2001, endoscopic ultrasound biliary drainage (EUS-BD) is an emerging technique useful in patients in whom ERCP biliary drainage failed or is not technically feasible due to duodenal stenosis or unreachable papilla[67,68]. A meta-analysis comparing EUS-BD *vs* percutaneous transhepatic biliary drainage in 312

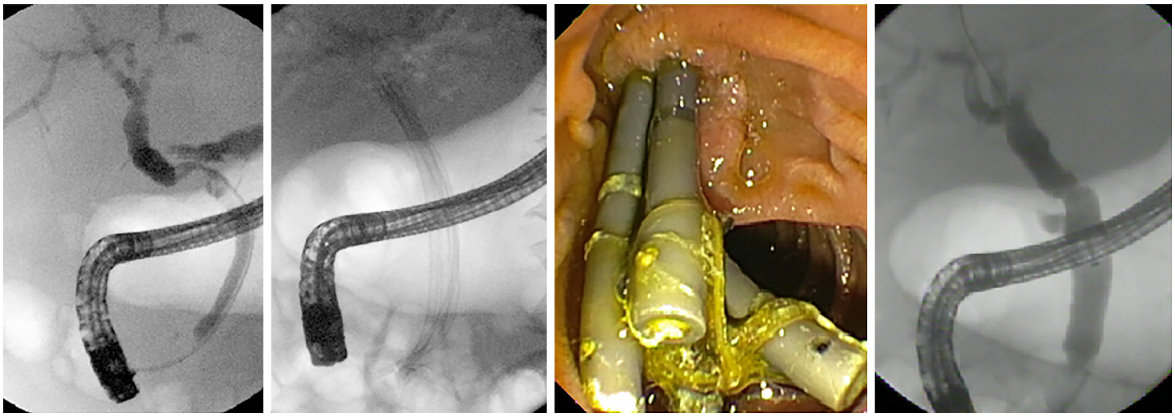

Figure 9 Multi-stenting treatment of anastomotic stenosis after liver transplantation. The image on the far right shows complete resolution of the stenosis.

patients demonstrated that clinical success was similar for both techniques, but complications were less frequent with EUS-BD[69]. Despite the apparently high cost of the device, reintervention rates and costs were found to be lower with EUS-BD in a retrospective expertise-based study[70]. In a systematic review and meta-analysis, Dhindsa *et al*[71] evaluated the technical success, clinical outcome, and rate of adverse events of EUS-BD reported in 23 studies published in peer-reviewed journals. The pooled rate of clinical success was 87.0%, technical success 91.5%, reintervention 6.5%, and adverse events 17.9%. The most common adverse events were biliary leaks and infection or stent migration, although a precise evaluation of the incidence of complication was hampered by the variability of adverse event rates, the heterogeneity of EUS-BD, performed *via* hepatogastrostomy, cholecystostomy, or choledochoduodenostomy, and the different techniques of drainage, such as plastic stents, metal stents, lumen-apposing metal stents (LAMS), nasobiliary drainage tubes, or a combination of these, used in the different studies[71].

The use of devices designed for EUS-guided drainage, such as LAMS (Boston Scientific, Marlborough, Massachusetts, United States), was first reported in 2011 and significantly contributed to improving the technical success and safety of EUS-BD. Nevertheless, this type of procedure requires an operator expert in interventional EUS and should be performed in a tertiary care referral center after a multidisciplinary discussion of the clinical case[72].

In a recent study by Anderloni *et al*[73] involving 46 consecutive patients with malignant distal biliary duct obstruction over a 3-year period, choledochoduodenostomy using LAMS showed a technical success rate of 93.5% and a clinical success rate of 97.7%, with an incidence of complication of 11.6%. The most serious complication was fatal bleeding, occurring in one case after 17 d from stent placement, while the remaining were food impaction in the stent and one migration of the stent [73]. In line with these results, a French multicenter study reported a technical and clinical success rate of 98.5% and 97.1%, respectively, with a short-term adverse event rate of 1.6% and a 6-mo stent patency rate of 91.4%[74]. Of note, in this French study the procedures were performed by 12 operators in 10 different centers. Each operator had experience of routine diagnostic EUS, including FNA and ERCP in the previous 5 years, and only four operators had previously performed > 20 EUS-BD. No difference in terms of technical success between operators was reported[74]. Despite these findings, data regarding the efficacy of EUS-BD by LAMS and the precise timing of intervention need to be confirmed in a randomized controlled trial.

Future treatment for BS

Radiofrequency ablation was recently proposed for the treatment of endobiliary malignancy, ablation of intraductal extension of ampullary adenomas, and recanalization of occluded metal stents[75]. The use of radiofrequency ablation in hilar BS was evaluated by Inoue *et al*[76] in a retrospective study of patients with unresectable malignant hilar biliary obstruction treated with radiofrequency ablation followed by biliary drainage with SEMS. The recurrence rate of biliary obstruction was 38.5% within a median time of 230 d. The findings of this study open up new therapeutic perspectives in patients with unresectable hilar BS, but further investigations are necessary to optimize the technique and determine its indication.

CONCLUSION

The management of BS can be complicated due to the difficulty in obtaining a correct differential tissue diagnosis between benign and malignant stenosis, especially in cases of hilar stenosis and when the tumor grows along the wall of the biliary tract. A shared multidisciplinary management approach to patients with BS is therefore necessary in order to exploit all the diagnostic techniques currently available and to select the most suitable therapy based on recent findings in the scientific literature.

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ORIGINAL ARTICLE

Retrospective Cohort Study

Clinical impact of gastrointestinal endoscopy on the early detection of pharyngeal squamous cell carcinoma: A retrospective cohort study

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Abstract

BACKGROUND

In recent years, with the growing availability of image-enhanced gastrointestinal endoscopy, gastroenterologists have contributed to the early detection of pharyngeal squamous cell carcinomas (SCC).

AIM

To clarify the clinical characteristics of pharyngeal SCCs detected by gastrointestinal endoscopy.

METHODS

This is a retrospective cohort study conducted in a single-center, a university hospital in Japan. We retrospectively assessed the clinical records of 522 consecutive patients with oropharyngeal or hypopharyngeal SCC who were

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examined in our hospital between 2011 and 2018. The lesions were classified into two groups: Group GE (detected by gastrointestinal endoscopy) and Group non-GE (detected by means other than gastrointestinal endoscopy). The clinical characteristics were compared between the two groups. Continuous data were compared using the Mann–Whitney *U* test. Pearson's χ^2 test or Fisher's exact test was used to analyze the categorical data and compare proportions. The Kaplan–Meier method was used to estimate the cumulative patient survival rates.

RESULTS

In our study group, the median age was 65 years and 474 patients (90.8%) were male. One hundred and ninety-six cases (37.5%) involved the oropharynx and 326 cases (62.5%) involved the hypopharynx. Three hundred and ninety-five cases (75.7%) had some symptoms at the time of diagnosis. One hundred and forty-five (27.8%) cases had concurrent ESCC or a history of ESCC. One hundred and sixty-four (31.4%) cases were detected by gastrointestinal endoscopy and classified as Group GE. The proportions of asymptomatic cases, cTis-1 cases and cases with no lymph node metastasis were significantly higher in Group GE than Group non-GE (61.6% *vs* 7.3%, $P < 0.001$, 32.9% *vs* 12.0%, $P < 0.001$ and 69.5% *vs* 19.0%, $P < 0.001$). Endoscopic laryngo-pharyngeal surgery or endoscopic submucosal dissection were performed in only 0.6% of the lesions in Group non-GE but in 21.3% of the lesions in Group GE ($P < 0.001$). Overall survival was significantly longer in Group GE than in Group non-GE ($P = 0.018$). The 2-year and 4-year survival rates were 82.5% and 70.7% in Group GE, and 71.5% and 59.0% in Group non-GE, respectively.

CONCLUSION

Gastrointestinal endoscopy plays an important role in the early detection and improving the prognosis of pharyngeal SCCs.

Key Words: Gastrointestinal imaging; Head and neck imaging; Gastrointestinal endoscope; Hypopharyngeal neoplasm; Oropharyngeal neoplasm; Endoscopic surgery

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Core Tip: This is the first study to explore the detection modality of oropharyngeal and hypopharyngeal squamous cell carcinomas (SCC). In this study, 31.4% of pharyngeal SCCs (15.4% of oropharyngeal SCCs and 42.3% of hypopharyngeal SCCs) were detected by gastrointestinal endoscopy. The clinical characteristics of the lesions detected by gastrointestinal endoscopy include a higher proportion of asymptomatic cases, cTis-1 cases, cases with no lymph node metastasis and cases treated by endoscopic laryngo-pharyngeal surgery/endoscopic submucosal dissection, leading to a better prognosis. This study highlights the important role of gastrointestinal endoscopy in the early detection and treatment of SCC in the otolaryngology field.

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INTRODUCTION

The pharynx is the most common site of head and neck cancer and, because pharyngeal cancers are often diagnosed at an advanced stage, the prognosis is poor[1-3]. Standard surgical resection or chemoradiotherapy (CRT) for advanced pharyngeal cancer lesions may severely reduce the patient's quality of life, with disorders of swallowing and speech function. Similar to other gastrointestinal tumors, superficial

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pharyngeal cancer can be treated by minimally invasive endoscopic resection that preserves organ function[4-6]. Therefore, strategies for the detection of pharyngeal cancer at an early stage and treatment with endoscopy, including endoscopic submucosal dissection (ESD) and endoscopic laryngo-pharyngeal surgery (ELPS), are crucial for preserving the quality of life and improving prognosis.

In recent years, image-enhanced endoscopy (IEE) systems, including narrow-band imaging (NBI) and blue laser imaging, have been reported to be useful for the early detection of cancer in the pharynx and esophagus[7,8]. Patients with head-and-neck squamous cell cancer (HNSCC) or esophageal squamous cell carcinoma (SCC) (ESCC) have a high risk of synchronous and metachronous SCCs, which has been recognized as the field cancerization phenomenon[9,10]. Therefore, patients with present or previous HNSCC or ESCC require careful endoscopic observation of the pharynx with IEE[11,12]. In general, pharyngeal cancers have been most often detected by otolaryngologists using rhino-laryngoscopy. Recently, many superficial pharyngeal cancers have been discovered by gastroenterologists, with the growing availability of IEE in gastrointestinal endoscopy. However, few studies have shown how much gastroenterologists contribute to the detection and treatment of pharyngeal cancer.

Previously, we investigated the modalities of detection of superficial hypopharyngeal cancerous lesions (Tis, T1 and T2), treated in our institution, and reported that gastroenterologists detected more hypopharyngeal cancer than otolaryngologists (75.2% to 24.8%)[13]. The aim of this study was to clarify the clinical characteristics of pharyngeal SCCs detected with gastrointestinal endoscopy, including superficial to advanced lesions.

MATERIALS AND METHODS

Patients

In this retrospective study, we assessed the clinical records of consecutive patients with oropharyngeal or hypopharyngeal SCC who underwent a detailed examination, including definitive diagnosis by pathologists and staging based on the TNM classification, in our hospital between January 2011 and December 2018. The first lesion detected during the study period was included in the analysis. If multiple lesions were detected at the same time, the largest lesion was included. We excluded patients who had undergone prior treatment of pharyngeal cancer at another hospital and/or had unspecified details of detection modality. The following data were reviewed retrospectively: The physician who detected the primary lesion (gastroenterologist, otolaryngologist, dentist, general physician), indication for examination of the pharynx, clinical manifestation, age at incidence, sex, tumor location, primary treatment, TNM classification[14], past history of ESCC, patient vital status (alive, deceased, lost to follow-up) and follow-up time.

We defined those with lesions detected by gastrointestinal endoscopy as Group GE and those with lesions detected by means other than gastrointestinal endoscopy (rhino-laryngoscopy or direct visualization by otolaryngologists, dentists and general physicians) as Group non-GE.

The oropharynx was divided into the following four subsites: (1) Anterior wall: Base of tongue; (2) Superior wall: Inferior surface of soft palate and uvula; (3) Lateral wall: Tonsil, tonsillar fossa, and pillars; and (4) Posterior wall. The hypopharynx was divided into the following three subsites: (1) Pyriform sinus; (2) Posterior wall; and (3) Post-cricoid region. We defined the symptomatic group as patients with any one of the following conditions: Sore throat, painful swallowing, pharyngeal discomfort, bleeding, swelling of cervical lymph nodes or hoarseness.

We evaluated the proportion of Group GE among all pharyngeal cancer, the clinical differences between Group GE and Group non-GE, and the trends in proportion of Group GE.

This study was approved by the ethical committee of our hospital and performed in accordance with the ethical principles associated with the Declaration of Helsinki.

Patient and public involvement

Patients and the public were not involved in the design, conduct, reporting, or dissemination of plans of the research.

Statistical analysis

Continuous data were compared using the Mann–Whitney U test. Pearson's χ^2 test or Fisher's exact test were used to analyze the categorical data and compare proportions.

The survival rates of patients were plotted using Kaplan–Meier curves, and the difference was evaluated using the log rank test. Cox regression analysis was used to estimate the hazard ratio and to calculate the 95% confidence interval. SPSS version 21.0 (IBM Corporation, Armonk, NY, United States) was used for all statistical analyses. P values < 0.05 (two-sided) denoted statistically significant differences. The statistical methods of this study were reviewed by our expert biostatistician, Jun Morinaga, MD.

RESULTS

From January 2011 to December 2018, 563 lesions (oropharyngeal and hypopharyngeal SCCs) in 535 patients were examined in our hospital. Of those, 41 lesions and 13 patients were excluded (28 lesions in 26 patients were excluded due to multiple primary lesions; seven lesions in seven patients had been treated at another hospital; and the details of the detection process were not specified for six lesions in six patients). Hence, a total of 522 lesions in 522 patients were enrolled in this study. The median duration of follow-up was 25.8 mo.

The characteristics of the study population are listed in Table 1. The median age was 65 years and 474 patients (90.8%) were male. One hundred and ninety-six cases (37.5%) were in the oropharynx and 326 cases (62.5%) were in the hypopharynx. Three hundred and ninety-five cases (75.7%) had symptoms of some kind at the time of diagnosis. The most common reason for the examination was the investigation of symptoms (71.1%). One hundred and sixty-four (31.4%) cases were detected by gastrointestinal endoscopy (Group GE). Among 358 cases detected other than by gastrointestinal endoscopy (Group non-GE), almost all lesions were detected by otolaryngologists (341 lesions) and the remainder were detected by dentists (14 lesions) and general physicians (three lesions). One hundred and forty-five (27.8%) cases had concurrent ESCC or a history of ESCC.

A comparison between Group GE and Group non-GE is shown in Table 2. There were no significant differences in sex or age. The proportion of symptomatic cases was significantly lower in Group GE (38.4% *vs* 92.7%, P < 0.001). The common reasons for the examination were follow-up or diagnostic work-up for ESCC (39.0%), incidental esophago-gastro-duodenoscopy (EGD) (28.7%) and investigation of symptoms (28.0%) in Group GE and investigation of symptoms (90.8%) in Group non-GE. Incidental EGD included screening for gastric cancer (46.8%), surveillance of gastric cancer (10.6%), investigation of abdominal symptom (10.6%), and others (31.9%). As for the primary site, the proportion of oropharynx lesions was significantly lower in Group GE than Group non-GE (15.9% *vs* 47.5%, P < 0.001). The proportion of lesions with concurrent or a history of ESCC was significantly higher in Group GE than Group non-GE (51.2% *vs* 17.0%, P < 0.001). The proportions of cTis-1 cases and cases with no lymph node metastasis were significantly higher in Group GE than Group non-GE (32.9% *vs* 12.0%, P < 0.001 and 69.5% *vs* 19.0%, P < 0.001). Meanwhile, there were no significant differences in the proportion of cases with distant metastases. As for the modality of treatment, ELSP/ESD was performed in only 0.6% of cases in Group non-GE, while 21.3% of cases in Group GE were treated with ELPS/ESD (P < 0.001). We showed a case of T1 hypopharyngeal cancer located in the left pyriform sinus and detected by gastrointestinal endoscopy with NBI (Figure 1). Under general anesthesia, *en bloc* resection by ESD was successfully completed.

Figure 2 shows the subsite of primary lesions and the proportion of Group GE by subsite. The proportions of Group GE in the oropharynx and hypopharynx were 15.4% and 42.3%, respectively. In the oropharynx, the proportions of Group GE in the anterior (8.0%) and lateral wall (8.5%) were significantly lower than the posterior wall (50.0%). On the other hand, in the hypopharynx, there was no significant difference in the proportion of Group GE by subsite.

Figure 3A shows a comparison of the proportion of Group GE between the first and second half periods (2011–2014 and 2015–2018). The proportion of Group GE was significantly larger in the second half period (24.0% *vs* 36.2%, P = 0.004). Consistent with this tendency, the proportion of cTis-1 lesions was significantly higher in the second half period (13.2% *vs* 22.0%, P = 0.015) (Figure 3B).

Kaplan–Meier curves of survival are shown in Figure 4. Overall survival was significantly longer in Group GE than in Group non-GE (HR: 0.63; 95%CI: 0.43-0.93; P = 0.018). The 2-year and 4-year survival rates were 82.5% and 70.7% in Group GE, and 71.5% and 59.0% in Group non-GE, respectively.

Table 1 Characteristics of the study population

	***n* = 522**
Sex, male/female	474 (90.8%)/48
Age, median, yr	65 (37-92)
Location	
Oropharynx	196 (37.5%)
Hypopharynx	326 (62.5%)
Symptomatic/Asymptomatic	395 (75.7%)/127
Indication for examination	
Investigation of symptoms	371 (71.1%)
Incidental EGD	47 (9.0%)
f/u or diagnostic work-up of ESCC	66 (12.6%)
f/u or diagnostic work-up of HN	17 (3.3%)
Incidental dental check	7 (1.3%)
Other	14 (2.7%)
Detected by GE/non-GE	164 (31.4%)/358
cTis-1/2/3/4	97 (18.6%)/177/102/146
cN -/+	182 (34.9%)/340
cM -/+	504 (96.6%)/18
Concurrent or history of ESCC y/n	145 (27.8%)/377

Summary of continuous variables, indicated as median and interquartile ranges. Categorical variables are indicated as the number of subjects and percentages. EGD: Esophagogastroduodenoscopy; f/u: Follow-up; ESCC: Esophageal squamous cell carcinoma; HN: Head and neck cancer; GE: Gastrointestinal endoscopy.

DISCUSSION

This study investigated the impact of gastrointestinal endoscopy on the detection of pharyngeal SCC. Of total 522 lesions, 164 (31.4%) in Group GE had a higher proportion of asymptomatic cases, cTis-1 cases, cases with no lymph node metastasis and cases treated by ELPS/ESD than Group non-GE, leading to a better prognosis. To the best of our knowledge, this is the first study to explore the detection modality of oropharyngeal and hypopharyngeal SCC in a large number of cases.

Until the advent of NBI, gastrointestinal endoscopists were unable to observe the pharynx in detail, thereby posing a challenge to the detection of pharyngeal cancer using gastrointestinal endoscopy. In 2010, the usefulness of NBI for the early detection of cancer in the pharynx was reported. Muto *et al*[7] conducted a multicenter, prospective, randomized controlled trial; 320 patients with ESCC were randomly assigned to primary white light imaging (WLI) followed by NBI or primary NBI followed by WLI in a back-to-back fashion. They reported that the sensitivity and accuracy were significantly higher in the NBI-first group than the WLI-first group in both the head and neck region and the esophagus (100% *vs* 7.7%; $P < 0.001$ for sensitivity, 85.7% *vs* 62.9%; $P = 0.02$ for accuracy, respectively). In a study of 424 consecutive patients subjected to surveillance endoscopy who had previously undergone CRT and/or surgery for esophageal SCC, Nonaka *et al*[15] reported that the detection rate for pharyngeal cancer was significantly higher when using NBI endoscopy with magnification (10.9%) compared with conventional endoscopy (1.2%) ($P < 0.0001$). Following these reports, careful endoscopic observation of the pharynx with IEE for patients with ESCCs became gradually popular among Japanese gastroenterologists[11,12,16,17]. These observations revealed the usefulness of gastrointestinal endoscopy for the detection of pharyngeal cancer among patients with esophageal SCC. However, the proportion and clinical characteristics of the lesions detected by gastrointestinal endoscopy among patients with pharyngeal cancer remained unclear. The advantage of the present study is to elucidate the clinical characteristics of

Table 2 Comparison between Group gastrointestinal endoscopy and Group non- gastrointestinal endoscopy

	Group GE *n* = 164	Group non-GE *n* = 358	*P* value
Sex, male	153 (93.3%)	321 (89.7%)	0.197
Age, median, yr	68 (42–90)	67 (37–92)	0.278
Asymptomatic/Symptomatic	101 (61.6%)/63 (38.4%)	26 (7.3%)/332 (92.7%)	< 0.001
Indication for examination			< 0.001
Investigation of symptoms	46 (28.0%)	325 (90.8%)	
Incidental EGD	47 (28.7%)	0	
f/u or diagnostic work-up of ESCC	64 (39.0%)	2 (0.6%)	
f/u or diagnostic work-up of HN	7 (4.3%)	10 (2.8%)	
Incidental dental check	0	7 (2.0%)	
Other	0	14 (3.9%)	
Location oropharynx/hypopharynx	26 (15.9 %)/138 (84.1%)	170 (47.5%)/188 (52.5%)	< 0.001
History or concurrent of ESCC, y/n	84 (51.2%)/80	61 (17.0%)/297	< 0.001
cTis-1/cT2-4	54 (32.9%)/110	43 (12.0%)/315	< 0.001
cN -/+	114 (69.5%)/50	68 (19.0%)/290	< 0.001
cM -/+	161 (98.2%)/3	343 (95.8%)/15	0.205
Treatment			
ELPS/ESD	35 (21.3%)	2 (0.6%)	< 0.001
Non-ELPS/ESD	129 (78.7%)	356 (99.4%)	
Surgery	23 (14.0%)	79 (22.1%)	
RT/CRT	84 (51.2%)	212 (59.2%)	
Chemotherapy	5 (3.0%)	13 (3.6%)	
BSC	9 (5.5%)	40 (11.2%)	
Unknown	8 (4.9%)	12 (3.4%)	

Continuous variables, indicated as the median and interquartile range. Categorical variables are indicated as the number of subjects and percentage. EGD: Esophagogastroduodenoscopy; f/u: Follow up; ESCC: Esophageal squamous cell carcinoma; HN: Head and neck cancer; ESD: Endoscopic submucosal dissection; ELPS: Endoscopic laryngo-pharyngeal surgery; GE: Gastrointestinal endoscopy; RT: Radiotherapy; CRT: Chemoradiotherapy; BSC: Best supportive care.

pharyngeal SCCs detected by gastrointestinal endoscopy.

A recent systematic review and meta-analysis revealed that the prevalence of head and neck second primary tumors in patients with ESCC was 6.7%, and 60% of all head and neck second primary tumors were located in the hypopharynx, with 18% in the oropharynx[18]. In our study, the percentage of concurrent ESCC or with a history of ESCC was 27.8%. Considering these data, the careful endoscopic observation of the pharynx of patients with present or previous ESCC is efficient, but it is insufficient because 70.7% of pharyngeal SCCs were not relevant to ESCCs. In Group non-GE, 92.7% of cases were symptomatic and only 0.6% of cases were treated by ELPS/ESD. The problem appears to be that patients do not visit hospital and receive an otolaryngology examination unless the cancer has progressed to a symptomatic stage. On the other hand, in Group GE, only 38.4% of cases were symptomatic and the proportion of cases treated by ELPS/ESD was significantly higher (21.3%) than Group non-GE. It is important to detect pharyngeal SCCs with gastrointestinal endoscopy while patients remain asymptomatic for further improvement in prognosis and preservation of function. On this basis, we should not pass through the pharynx without due caution in patients with risk factors (*e.g.*, smoking, alcohol consumption), even if they have no history of ESCC and no symptoms. In the present study, pharyngeal cancer was detected in hospitals, as well as clinics and health examination centers. Moreover, the numbers of lesions detected by gastrointestinal endoscopy have been increasing (Figure 3). Furthermore, due to advances in endoscopic treatment, we have been able

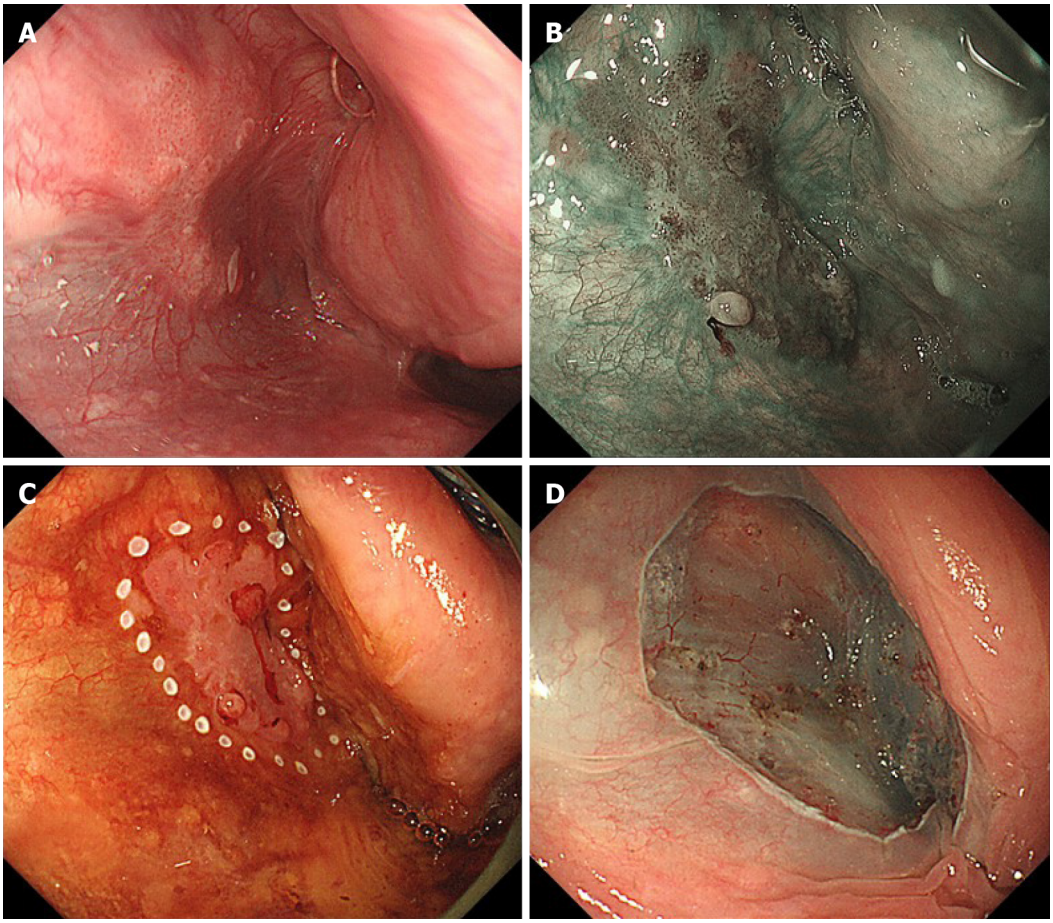

Figure 1 A case of T1 hypopharyngeal cancer located in the left pyriform sinus, detected by gastrointestinal endoscopy. A: The lesion was recognized as a slightly reddish area under white light image endoscopy; B: The lesion was clearly visualized using narrow-band imaging; C, D: Under general anesthesia, *en bloc* endoscopic submucosal dissection was successfully completed.

to remove superficial pharyngeal lesions by ELPS/ESD, without impairment of pharyngeal function[19,20]. We emphasize that gastrointestinal endoscopists can improve the prognosis of patients with pharyngeal cancer by careful observation of the pharynx in routine clinical practice, and should take a more active role both in the detection and treatment of this type of cancer.

In our study, the proportions of lesions in the anterior and lateral wall of oropharynx were extremely low in Group GE (7.8% and 8.5%, respectively). One of the reasons is that the lateral and anterior walls of the oropharynx are anatomically difficult to observe using transoral endoscopy, so even advanced cancer may be easily missed if the endoscope is passed too quickly through the oropharynx[21]. The other cause is possibly related to human papillomavirus (HPV). HPV infection has been identified as a risk factor for oropharyngeal SCCs, especially involving the tonsils and base of the tongue[22]. Because HPV infects the basal layer of the tonsillar crypt, cancer arises from the deeper areas and is not always exposed at the luminal surface at an early stage. Thus, endoscopic diagnosis tends to be difficult compared to HPV-unrelated pharyngeal SCCs[23]. In this study, we were not able to show the percentage of HPV-related cancer due to insufficient data. Although early pharyngeal cancers were detected mostly by gastroenterologists, considering that some lesions are difficult to detect with gastrointestinal endoscopy, pharyngeal examination conducted by otolaryngologists and gastroenterologists in cooperation will be required for further improvement of cancer detection.

There were some limitations in the present study. Firstly, it is a retrospective review of hospital records from a single center. Therefore, the history of gastrointestinal endoscopic examination was uncertain in Group non-GE and we could not determine how often gastroenterologists had missed the pharyngeal lesions. Furthermore, we could not survey the experiences of individual physicians or the accessibility to gastrointestinal endoscopy and otolaryngology services in individual residential areas. In the future, a prospective study should be designed to address this subject. Secondly, there was referral filter bias because almost all ELPS/ESD cases were treated in our

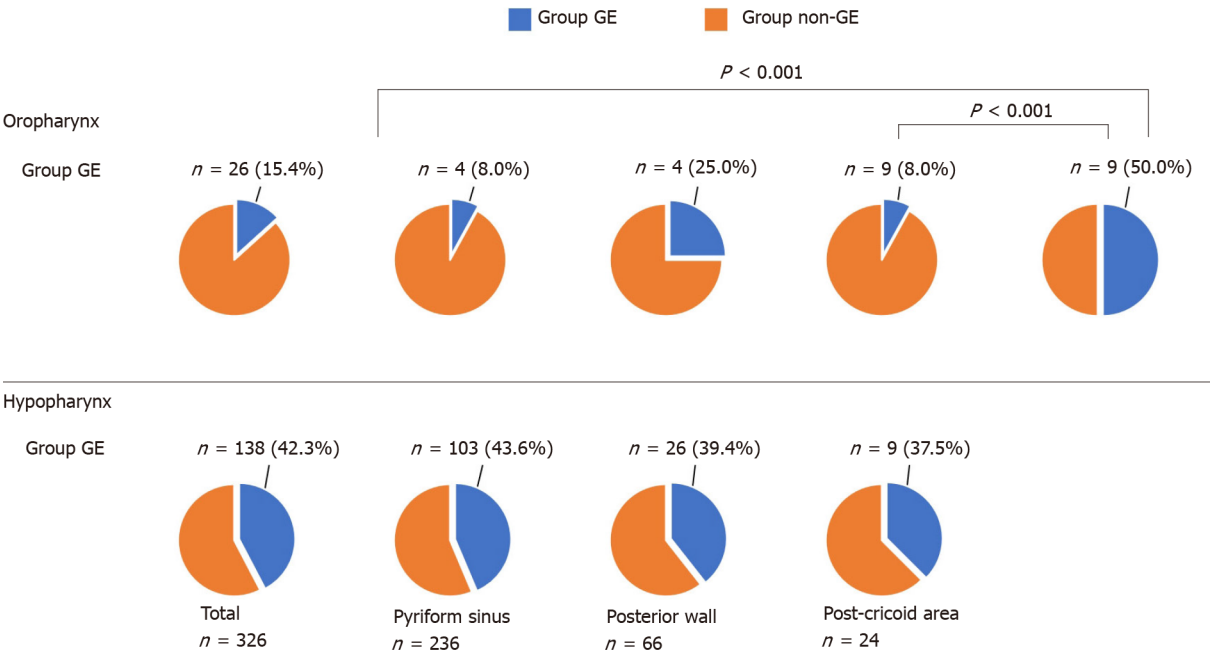

Figure 2 The subsites of primary lesions and the proportion of Group gastrointestinal endoscopy by subsite. The proportions of Group gastrointestinal endoscopy (GE) in the oropharynx and hypopharynx were 15.4% and 42.3%, respectively. Among the lesions in the oropharynx, the proportions of Group GE in the anterior and lateral wall were lower than the posterior wall. There was no significant difference in the proportion of Group GE by subsite in the hypopharynx.

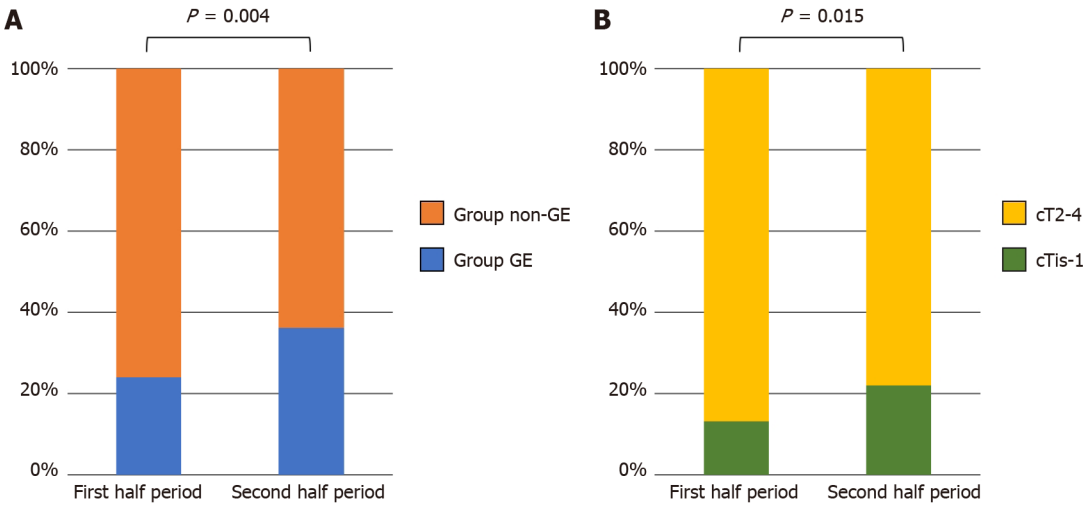

Figure 3 Trends in the detection modality and clinical stage of pharyngeal cancer. A: A comparison of the proportion of Group gastrointestinal endoscopy between the first and second half periods (2011–2014 and 2015–2018); B: A comparison of the proportion of cTis-1 lesions between first and second half periods (2011–2014 and 2015–2018). Group GE: Group gastrointestinal endoscopy.

hospital in Kumamoto prefecture. This would increase the proportion of Group GE. However, as our hospital is the only university hospital in Kumamoto prefecture, most advanced cases which required surgery or CRT were referred here, as well as ELPS/ESD cases, and we consider our data represent the current situation in Kumamoto prefecture.

CONCLUSION

Gastrointestinal endoscopy is playing an increasingly important role in the detection of pharyngeal SCCs, considering that 31.4% of all cases and almost all asymptomatic cases were detected by gastrointestinal endoscopy. For preserving the quality of life

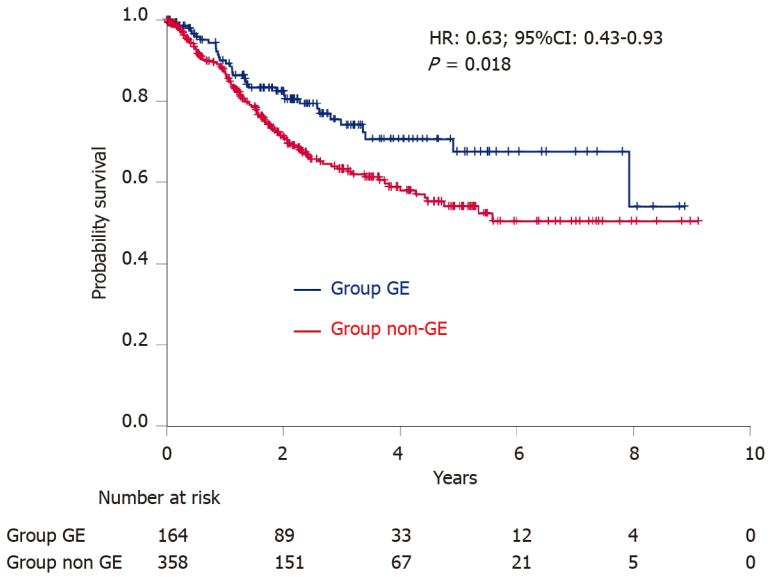

Figure 4 Kaplan–Meier estimates of overall survival. HR: Hazard ratio; CI: Confidence interval; GE: Gastrointestinal endoscopy.

and improving the prognosis of pharyngeal SCCs, it is important to detect the lesions using gastrointestinal endoscopy, while they are asymptomatic.

ARTICLE HIGHLIGHTS

Research background

Recently, many pharyngeal cancers have been discovered by gastroenterologists, with the growing availability of image enhanced endoscopy in gastrointestinal endoscopy. However, few studies have shown how much gastroenterologists contribute to the detection and treatment of pharyngeal cancer. In particular, the details of the lesions detected by the gastrointestinal endoscopy are unknown.

Research motivation

To highlight that gastrointestinal endoscopists should take a more active role both in the detection and treatment of pharyngeal cancer.

Research objectives

To clarify the importance of gastrointestinal endoscopy in detection and treatment of pharyngeal cancer.

Research methods

In this retrospective cohort study, the authors assessed the clinical records of consecutive 522 patients with oropharyngeal or hypopharyngeal cancer in our hospital between January 2011 and December 2018. The lesions were classified into two groups: Group GE (detected by gastrointestinal endoscopy) and Group non-GE (detected by means other than gastrointestinal endoscopy), and the clinical characteristics were compared between the two groups.

Research results

Of total 522 lesions, 164 (31.4%) in Group GE had a higher proportion of asymptomatic cases (61.6% *vs* 7.3%, $P < 0.001$), cTis-1 cases (32.9% *vs* 12.0%, $P < 0.001$), cases with no lymph node metastasis (69.5% *vs* 19.0%, $P < 0.001$) and cases treated by endoscopic laryngo-pharyngeal surgery/endoscopic submucosal dissection (21.3% *vs* 0.6%, $P < 0.001$) than Group non-GE, leading to a better prognosis.

Research conclusions

To the best of our knowledge, this is the first study to explore the detection modality of oropharyngeal and hypopharyngeal squamous cell carcinomas (SCC) in a large number of cases. Gastrointestinal endoscopy plays an important role in the early

detection and improving the prognosis of pharyngeal SCCs.

Research perspectives

In the future, a multicenter prospective study should be designed in a set up where equal accessibility to gastrointestinal endoscopy and otolaryngology services is available.

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ORIGINAL ARTICLE

Retrospective Study

Follow-up outcomes in patients with negative initial colon capsule endoscopy findings

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Author contributions: Nakaji K analyzed the data and wrote the manuscript; Nakaji K, Kumamoto M, Yodozawa M, and Okahara K performed the colon capsule endoscopy and collected the data; Suzumura S supervised the statistical analysis and Nakae Y supervised the study.

Institutional review board statement: The Ethical Review Committee at Aishinkai Nakae Hospital approved this retrospective study on February 12, 2021 (approval No. 015).

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Abstract

BACKGROUND

Colon capsule endoscopy (CCE), which became clinically applicable in 2006, is a simple and noninvasive procedure to evaluate colonic diseases; the accuracy of second-generation CCE, introduced in 2009, has dramatically improved. Currently, CCE is used as an alternative method for colorectal cancer screening, as well as for evaluating the mucosal lesions of inflammatory bowel disease, in cases where performing colonoscopy (CS) is difficult. However, the outcomes of CCE are uncertain.

AIM

To investigate the outcomes of Japanese patients with negative findings (no polyps or colorectal cancer) on initial CCE.

METHODS

This retrospective, single-center study was conducted at the Endoscopic Center at Aishinkai Nakae Hospital. This study included patients who underwent continuous CCE between November 2013 and August 2019, that exhibited no evidence of polyps or colorectal cancer at the initial CCE, and could be followed up using either the fecal immunochemical test (FIT), CS, or CCE. The observational period, follow-up method, presence or absence of polyps and colorectal cancer, pathological diagnosis, and number of colorectal cancer deaths were evaluated.

RESULTS

Thirty-one patients (mean age, 60.4 ± 15.6 years; range, 28–84 years; 14 men and 17 women) were enrolled in this study. The reasons for performing the first CCE

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were screening in 12, a positive FIT in six, lower abdominal pain in nine, diarrhea in two, and anemia in two patients. The mean total water volume at the time of examination was 3460 ± 602 mL (2250–4800 mL), and a total CS was performed in 28 patients (90%). The degree of cleanliness was excellent in 15 patients and good in 16, and no poor cases were observed. No adverse events, such as retention or capsule aspiration, were observed in any of the patients. The mean follow-up period was 3.1 ± 1.5 years (range, 0.3–5.5 years). Follow-up included FIT in nine, CS in 20, and CCE in four patients (including duplicate patients). The FIT was positive in two patients, while CS revealed five polyp lesions (three in the ascending colon, one in the transverse colon, and one in the descending colon), with sizes ranging between 2 mm and 8 mm. Histopathological findings revealed a hyperplastic polyp in one patient, and adenoma with low grade dysplasia in four patients; colorectal cancers were not recognized. In the follow-up example by CCE, polyps and colorectal cancer could not be recognized. During the follow-up period, there were no deaths due to colorectal cancer in any of the patients.

CONCLUSION
We determined the outcomes in patients with negative initial CCE findings.

Key Words: Colon capsule endoscopy; Negative findings; Observation; Colorectal polyps; Colorectal cancer; Colorectal cancer death

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Core Tip: Colon capsule endoscopy is becoming popular as a screening test for colorectal cancer in patients where colonoscopy is difficult. Its accuracy is comparable to that of colonoscopy; however, the outcomes are unknown. This study evaluated the follow-up methods, presence or absence of polyps and colorectal cancer, and cancer deaths after follow-up in Japanese patients with negative capsule endoscopy findings.

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INTRODUCTION

The number of patients with colorectal cancer has been increasing in Japan[1], compared with the United States. It is the primary cause of cancer death in women, and third most common cause in men[1]. In Japan, fecal occult blood testing using the two-day method is performed for colorectal cancer screening in patients aged 40 years or older, while colonoscopy (CS) is performed in patients with at least one positive fecal immunochemical test (FIT)[1]. Still, although CS is the gold standard for colorectal cancer screening, the frequency of CS following a positive FIT is approximately 60%[1]. This may be due to fear of perforation and hemorrhage caused by the invasive nature of CS. Colon capsule endoscopy (CCE) is noninvasive and convenient; additionally, during the coronavirus disease 2019 (COVID-19) pandemic, CCE has drawn attention as a home-based test that does not pose a risk of severe acute respiratory syndrome coronavirus 2 infection[2]. Second-generation CCE has dramatically improved accuracy by incorporating a wide field of view and adaptive frame rate (adjusting 4–35 images/s to accommodate the capsule movement)[3], and is now regarded a noninvasive method for colorectal cancer screening in patients where CS is difficult[4]. Since 2020 in Japan, the indications have been expanded to include patients with the physical burdens associated with CS, such as hypertension, diabetes, and chronic obstructive pulmonary disease; the number of examinations is therefore expected to increase in the future.

Conversely, there are concerns regarding CCE overlooking colorectal polyps and cancers during long-term follow-up that CS would otherwise have been detected in patients who present negative initial CCE results; intermediate cancers and cancer deaths may have been caused as a result. To the best of our knowledge, there are no reports regarding the long-term follow-up of patients screened for colorectal cancer with initial negative initial CCE results; therefore, we evaluated the efficacy of initial CCE results through the follow-up of patients without polyps or colorectal cancer.

MATERIALS AND METHODS

Patient selection

This retrospective, single-center study included consecutive patients who underwent CCE at the outpatient unit of Aishikai Nakae Hospital for colorectal cancer screening between November 2013 and August 2019 due to difficulty performing CS (either the colonoscope could not be inserted into the cecum, or CS was expected to be challenging to perform due to postoperative adhesions). Of these patients, those without findings on initial CCE (defined as those without polyps of any size and/or cancerous lesions) were followed up. Inclusion criteria for the study were patients who underwent follow-up with either FIT, CS, or CCE; patients were excluded if they had inflammatory bowel disease or were previously found to have a polyp or colorectal cancer. Exclusion criteria for performing CCE included dysphagia, pacemaker placement, and possible pregnancy. This study was conducted under the Declaration of Helsinki and was approved by the ethics committee of Aishinkai Nakae Hospital on February 12, 2021 (No. 015). Informed consent was obtained in the form of opt-out on the bulletin board in the hospital. Those who were withdrew were excluded from the study.

Definition of follow-up from initial CCE

Follow-up from initial CCE was defined as patients reexamined over 3-month intervals after the first CCE, either by the FIT, CS, or CCE. The FIT was performed on two separate days; one positive test was considered positive, and two negative tests were considered negative.

The CCE procedure

PillCamCOLON2 (Medtronic, Minneapolis, United States) was used for all patients. Pretreatment began the day before the examination. The patients ingested a low-residue diet test meal at home for breakfast, lunch, and dinner, and at 19:00, they drank a hypertonic solution by dissolving 50 g of magnesium citrate (Magcolol P; Horii Pharmaceutical Co., Ltd., Osaka) in 180 mL of water. Before bedtime, they had 10 mg of 0.75% sodium picosulfate with 100 mL of water. On the day of the examination, the patients fasted during the morning, after which they drank 1000 mL of ascorbic acid-containing hypertonic polyethylene glycol solution (Asc-PEG; Mobiprep; EA Pharma, Tokyo) and 500 mL of water. The patients' stool frequency and properties were checked, and stool was required for a clear liquid state. Thereafter, the sensor array was fitted, and the capsule was swallowed after taking 20 mg of mosapride with 100 mL of water. Metoclopramide (10 mg) was injected intramuscularly when the small intestine did not reach 60 min after capsule swallowing. An additional 10 mg of metoclopramide was administered if the capsule did not reach the small intestine after 120 min). Once in the small intestine, 30 mL of aromatic castor oil and 100 mL of Asc-PEG were added. After reaching the large intestine, patients ingested 400 mL of Asc-PEG and 250 mL of water over 30 min. Subsequently, 500 mL of Asc-PEG and 250 mL of water were taken (over 30 min) to expel the capsule. After the capsules reached the small intestine, exercises-such as walking and stair ascending and descending exercises-were encouraged. If capsules were not expelled by 5 p.m. of the same day, the following options were considered: (1) An intramuscular injection of 10 mg metoclopramide; (2) Oral administration of 30 mg castor oil and 100 mg water; (3) Oral administration of 50 g of magnesium citrate dissolved in 180 mg of water, or (4) Administration of 60 mg of glycerin enema if there was no discharge of the colon capsule (Figure 1).

CCE reading

After completing the study, the data recorder was downloaded to a workstation equipped with dedicated interpretation software (RAPID software v8.0 or v8.3). The

Day procedure	
-1	Low residual diet
	A hypertonic solution prepared by dissolving 50 mg of magnesium citrate in 180 mg of water
	10 mg of 0.75% sodium picosulfate and 80 mg of water at bedtime
0	500-1000 mg of ascorbic acid-containg polyethylene glycol solution and 250-500 mg of water until the stool became clear
	Capsule ingestion with 20 mg of mosapride
	Booster 1: 30 mg of castor oil and 100 mg of acid-containg polyethylene glycol solution
	Booster 2: 400 mg of ascorbic acid-containg polyethylene glycol solution and 250 mg of water
	Booster 3: 500 mg of ascorbic acid-containg polyethylene glycol solution and 250 mg of water
	Other options (If the capsule did not discharge): Intramuscular administration of 10 mg of metoclopramide or oral administration of 30 mg of castor oil and 100 mg of water or oral administration of 50 mg of magnesium citrate dissolved in 180 mg of water
	60 mg of glycerin enema

Figure 1 Colon capsule endoscopy procedure.

following parameters were examined: laxative dose, intestinal transit time (time from the capsule reaching the duodenum to the end of the ileum), colonic transit time (time from capsule reaching the cecum to exit the anus), total colic observation rate (when the capsule emptying through the anus or dentate line can be confirmed), and intestinal lavage rate. Intestinal cleanliness was graded on a 4-point Leighton-Rex scale [5] by five segments of the large intestine, defined as "excellent" (only a tiny amount of stool), "good" (small amounts of stool or cloudy fluid, but not sufficient to interfere with interpretation), "fair" (cloudy fluid if it completely precluded reliable examination), and "poor" (a large amount of stool). The cleanliness of the entire colon was evaluated as appropriate by adopting the lowest rating for each segment. The findings were read by a Japanese Society for Capsule Endoscopy certified support technician and one or more experienced physicians.

Adverse events were defined as the retention of capsules (stay in the intestine with the inability to confirm anal emptying of the capsule for at least 14 d) and consequent intestinal obstruction, Mallory-Weiss syndrome, intestinal perforation, vomiting due to oral laxatives, and aspiration pneumonia. In this study, we investigated the following data in patients: (1) Observation period; (2) Follow-up method; (3) Presence or absence of polyps and colorectal cancer; (4) Final pathologic diagnosis; (5) Presence or absence of adverse events, and (6) Cancer-related deaths.

Statistical analysis

All continuous variables are presented as means and standard deviations. Statistical analysis was performed using IBM SPSS Statistics for Windows (SPSS Inc., Chicago, IL, United States).

RESULTS

During the study, 208 patients underwent CCE for colorectal cancer screening; 82 patients were found to be negative for polyps and/or cancerous lesions after the first CS capsule. Of these, 31 patients were followed up *via* either FIT, CS, or CCE; the remaining 51 patients were not followed-up *via* either FIT, CS, or CCE since their initial CCE. The characteristics of patients with negative CCE results are shown in Table 1. The mean age of the cohort was 60.4 years, and 45.2% (n = 14) were male. The most common reason for performing CCE was screening results (n = 12; patients aged over 40 years, with no symptoms). No adverse events, such as retention or capsule aspiration, were observed.

Table 1 Characteristics of patients with negative colon capsule endoscopy results, n (%)

Total number of patients		*n* = 31
Gender (*n*)		
	Female	17
	Male	14
Age (yr, range)		60.4 ± 15.6 (28 - 84)
Reasons (*n*)		
	Screening	12
	Fecal immunochemical test positive (*n*)	6
	Lower abdominal pain (*n*)	9
	Diarrhea (*n*)	2
	Anemia (*n*)	2
Indication (*n*)		
	Incomplete colonoscopy (*n*)	0
	Anticipated difficulty of total colonoscopy (*n*)	31
CCE completion		28 (90)
Cleanliness (*n*)	Excellent, good, fair, poor	15, 16, 0, 0
Total water content		3460 ± 602 mL (2250-4800 mL)
Adverse events (*n*)		0

CCE: Colon capsule endoscopy.

The characteristics of colonic polyps found during the follow-up period of patients with negative CCE results are shown in Table 2; the mean follow-up period was 3.1 years. CS was the most common method of follow-up after initial CCE (*n* = 20). Five colonic polyps (three in the ascending colon, one in the transverse colon, and one in the descending colon) were identified through follow-up CS; based on the Narrow-band imaging International Colorectal Endoscopic classification[6], these were classified as type 1 and 2 polyps. Histopathological findings included a hyperplastic polyp in one patient, and adenoma with low grade dysplasia in four patients, while in cases followed-up by CCE, colonic polyps and colorectal cancer could not be identified. Excluding symptomatic patients, screening was followed by CS in seven, FIT in three, and CCE in two patients for an average of 2.8 years; no polyps or colorectal cancers were found through either method. During the follow-up period, no deaths due to colorectal cancer occurred in any of the patients. Representative images of follow-up on CS are presented in comparison with the initial CCE findings (Figure 2).

DISCUSSION

To the best of our knowledge, this is the first follow-up study of negative initial CCE findings in Japanese patients. Colorectal cancer was not observed in any of the cases, while only small polyps were detected during the follow-up period. The widespread use of screening tests for colorectal cancer screening with FIT is expected to increase the frequency of CSs in the future; however, the number of skilled physicians performing CS is limited. Additionally, as the COVID-19 pandemic continues in the future, conventional endoscopic education becomes difficult[7]; the number of skillful physicians performing CS may not be expected to increase accordingly[7]. To compensate for this situation, noninvasive and straightforward CCE screening for colorectal cancer has been and should continue to be examined. However, the diagnostic reading of CCE is challenging. It usually requires a reading of 50000–60000 frames, may have only one or a few frames of essential findings, and is always at risk of overlooking an interpreter's findings[8]; thus, initial reviews by other clinical staff

Table 2 Characteristics of polyp lesions identified *via* colonoscopy during the follow-up period from colon capsule endoscopy negative results

	Number	Size (mm)	Shape	Histology	Intervals (years)
Cecum	0	-	-	-	-
Ascending colon	3	4, 4, 2	Semipedunculated type	Tubular adenoma with low grade dysplasia	5, 5, 1.8
Transverse colon	1	8	Semipedunculated type	Tubular adenoma with low grade dysplasia	2.4
Descending colon	1	3	Semipedunculated type	Hyperplastic polyp	1.8
Sigmoid colon	0	-	-	-	-
Rectum	0	-	-	-	-

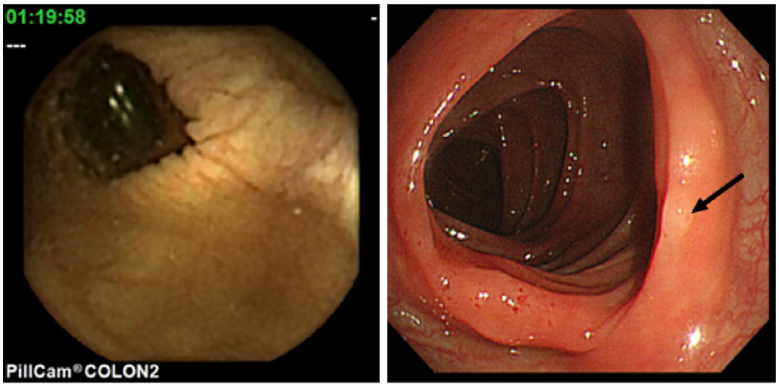

Figure 2 Representative images. Follow-up on colonoscopy (Right) is presented with the initial negative colon capsule endoscopy findings (Left): An arrow indicates an adenoma with low grade dysplasia in the transverse colon. CCE: Colon capsule endoscopy; CS: Colonoscopy.

(for example, endoscopic nurses) are required[9]. Additionally, while interpretive assistance using artificial intelligence has been studied[10], it is not yet a widely established method in routine clinical practice at the research stage. Follow-up of CCE is therefore necessary-including examination of interval cancers-without overlooking significant polyp findings observed during the initial CCE that would have been detected by CS.

In the guidelines for colorectal cancer screening[11], sigmoidoscopy, multitargeted stool DNA testing (FIT-DNA), computed tomography colonography (CTC), and CCE are recommended for patients aged 50–75 years when FIT or CS is not desirable. At these intervals for follow-up, FIT is recommended annually, CS every 10 years, FIT-DNA every 3 years, sigmoidoscopy every 5 years, CTC every 5 years, and CCE every 5 years. In our review of CCE, no advanced neoplasia was found at approximately 5-year intervals; colorectal screening with CCE every 5 years was therefore considered appropriate for Japanese patients in this study.

In a review of other modalities with negative imaging, Heisser *et al*[12] reported in a meta-analysis of CS studies that when stratified according to negative CS results from 1–5 years, 5–10 years, or more than 10 years, the detection of polyps was 20.7%, 23.0%, and 21.9%, respectively; advanced neoplasia, including cancer, was observed in 2.8%, 3.2%, and 7.0% of cases, respectively. In a retrospective study of negative CTC results from a single institution, Pickhardt *et al*[13] reported that 12.1% of the patients had polyps 6 mm or larger in diameter, while 0.1% had advanced neoplasia-including cancer-in 10 years of follow-up. Although direct comparison is difficult due to differences regarding the number of patients, the definition of negative findings, and the duration of observation compared with this study, the 5-year follow-up results of their study demonstrated that 12.9% of all polyp lesions, 3.2% of polyps 6 mm or more, 0% of advanced neoplasia including cancer, and the other negative results were better than the other modalities.

In this study, CS was the most common method used for follow-up after the first CCE, followed by FIT and CCE. The widespread use of CS in Japan and the high cost of CCE may have contributed to this observation. At present, there is a report regarding improvement of the capsule discharge rate using castor oil as a booster[14].

Our study demonstrated that polyp lesions found after the first CCE were more frequent in the ascending colon. Evaluation of negative CS and CTC results indicated that many cases of polyps were found in the right-sided colon during the follow-up period. Although the cause is unknown, it is believed that in our case, the lesions were often overlooked as the capsule had passed quickly in the ascending colon.

This study has several limitations. First, this was a single-center retrospective study with a small number of cases; however, as a single-center study, follow-up of the same patient was possible. Second, the observational period was considerably short; additional long-term follow-up is necessary in the future. Third, the follow-up method was not standardized; this is a limitation of retrospective studies, and it is of particular concern that all patients who underwent the FIT were negative at follow-up in the present study. Still, there have been reports of colorectal cancer in FIT-negative patients[15]; thus, the possibility of colorectal cancer inclusion in these cases cannot be ruled out. It is necessary to follow up in CS in these cases. Fourth, there is a possibility that lesions could be overlooked during interpretation of the first CCE; however, in this study, we thoroughly reviewed the entire image. Further progress regarding the interpretation of CCE by artificial intelligence will help to provide more accurate interpretations. Finally, because CCE moves back and forth, the possibility of overcounting polyp lesions and flat polyp lesions has not been investigated in this study and should be considered in the future.

CONCLUSION

In the present study, follow-up of patients with negative initial CCE results revealed no colorectal cancer; only small polyps were found.

ARTICLE HIGHLIGHTS

Research background

Colon capsule endoscopy (CCE) is a noninvasive and easy procedure for detecting colorectal lesions when difficult to perform colonoscopy (CS). The incidence of CCE has been increasing due to its noninvasive nature and low risk of infection during the Covid-19 pandemic; however, its follow-up on efficacy remains unknown.

Research motivation

Currently, guidelines recommend that patients with no significant findings on initial CCE should repeat CCE every five years, or follow up with another screening test. However, there is limited evidence in clinical practice.

Research objectives

The study's main objective was to investigate the follow-up outcomes in Japanese patients without polyp and colonic cancer at the initial CCE.

Research methods

Thirty-one consecutive Japanese patients negative for polyp and cancer lesions on initial CCE were analyzed.

Research results

We propose that researchers conduct a multicenter, prospective, long-term follow-up of initial CCE screening results.

Research conclusions

Our study determined the outcomes of Japanese patients with negative CCE results.

Research perspectives

The mean follow-up period was 3.1 years; CS was determined to be the most common method of follow-up after the initial CCE (n = 20). Five colonic polyps (three in the ascending colon, one in the transverse colon, and one in the descending colon) were identified through follow-up CS; based on the Narrow-band imaging International Colorectal Endoscopic classification, these were classified as type 1 and 2 polyps. Histopathological findings included a hyperplastic polyp in one patient, and adenoma

with low grade dysplasia in four patients; no deaths due to colorectal cancer, or severe adverse events, were observed in any patient during follow-up.

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ORIGINAL ARTICLE

Retrospective Study

Safety of upper endoscopy in patients with active cocaine use

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Institutional review board statement: This study was reviewed and approved by the Ethics Committee of the John H. Stroger, Jr. Hospital of Cook County

Informed consent statement: Patients were not required to give informed consent to the study because the analysis used anonymous clinical data that were obtained after each patient agreed to treatment by written consent.

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Abstract

BACKGROUND

Cocaine is a synthetic alkaloid initially viewed as a useful local anesthetic, but which eventually fell out of favor given its high addiction potential. Its predominantly sympathetic effects raise concern for cardiovascular, respiratory, and central nervous system complications in patients undergoing procedures. Peri-procedural cocaine use, often detected *via* a positive urine toxicology test, has been mostly addressed in the surgical and obstetrical literature. However, there are no clear guidelines on how to effectively risk stratify patients found to be positive for cocaine in the pre-operative setting, often leading to costly procedure cancellations. Within the field of gastroenterology, there is no current data available regarding safety of performing esophagogastroduodenoscopy (EGD) in patients with recent cocaine use.

AIM

To compare the prevalence of EGD related complications between active (≤ 5 d) and remote (> 5 d) users of cocaine.

METHODS
In total, 48 patients who underwent an EGD at John H. Stroger, Jr. Hospital of Cook County from October 2016 to October 2018 were found to have a positive urine drug screen for cocaine (23 recent and 25 remote). Descriptive statistics were compiled for patient demographics. Statistical tests used to analyze patient characteristics, procedure details, and preprocedural adverse events included *t*-test, chi-square, Wilcoxon rank sum, and Fisher exact test.

RESULTS
Overall, 20 periprocedural events were recorded with no statistically significant difference in distribution between the two groups (12 active *vs* 8 remote, $P = 0.09$). Pre- and post-procedure hemodynamics demonstrated only a statistically, but not clinically significant drop in systolic blood pressure and increase in heart rate in the active user group, as well as drop in diastolic blood pressure and oxygen saturation in the remote group ($P < 0.05$). There were no significant differences in overall hemodynamics between both groups.

CONCLUSION
Our study found no significant difference in the rate of periprocedural adverse events during EGD in patients with recent *vs* remote use of cocaine. Interestingly, there were significantly more patients (30%) with active use of cocaine that required general anesthesia as compared to remote users (0%).

Key Words: Gastrointestinal endoscopy; Cocaine-related disorders; General anesthesia; Risk factors; Local anesthetics; Retrospective studies

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Core Tip: There is no data available regarding safety of performing an esophago-gastroduodenoscopy in patients with evidence of recent cocaine use. This study compared the prevalence of procedure complications between active and remote cocaine users and found no statistically significant difference between the two groups. Pre- and post-procedure hemodynamics demonstrated only statistically, but not clinically significant changes in blood pressure, heart rate, and oxygenation. Results suggest relative safety in performing this procedure on active cocaine users. Patients in the active group required more general anesthesia; however, given nature of study, the reasoning behind this sedation choice was difficult to determine.

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INTRODUCTION

Illicit drug abuse remains an ongoing public health crisis in the United States. As of 2018, 11.7% of the population over the age of 12 were illegal drug users. Of these, 2% reported regular use of cocaine[1]. Given the self-reporting nature of these statistics, there is reasonable concern that these values may be a significant underestimation of the actual number of active cocaine users in the population[2]. In the medical literature, cocaine's predominantly sympathetic effects have been linked to a myriad of cardiovascular, respiratory, and central nervous system complications that may compromise patient stability when undergoing a procedure. Major cardiac abnormalities such as tachycardias, hypertension, myocardial ischemia or infarction, and various arrhythmias are at the forefront of concern[3]. Pulmonary edema, pulmonary hemorrhages, and pulmonary barotrauma have been attributed to the use of smoked "crack" cocaine[4]. Lastly, cocaine has also been implicated in several neurological complications including hemorrhage, stroke, seizures, and coma[5,6].

additional data are available.

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Table 1 Patient characteristics

		Active cocaine users, *n* = 23	Remote cocaine users, *n* = 25	*P* value[3]
Age, yr, *n*[2]	(Avg. ± SD)	51.0 ± 9.5	54.8 ± 10.9	0.210[4]
Sex, *n*[1]	Male	19	11	0.006[5]
	Female	4	14	
Ethnicity, *n*[1]	White	1	2	0.889[6]
	African American	17	19	
	Hispanic	5	4	
EKG, *n*[1]	Normal	8	9	0.757[5]
	Abnormal	14	13	
	No EKG	1	3	
Comorbidities, *n*[1]	Pulmonary	8	8	0.838[5]
	Cardiac	4	4	1.000[6]
	Renal	1	3	0.610[6]
	Liver	4	12	0.025[5]
	Hypertension	7	12	0.214[5]
	Other drug abuse	12	17	0.263[5]
	Neurologic	0	1	1.000[6]
	Obesity	1	2	1.000[6]
	Infectious	1	13	0.0003[5]
	Malignancy	1	3	0.610[6]
	Diabetes	1	3	0.610[6]
	Other	3	3	1.000[6]

[1]Categorical value. Presented as frequency.
[2]Continuous variables. Presented as mean value and standard deviation.
[3]Compared to alpha value < 0.05 for significance.
[4]*t*-test.
[5]chi-SQ.
[6]Fisher exact test.
EKG: Electrocardiogram

Jeffcoat *et al*[7] published one of the first studies exploring the differences in common routes of administration of cocaine including intravenous injection, nasal insufflation, and smoke inhalation. From this paper, the elimination half-life of cocaine was calculated to range between 69-78 min depending on the mode of administration. Using more modern laboratory assays for detection, the plasma half-life of cocaine has been determined to range between 0.7–1.5 h while the urine detection window is typically less than 1 d[8]. Cocaine's main inactive metabolite, benzoylecgonine, has a plasma half-life of 5.5–7.5 h and a urine drug screen (UDS) window of 1–2 d[9]. These values can vary depending on differences in renal function, and frequency of cocaine use. In fact, benzoylecgonine has been detected in the urine up to 10-14 d after heavy cocaine use[10].

Pre-procedural management of a patient with recent cocaine use, typically determined *via* a positive urine toxicology test detecting benzoylecgonine, has been mostly addressed in the surgical and obstetrical literature. Within these fields, only a handful of cases have been published reporting cardiac arrhythmias, hypertension, and myocardial ischemia while intoxicated with cocaine and under general anesthesia [11]. In the setting of elective surgeries, larger studies such as Hill *et al*[12] demonstrated no greater risk for intraprocedural complications for non-toxic cocaine users when compared to drug-free patients. Baxter and Alexandrov[13] showed statistically significantly higher baseline systolic pressure, mean arterial pressure, and heart rate differences in the cocaine-positive cohort, but ultimately these were not deemed

clinically significant values. More recently, Moon *et al*[14] determined that cocaine positive patients did not demonstrate significantly different medication requirements as compared to cocaine-negative patients.

Despite the existence of this data, there remains no standard for practice on how to proceed with procedures this patient population. As such, practitioner preference is often used to determine the main course of action, leading to same day cancellations of procedures, resulting in waste of clinical time and resources[15]. There have been no direct published works addressing complications encountered during gastrointestinal endoscopies in patients with positive cocaine drug screens. This retrospective, single-center study aims to determine the safety of EGD with anesthesia support in patients who abuse cocaine, both actively and remotely.

MATERIALS AND METHODS

Records were reviewed from patients who underwent EGD at John H. Stroger, Jr. Hospital of Cook County from October 2016 to October 2018. Those with a cocaine positive UDS within less than 6 mo were identified. Remote cocaine users were classified as individuals with positive cocaine screen > 5 d, up to 6 mo from procedure, while active cocaine users had a positive UDS within 5 d. The study was approved by the institutional review board.

Demographic data including age, ethnicity, and comorbidities (pulmonary, cardiac, renal, liver, hypertension, other drug abuse, neurologic, obesity, infectious disease, malignancy, diabetes, and other medical conditions) were recorded. Procedural details such as American Society of Anesthesiologists Classification (ASA class), urgency level of procedure, type of anesthesia, location (inpatient *vs* outpatient), and length of stay, were also collected. Periprocedural adverse events such as hypotension, tachycardia, nausea/vomiting, and oxygen desaturation were recorded. The outcomes measured included hemodynamic changes in blood pressure, heart rate, respiratory rate, and oxygen saturation, pre- and post-procedure.

All patient data was analyzed using STATA/SE 12.0 and Excel version 365 (Microsoft). Several statistical tests were used to analyze patient characteristics, procedure details, and preprocedural adverse events including *t*-test, chi-square, Wilcoxon rank sum, and Fisher exact test. All *P*-values < 0.05 were considered statistically significant.

RESULTS

A total of 2122 patients were identified during the study period; 129 patients had a positive drug screen of which 48 were positive for cocaine. Active users (23) were predominately male (83%) and African American (74%). Remote users (25) were 44% female and predominantly African American (76%). There was a significant difference male gender predominance in the active group compared to the remote ($P = 0.006$). A substantial number of patients in both groups had abnormal admitting electrocardiogram (14 active *vs* 13 remote) and both were found to have concurrent drug abuse (12 active *vs* 17 remote) as their most prevalent comorbidity (Table 1). There was no significant difference between groups for both categories, although liver and infectious comorbidities were more prevalent in the remote group ($P = 0.025$, 0.0003).

Patients in both groups underwent urgent procedures (17 active *vs* 14 remote) with no statistical difference ($P = 0.195$); although the active group was treated more often in the inpatient setting ($P = 0.024$). ASA class III was most prevalent among the two groups (14 active *vs* 21 remote) although more predominant in the remote group ($P = 0.046$). Monitored anesthesia care (MAC) sedation was the preferred anesthesia support over general anesthesia (16 active *vs* 25 remote) ($P = 0.003$). Hospitalizations were longer for remote *vs* active patients ($P = 0.003$), (Table 2). Overall, 20 periprocedural adverse events occurred among the 48 patients. Although not statistically significant, active users had more events compared to remote users (12 *vs* 8, $P = 0.09$) defined as documented oxygen desaturation during the procedure, use of vasopressor, rate-controlling, or anti-nausea medications (Table 3).

Pre- and post-procedure hemodynamics demonstrated a statistically significant, but not clinically significant, drop in systolic blood pressure (136/77 pre-procedure *vs* 129/76 post-procedure, $P = 0.03/0.64$), as well as an increase in heart rate (73 pre-procedure *vs* 76 post-procedure, $P = 0.04$) in the active user group. In the remote user group, there was also a statistically significant, but not clinically significant, drop in

Table 2 Procedure details

		Active cocaine users, *n* = 23	Remote cocaine users, *n* = 25	*P* value[3]
Urgency, *n*[1]	Non-urgent	6	11	0.195[4]
	Urgent	17	14	
Location, *n*[1]	Inpatient	22	17	0.024[5]
	Outpatient	1	8	
ASA Class, *n*[1]	Class II	9	3	0.046[5]
	Class III	14	21	
	Class IV	0	1	
LOS, *n*2	(Avg day ± SD)	5.4 ± 3.6	5.6 ± 11.9	0.018[6]
Type of Anesthesia,	MAC	16	25	0.003[5]
n[1]	General	7	0	

[1]Categorical value. Presented as frequency.
[2]Continuous variables. Presented as mean value and standard deviation.
[3]Compared to alpha value < 0.05 for significance.
[4]chi-SQ.
[5]Fisher exact test.
[6]Wilcoxon rank sum test.
ASA Class: American Society of Anesthesiologists Classification; LOS: Length of stay; MAC: Monitored anesthesia care.

Table 3 Periprocedural adverse events

	Active cocaine users, *n* = 23	Remote cocaine users, *n* = 25	*P* value[2]
Cumulative complications, *n*[1]	12	8	0.09
Oxygen desaturation, *n*[1]	1	2	1.000[3]
Nausea/vomiting, *n*[1]	7	2	0.068[3]
Hypotension, *n*[1]	4	4	1.000[3]
Tachycardia, *n*[1]	0	0	NA

[1]Categorical value. Presented as frequency.
[2]Compared to alpha value < 0.05 for significance.
[3]Fisher exact test.

diastolic blood pressure (130/80 pre-procedure *vs* 124/74 post-procedure, P = 0.34/0.01) and oxygen saturation (98 pre-procedure *vs* 97 post-procedure, P = 0.04). There were no significant differences in overall hemodynamics between both groups when compared *via* two-sample *t*-test (Table 4).

DISCUSSION

To the best of our knowledge, our project is the first retrospective, single-center study aimed at determining the safety of EGD under anesthesia in patients who have recently abused cocaine with comparison to remote users. Although cumulatively there were more reported periprocedural adverse events in patients with active cocaine use compared to patients with remote cocaine use undergoing endoscopy, the primary result of this study was that ultimately this difference was statistically insignificant. Moreover, the statistically significant differences in preprocedural and postprocedural hemodynamics both within and across groups were, much like in the Baxter *et al*[13] study, not deemed clinically significant[14]. There was no reported mortality in any of the groups.

Table 4 Hemodynamic outcomes

	Active cocaine users, *n* = 23	Remote cocaine users, *n* = 25	*P* value[2,3]		
Blood pressure pre-procedure	136/77 (17/13)	130/80 (19/12)	0.14/0.38	Active: 0.03/0.64	Remote: 0.34/0.01
Blood pressure post-procedure (mmHg ± SD), *n*[1]	129/76 (15/11)	124/74 (27/12)	0.46/0.52		
Heart rate pre-procedure	73 (12)	78 (16)	0.16	0.04	0.27
Heart Rate post-procedure (BPM ± SD), *n*[1]	76 (13)	81 (16)	0.28		
Respiratory rate pre-procedure	19 (2)	19 (4)	0.95	0.11	0.42
Respiratory rate post-procedure (BPM ± SD), *n*[1]	18 (3)	20 (5)	0.10		
Oxygen saturation pre-procedure	98 (2)	98 (1)	0.43	0.74	0.04
Oxygen saturation post-procedure (% ± SD), *n*[1]	98 (2)	97 (3)	0.12		

[1]Continuous variables. Presented as mean value and standard deviation.
[2]Compared to alpha value < 0.05 for significance.
[3]*t*-test.

A unique component to our study, in contrast to much of the available literature, is the overwhelming preponderance of MAC used *vs* general anesthesia in both cohorts. MAC is a type of anesthesia commonly used in diagnostic or therapeutic procedures such as endoscopies as it can be titrated to maintain spontaneous breathing and airway reflexes[16]. For endoscopic procedures, especially in the ambulatory setting, the rapid recovery of MAC is ideal for high volume centers. In contrast, under general anesthesia, patients undergo a drug-induced loss of consciousness that prevents any ability to respond purposefully and often necessitate airway support[16]. Further analysis into the two cohorts of our study showed that active users were more likely to undergo the EGD under general anesthesia, 30%, *vs* remote users, 0%. Unfortunately, given the retrospective nature of the study and the small sample size, the reasoning behind this deviation in anesthesia type could not be further dissected. However, it may point to some component in the patient's clinical status that swayed the anesthesiologist to favor one form over the other.

As previously mentioned, given the retrospective nature of this study, there are several limitations that must be addressed. Despite the two-year timespan for chart review, our total sample population of cocaine positive patients, both active and remote, remained small. This was to be expected as UDS are not part of the standard pre-procedural work up of a patient undergoing an EGD. Additionally, similarly to what was mentioned in Moon *et al*[14], selection bias is likely at play in the sample population as individuals that undergo a procedure even after a positive cocaine UDS are more likely to need urgent intervention[14]. Lastly, despite the stratification of active *vs* remote users based off UDS timing, there are several unknown factors that could not be standardized such as the exact time span between the last drug use and the procedure date, quantity of cocaine consumed, and other confounding factors such as co-morbid polysubstance abuse. As such, the generalizability of the results of our current study is difficult to determine and larger studies are needed to corroborate our findings.

In summary, the findings of our study suggest that there are no significant differences in periprocedural adverse events or hemodynamic disturbances in active *vs* remote cocaine users undergoing an EGD with anesthesia support. Further investigation *via* larger prospective studies, containing a cocaine-negative control group, in which the type of anesthesia used can be standardized may elucidate any true difference in adverse events rates between MAC *vs* general anesthesia in this patient population. Additionally, given the wide range of drug agents used for MAC, other studies may be needed to identify which agents, if any, would be safer for use in cocaine positive patients or those suspected to have had recent cocaine abuse.

CONCLUSION

In conclusion, performing an EGD in patients with recent cocaine use, as evidenced by a positive UDS test, appears to be relatively safe, supporting forgoing procedure cancellation in this patient population.

ARTICLE HIGHLIGHTS

Research background

Procedure delay in patients with a recent history of cocaine use due to concerns of possible adverse events can compromise patient care and incur undue healthcare costs.

Research motivation

There is a paucity of literature available to risk stratify patients with recent cocaine use undergoing endoscopic procedures.

Research objectives

We endeavored in this study to evaluate the relative safety of performing an esophagogastroduodenoscopy (EGD) in this specific patient population.

Research methods

Pre- and post-procedure hemodynamics were recorded and as well as frequency of adverse events. Using statistical tests including *t*-test, chi-square, Wilcoxon rank sum, and Fisher exact test, our data analysis results suggested no statistically significant differences in periprocedural adverse events or clinically significant hemodynamic disturbances in active (< 5 d) *vs* remote cocaine users (> 5 d).

Research results

Our study found no significant difference in the rate of periprocedural adverse events during EGD in patients with recent *vs* remote use of cocaine.

Research conclusions

Performing an EGD in patients with recent cocaine use appears to be safe.

Research perspectives

Given the retrospective nature of this study, we hope our results generate more interest to explore this topic further in larger, prospective studies.

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ORIGINAL ARTICLE

Observational Study

Association between mucosal surface pattern under near focus technology and *Helicobacter pylori* infection

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Author contributions: Martins BC and Fiuza F contributed study concept and design; all authors contributed equally acquisition of data; Martins BC and Fiuza F contributed analysis and interpretation of data; Martins BC, Fiuza F, Ide E and Maluf-Filho F contributed drafting manuscript; all authors participated in critical review and approved the final draft submitted.

Institutional review board statement: The study was reviewed and approved by the ethical committee of Hospital

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Abstract

BACKGROUND

Many studies evaluated magnification endoscopy (ME) to correlate changes on the gastric mucosal surface with *Helicobacter pylori* (*H. pylori*) infection. However, few studies validated these concepts with high-definition endoscopy without ME.

AIM

To access the association between mucosal surface pattern under near focus technology and *H. pylori* infection status in a western population.

METHODS

Cross-sectional study including all patients referred to routine upper endoscopy. Endoscopic exams were performed using standard high definition (S-HD) followed by near focus (NF-HD) examination. Presence of erythema, erosion, atrophy, and nodularity were recorded during S-HD, and surface mucosal pattern was classified using NF-HD in the gastric body. Biopsies were taken for rapid urease test and histology.

RESULTS

One hundred and eighty-seven patients were analyzed from August to November 2019. Of those, 47 (25.1%) were *H. pylori*+, and 42 (22.5%) had a previous *H. pylori* treatment. In the examination with S-HD, erythema had the best sensitivity for *H. pylori* detection (80.9%). Exudate (99.3%), nodularity (97.1%), and atrophy (95.7%) demonstrated better specificity values, but with low sensitivity (6.4%-19.1%). On the other hand, the absence of erythema was strongly associated with *H. pylori*- (negative predictive value = 92%). With NF-HD, 56.2% of patients presented type

Alemão Oswaldo Cruz, São Paulo, Brazil (number of approval 3.577.527).

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STROBE statement: The authors have read the STROBE Statement-checklist of items, and the manuscript was prepared and revised according to the STROBE Statement-checklist of items.

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1 pattern (regular arrangement of collecting venules, RAC), and only 5.7% of RAC+ patients were *H. pylori*+. The loss of RAC presented 87.2% sensitivity for *H. pylori* detection, 70.7% specificity, 50% positive predictive value, and 94.3% negative predictive value, indicating that loss of RAC was suboptimal to confirm *H. pylori* infection, but when RAC was seen, *H. pylori* infection was unlikely.

CONCLUSION

The presence of RAC at the NF-HD exam and the absence of erythema at S-HD were highly predictive of *H. pylori* negative status. On the other hand, the loss of RAC had a suboptimal correlation with the presence of *H. pylori*.

Key Words: Diagnosis; Endoscopy; Gastric infection; Gastritis; *Helicobacter pylori*; Sensitivity and specificity

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Core Tip: Imaging advances in endoscopy significantly improved our diagnostic capability. While magnification endoscopy is well incorporated in Asian countries, in Western countries most upper endoscopes devices are not equipped with this feature. In this study, we evaluated the near focus technology to access mucosal surface pattern and correlate with *Helicobacter pylori* infection. We believe this article will be of great interest to endoscopist in the Western, as there is still a room for better understanding gastric mucosal surface pattern and near focus technology.

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INTRODUCTION

The relationship between *Helicobacter pylori* (*H. pylori*) infection, chronic gastritis, and the development of gastric cancer is well established[1-4]. Eradication of *H. pylori* in patients with non-atrophic chronic gastritis could lead to regeneration of normal mucosa and interruption of Correa's cascade[1,5,6]. In this sense, a technology that helps with diagnosis of *H. pylori*-associated gastritis is useful.

In recent years, many advances in endoscopic imaging have surged, allowing for better characterization of gastric mucosal patterns. High definition (HD) magnification endoscopy (ME) can increase the image view from 1.5× to 150× and allow the visualization of objects that are 10-71 μm in diameter[7]. In 2001, Yao and Oishi[8] described the characteristics of normal gastric mucosa with image magnification. In the following year, Yagi *et al*[9] described the differences between the magnified view of normal gastric mucosa from the pattern seen in patients with *H. pylori*-associated gastritis. A more detailed classification was used by Anagnostopoulos *et al*[10] to distinguish normal gastric mucosa, *H. pylori*-associated gastritis, and gastric atrophy in a Western population. Since then, several articles have studied the association between ME and histological findings[9,11,12].

However, endoscopes with magnification are scarce in Western countries. In 2016, Olympus launched the Near Focus (or Dual Focus) technology on conventional 190 endoscopes for the Western market, which consists of a variable focus lens system, allowing for close examination of the mucosa (2-6 mm) without definition loss[13].

Although there are many studies correlating the findings of ME and *H. pylori* status, only a few validated these findings with HD endoscopes without ME[14-18]. Moreover, most of these studies were conducted in Asian countries, in centers with high expertise with magnifying images[9,12].

The aim of this study is to access the association between mucosal surface pattern under near focus high-definition (NF-HD) technology and *H. pylori* infection status in

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a western population.

MATERIALS AND METHODS

This was a cross-sectional study conducted from August to November 2019 at the Endoscopy Center of the Hospital Alemao Oswaldo Cruz (São Paulo, Brazil). The ethical committee of our institution (approval number 3.577.527) approved this research. It is in accordance with the Declaration of Helsinki.

Inclusion criteria were patients referred to routine diagnostic upper gastrointestinal endoscopy for dyspepsia symptoms who agreed to sign the informed consent form. Exclusion criteria were patients using proton pump inhibitors (PPIs) or H2 inhibitors in the last 10 d prior to endoscopy, patients with previous gastric surgeries (gastroplasty or gastrectomy), gastric stasis, hypertensive gastropathy, patients under 18 years of age, and non-elective indications (upper gastrointestinal bleeding, foreign body, *etc.*).

Baseline data that included age, gender, symptoms, medications, and previous *H. pylori* treatment were recorded.

Primary and secondary endpoints

The primary endpoint was to assess if NF-HD examination of gastric mucosal surface patterns could predict *H. pylori* status. The secondary endpoint was to assess if any other features observed with standard focus high definition (S-HD) white light examination was associated with *H. pylori* status.

Endoscopic procedures and near focus classification

All procedures were performed under anesthesiologist-assisted sedation with propofol. Before the procedures, every patient received a solution containing 200 mL of water and simethicone to help clean the stomach and improve visualization of the gastric mucosa. All examinations were performed with an Olympus CV-190 gastroscope. The images were captured by the BSCap™ system with a minimum of 10 photos, according to the European standard[19].

The examinations were performed by nine senior endoscopists (over 10 years of experience). Subsequently, two other endoscopists (Fiuza F and Martins BC), who had training on magnification imaging, reviewed all images and standardized the responses. Endoscopists who performed the exams had information about previous *H. pylori* infection. Fiuza F and Martins BC were blinded for previous and present *H. pylori* infection.

Initially, a complete exam was performed using S-HD white light view, and the characteristics of gastric mucosa were recorded: erythema, erosion, exudate, atrophy, and nodularity (Figure 1). Next, the near focus (NF-HD) exam was performed (Figure 2), with particular attention to the greater curvature and anterior wall of the medium gastric body, according to Yagi *et al*[9].

The gastric mucosal surface pattern was classified based on the classification proposed by Anagnostopoulos *et al*[10]: Type 1: Honeycomb-type subepithelial capillary network (SECN) with regular arrangement of collecting venules (RAC) and regular round pits; Type 2: Honeycomb-type SECN with regular round pits, with or without sulci but with loss of collecting venules; Type 3: Loss of normal SECN and collecting venules and with white enlarged pits surrounded by erythema; and Type 4: Loss of normal SECN and round pits, with irregular arrangement of collecting venules.

Gastric biopsies and histological examination

Gastric biopsies were collected for evaluation with the rapid urease test (RUT-Uretest®, RenyLab): One sample in the lesser curvature of the antrum close to the *incisura angularis* and the other in the greater curvature of the medium body. Next, gastric biopsies were collected for anatomopathological (AP) study: Two samples from the body and two from the antrum (greater and lesser curvature in each region), as oriented by the IV Brazilian Consensus on *Helicobacter pylori* Infection[3]. *H. pylori* infection was considered positive when at least one of the methods was positive.

Gastric biopsies were sent for histologic evaluation by a senior pathologist who was blinded from the endoscopic findings related to inflammation of gastric mucosa. Hematoxylin eosin staining was used for assessment of gastritis and Giemsa for *H. pylori* status. When gastritis was present at histology, but *H. pylori* was negative, immunohistochemical analysis for *H. pylori* antigen was performed.

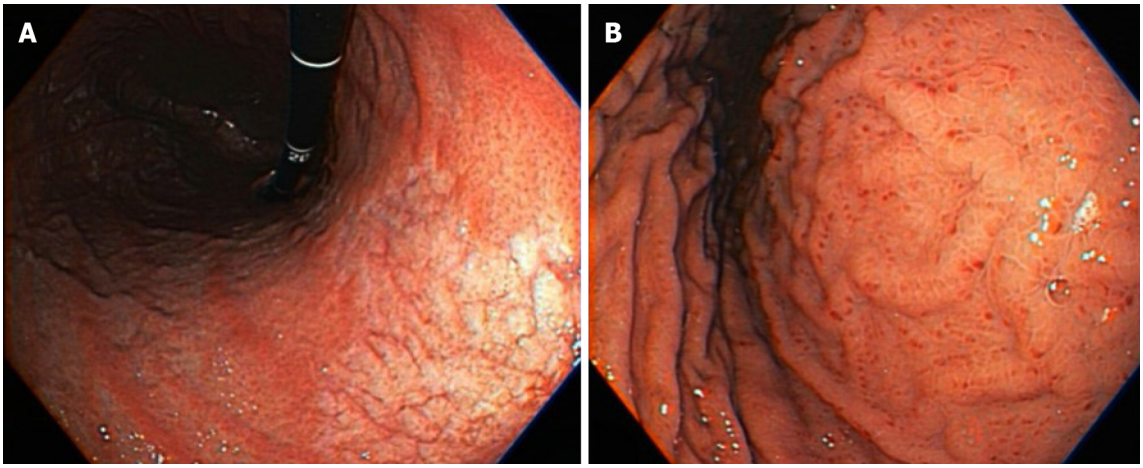

Figure 1 Standard high definition examination. A: Atrophy in the lesser curvature of the gastric body; B: Erythema of gastric body.

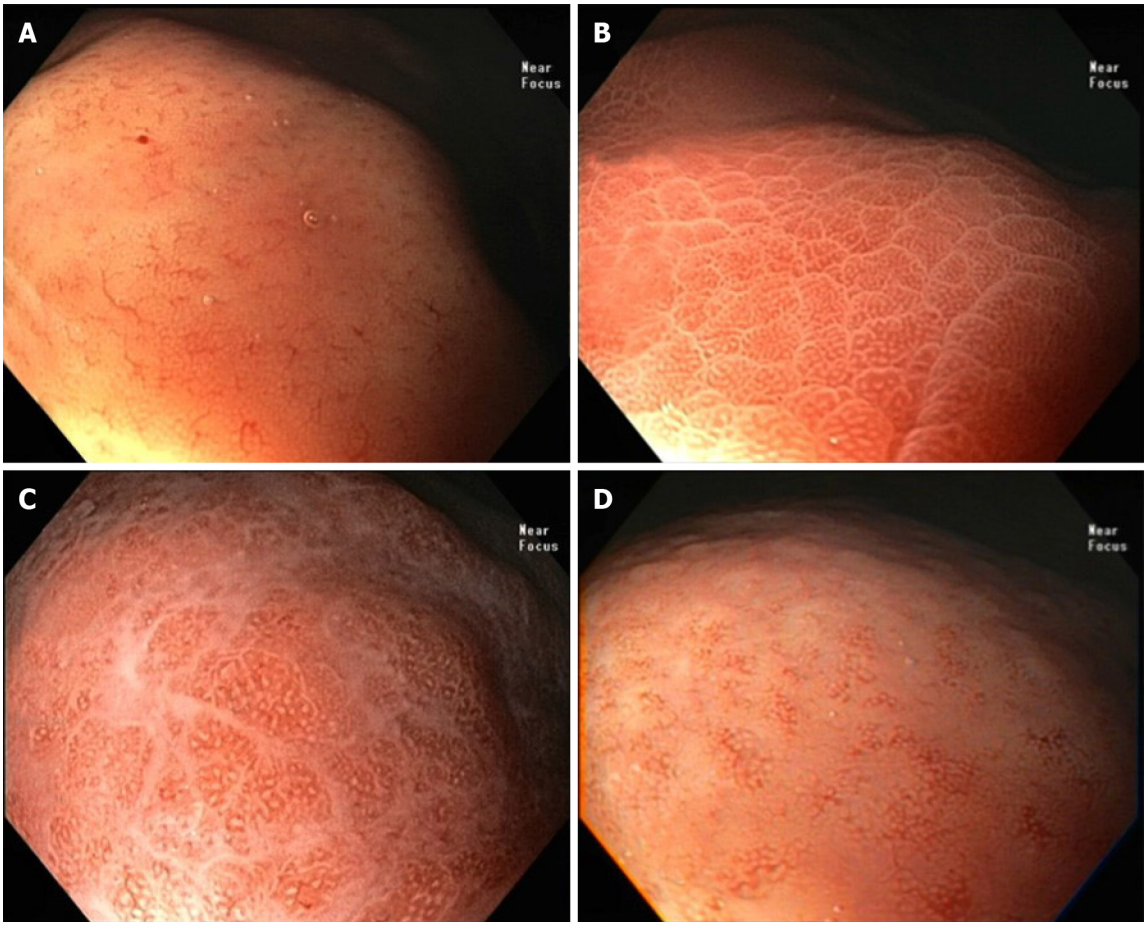

Figure 2 Near focus examination of gastric body. A: Type 1: regular arrangement of collecting venules and regular round pits; B: Type 2: regular round pits, with erythema, sulci and loss of collecting venules; C: Type 3: loss of normal subepithelial capillary network (SECN) and collecting venules and with white enlarged pits surrounded by erythema and exudate; D: Type 4: loss of normal SECN and round pits, with irregular arrangement of collecting venules.

Statistical analysis and sample size calculation

Based on the results of previous studies[10,11,20], expecting a sensitivity of 94%, specificity of 95%, and a prevalence of infection of 40%, using an error margin of ± 6% and an alpha error of 5%, we estimated a sample size of 150 patients. Assuming a drop-out rate of 25%, the sample size was increased to 180 patients.

Measures of central tendency and dispersion were calculated for quantitative variables, as well as absolute and relative frequencies for categorical variables. The association between categorical variables was assessed using the chi-square test.

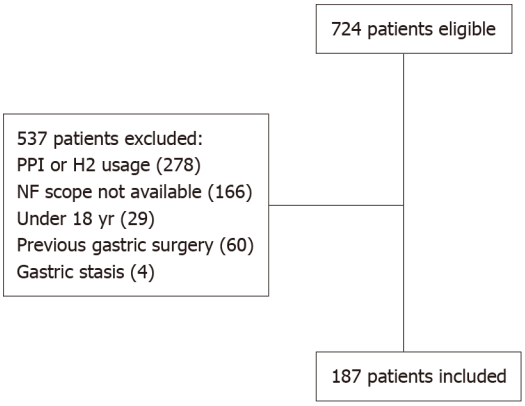

Figure 3 Study flowchart. PPI: Proton pump inhibitor; NF: Near focus.

For the evaluation of the endoscopic diagnostic value, we estimated the sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), area under the ROC curve and their respective 95% confidence intervals (CI) for the findings at S-HD and NF-HD. For all statistical tests, an alpha error of 5% was established, that is, the results were considered statistically significant when $P < 0.05$. All analyses were performed with Stata Software version 15.1.

RESULTS

A total of 724 patients met the inclusion criteria and were eligible for this study. Five hundred thirty-seven patients were excluded: 278 due to PPI or H2 inhibitors usage in the previous 10 d, 166 due to NF endoscopes not available at the time of exam, 29 patients were under 18 years old, 60 due to previous gastric surgery, and 4 due to gastric stasis. Finally, 187 patients were included in the study (Figure 3). The majority of patients were female (60.5%), with a mean age of 50.1 years. Forty-two patients (22.5%) had been previously treated for *H. pylori* infection with an average interval of 48.2 mo (range 3-180 mo). The most prevalent symptom was epigastric pain (44.4%), followed by heartburn (21.4%). *H. pylori* was positive in 47 patients (25.1%), of which 42 were positive by both methods, four only by AP and one only by RUT (Table 1).

Endoscopic findings with standard focus

Upon initial examination of the gastric body with S-HD (Table 2), the finding with the best sensitivity for *H. pylori* detection was erythema (80.9%), present in 75 patients. Exudate (99.3%), nodularity (97.1%), and atrophy (95.7%) demonstrated better specificity values, but with low sensitivity (6.4%-19.1%). On the other hand, the absence of erythema on the gastric body was strongly associated with the absence of *H. pylori* infection (NPV = 92.0%).

In the antrum, all findings showed sensitivity below 75% (Table 2). Nodularity (98.6%) and atrophy (96.4%) had the best values for specificity, but both had low sensitivities (10.6%-23.4%). Exudate, although presenting with 100% specificity, was found in only one patient.

Endoscopic findings with near focus

With the use of NF (Table 3), the majority of patients presented with a type 1 pattern (56.2%), followed by type 2 (30.5%), type 3 (9.6%), and type 4 (3.7%). Type 1 pattern is the only one in which RAC is seen. Only six patients (5.7%) with RAC + were *H. pylori* positive. The loss of RAC presented with a sensitivity of 87.2% for *H. pylori* detection and a NPV of 94.3%, indicating that *H. pylori* infection was less likely when RAC was seen. All patients with type 4 pattern were *H. pylori* positive (PPV of 100%), albeit only seven patients presented with this pattern. Among patients with successful previous *H. pylori* treatment ($n = 25$), 21 (91.3%) were RAC positive (Table 4). Loss of RAC had a NPV of 91.3%, specificity of 84%, and an accuracy of 85.7% (Table 5).

Rapid urease test results

Four patients had RUT negative, but AP positive, and one patient had RUT positive and AP negative. Thus, RUT presented with a sensitivity of 91.5%, specificity of 100%,

Table 1 Patient's characteristics

Characteristics	Total (%)	*H. pylori* + (%) 47 (25.1%)	*H. pylori*-(%) 140 (74.9%)	*P* value
Age, yr				0.580
< 50	85 (45.5)	23 (48.9)	62 (44.3)	
> 50	102 (54.5)	24 (51.1)	78 (55.7)	
Gender				0.629
Male	74 (39.5)	20 (42.5)	54 (38.6)	
Female	113 (60.5)	27 (57.5)	86 (61.4)	
Symptoms				
Epigastric pain	83 (44.4)	26 (55.3)	57 (40.7)	0.081
Heartburn	40 (21.4)	9 (19.1)	31 (22.1)	0.665
Previous treated *H. pylori* infection	42 (22.5)	17 (36.2)	25 (17.9)	0.009

Chi-square test. *Helicobacter pylori*: *H. pylori*.

Table 2 Endoscopic findings with standard focus high definition white light and association with *Helicobacter pylori* infection

Location	Feature	Patients	Sensitivity % (95%CI)	Specificity % (95%CI)	PPV % (95%CI)	NPV % (95%CI)	AUC % (95%CI)	Accuracy % (95%CI)
Body	Erythema	75	80.9 (66.7-90.9)	73.6 (65.5-80.7)	50.7 (38.9-62.4)	92.0 (85.3-62.4)	0.77 (0.70-0.84)	75.4 (68.6-81.4)
	Erosion	16	10.6 (3.6-23.1)	92.1 (86.4-96.0)	31.3 (11.0-58.7)	75.4 (68.3-81.7)	0.51 (0.46-0.56)	71.7 (64.6-78.0)
	Exudate	4	6.4 (1.3-17.5)	99.3 (96.1-100)	75.0 (19.4-99.4)	76.0 (69.1-82.0)	0.53 (0.49-0.56)	75.9 (69.2-81.9)
	Atrophy	15	19.1 (9.1-33.3)	95.7 (90.9-98.4)	60.0 (71.0-83.9)	77.9 (71.0-83.9)	0.57 (0.52-0.63)	76.5 (69.7-82.3)
	Nodularity	7	6.4 (1.3-17.5)	97.1 (92.8-99.2)	42.9 (9.9-81.6)	75.6 (68.6-81.6)	0.52 (0.48-0.56)	74.3 (67.4-80.4)
Antrum	Erythema	87	72.3 (57.4-84.4)	62.1 (53.6-70.2)	39.1 (28.8-50.1)	87.0 (78.8-92.9)	0.67 (0.60-0.75)	64.7 (57.4-71.5)
	Erosion	38	21.3 (10.7-35.7)	80.0 (72.4-86.3)	26.3 (13.4-43.1)	75.2 (67.4-81.9)	0.51 (0.44-0.57)	65.2 (57.9-72.0)
	Exudate	1	2.1 (0.5-11.3)	100 (97.4-100)	100 (2.5-100)	75.3 (68.4-81.3)	0.51 (0.49-0.53)	75.4 (68.6-81.4)
	Atrophy	16	23.4 (12.3-38.0)	96.4 (91.9-98.8)	68.8 (41.3-89.0)	78.9 (72.1-84.8)	0.60 (0.54-0.66)	78.1 (71.4-83.8)
	Nodularity	7	10.6 (3.5-23.1)	98.6 (94.9-99.8)	71.4 (29.0-96.3)	76.7 (69.8-82.6)	0.55 (0.50-0.59)	76.5 (69.7-82.3)

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under receiver operating characteristic curve.

PPV of 100%, NPV of 97.2%, and accuracy of 97.9%.

DISCUSSION

An endoscopic mucosal sample is the most common method used for *H. pylori* detection. However, it generates costs associated with biopsy forceps, reagent agents, vials, and pathologists, in addition to the risk of bleeding and other complications. Thus, a diagnostic method that excludes the need for large-scale biopsies with good cost-effectiveness is welcome both economically and logistically.

In 2002, Yagi *et al*[11] described the magnified view of *H. pylori* negative gastric mucosa and showed that the identification of collecting venules and capillaries forming a network with gastric pits in the center is indicative of *H. pylori*-negative normal mucosa. This pattern was named RAC. In a study with 557 patients submitted to endoscopy, the same authors demonstrated that the presence of RAC had a sensitivity of 93.6% and specificity of 96.2% as an indicator of a normal stomach without *H. pylori*[11]. Similar findings were reported by Anagnostopoulos *et al*[10], in a study including 95 patients in a Western population. The authors applied ME in the gastric body and showed that type 1 pattern predicted normal gastric mucosa with a

Table 3 Association between classifications and *Helicobacter pylori* infection of the gastric body

RAC	Classification	*Helicobacter pylori* status (%)		Total (%)
		Negative	Positive	
RAC +				
	Type 1	99 (94.3)	6.0 (5.7)	105 (56.2)
RAC -				
	Type 2	35 (61.4)	22 (38.6)	57 (30.5)
	Type 3	6 (33.3)	12 (66.7)	18 (9.6)
	Type 4	0 (0.0)	7 (100.0)	7 (3.7)
	Types 2, 3 and 4	41 (50)	41 (50)	82 (43.8)
Total		140 (74.9)	47 (25.1)	187 (100)

Chi-square test; $P < 0.001$. RAC: Regular arrangement of collecting venules.

Table 4 Association between regular arrangement of collecting venules and *Helicobacter pylori* infection in patients with previous *Helicobacter pylori* treatment

Classification	*Helicobacter pylori* status (%)		Total (%)
	Negative	Positive	
RAC +	21 (91.3)	2 (8.7)	23 (54.8)
RAC -	4 (21.1)	15 (78.9)	19 (45.2)
Total	25 (59.5)	17 (40.5)	42 (100)

RAC: Regular arrangement of collecting venules.

Table 5 Loss of regular arrangement of collecting venules with near focus high-definition examination in the gastric body and correlation with *Helicobacter pylori* infection

Loss of RAC	Sensitivity% (95%CI)	Specificity% (95%CI)	PPV % (95%CI)	NPV % (95%CI)	AUC % (95%CI)	Accuracy % (95%CI)
Overall (n = 187)	87.2 (74.3-95.2)	70.7 (62.4-78.1)	50.0 (38.7-61.3)	94.3 (88.0-97.9)	0.79 (0.73-0.85)	74.5 (67.6-80.5)
Patients without previous *Helicobacter pylori* treatment (n = 145)	86.7 (69.3-96.2)	67.8 (58.5-76.2)	41.3 (29.0-54.4)	95.1 (88.0-98.7)	0.77 (0.69-0.85)	71.7 (63.6-78.9)
Patients with previous *Helicobacter pylori* treatment (n = 42)	88.2 (63.6-98.5)	84.0 (63.9-95.5)	78.9 (54.4-93.9)	91.3 (72.0-98.9)	0.86 (0.73-0.97)	85.7 (71.5-94.6)

CI: Confidence interval; PPV: Positive predictive value; NPV: Negative predictive value; AUC: Area under receiver operating characteristic curve.

sensitivity of 92.7%, specificity of 100%, PPV of 100%, and NPV of 83.8%. However, magnification is time-consuming, requires training, and is not widely available in western centers. Therefore, the use of NF becomes an alternative due to its feasibility and availability.

In this study, we evaluated near-focus imaging for the diagnosis of *H. pylori* status of gastric mucosa. We showed that the loss of RAC had a sensitivity of 87% for detection of *H. pylori* and a NPV of 94.3%. Only six patients with RAC + were positive for *H. pylori*. In other words, if RAC was present, the probability of a *H. pylori* negative mucosa was 94.3%. In a prospective study with 140 patients, Garcés-Durán *et al*[14] used Olympus 190 gastroscopes to evaluate if the presence of RAC could rule out *H. pylori* infection in a western population. The authors did not mention if they applied NF to examine the gastric mucosa, so it is assumed that only S-HD exam was performed. The authors found a sensitivity and NPV of 100% for the exclusion of *H.*

pylori infection in RAC+ patients. In a congress report communication, Jang *et al*[18] compared NF + NBI with SD-WL for predicting *H. pylori* status. The sensitivity, specificity, PPV, and NPV were 86.5%, 84.1%, 84.1%, and 88.3% for NF + NBI and 57.7%, 92.1%, 53.0%, and 72.5% for SD-WL endoscopy, respectively. In a pediatric population (children and adolescents) using standard endoscopes, Machado *et al*[16] demonstrated that the absence of RAC had a sensitivity of 96.9% and a specificity of 88.1% in predicting *H. pylori* infection. Glover *et al*[21] showed that RAC becomes less visible with increasing age, presenting NVP of 93.0% for patients below 50 years and NVP of 90.7% for all ages. Table 6 shows a comparison between studies that addressed the association of RAC with *H. pylori* status. On the other hand, loss of RAC was present in 49/96 (51%) *H. pylori* negative patients in the study of Garcés-Durán *et al* [14], while in our study, loss of RAC was present in 41/140 (29%) *H. pylori* negative patients. This difference could be explained by the use of NF in our study. NF increased the sensitivity to identify capillary venules. Therefore, NF-HD resulted in increased specificity but decreased sensitivity for *H. pylori* detection applying the "loss of RAC" signal.

Although RAC identification with HD endoscopes has good accuracy to screen *H. pylori* negative patients, it seems that the loss of RAC is not so specific to confirm *H. pylori* infection. In this study, the loss of RAC was associated with *H. pylori* infection in only 50.6% (41/81) of the cases, with a PPV of 50%. These findings are in accordance with other studies where RAC negative patients presented *H. pylori* infection in 40-47.3% of patients[14,21,22]. With ME, Anagnostopoulos *et al*[10] presented that types 2 and 3 together had a specificity of 92.7% and PPV of 83.8% for predicting *H. pylori* infection.

Taken together, sensitivity of "loss of RAC" to predict *H. pylori* infection varied from 66% to 100% and specificity varied from 48% to 100%. Excluding the studies that used ME, the one with higher sensitivity was also the one with lower specificity[14]. The wide variability of sensitivity and specificity of RAC identification and *H. pylori* status among studies might be explained by different technology applied and different endoscopists' expertise. Apparently, there is lower variability of NPV among studies, meaning that the presence of RAC is a good indicator of *H. pylori* negative status.

Besides RAC, the best S-HD criteria to screen for *H. pylori* negative patients in this study was erythema, with NPV of 92%. The sensitivity of erythema for *H. pylori* detection was 80.9%, specificity 73.6%, and PPV 50.7%. Exudate, atrophy, and nodularity were the most specific findings. In a multicenter study including 24 facilities in Japan, Kato *et al*[23] studied the association of body erythema and *H. pylori* infection with S-HD. Spotty redness had sensitivity of 70.3%, specificity of 73.8, PPV of 75%, and NPV of 69.1%; diffuse redness, sensitivity of 83.4%, specificity of 66.9, PPV of 73.8%, and NPV of 78.4%. Machado *et al*[16] highlighted nodularity in children and adolescents as a strong predictor of *H. pylori* infection (98.5%). Absence of nodularity was associated with the presence of RAC, virtually excluding the probability of *H. pylori* (post-test probability 0.78%). In a series of 200 gastroscopic examination with S-HD[22], the presence of RAC and the Kimura-Takemoto classification grade C1 were predictive of *H. pylori* negative status, while atrophic changes and diffuse redness without RAC were significantly associated with *H. pylori* infection.

The awareness of these findings may lead endoscopists to change some practices during elective routine endoscopy. For example, many patients may be referred to endoscopy while using continuous PPI, which is known to decrease sensitivity of RUT and AP tests[3]. In this sense, findings of diffuse erythema, atrophy, or exudate on white light examination, as well as loss of RAC on NF exam, may lead the endoscopist to use more resources to increase the yield of *H. pylori* detection. This may include collecting more fragments and/or performing biopsies for histopathological analysis besides RUT. We also believe that a closer look at the mucosa must be routinely incorporated in elective upper endoscopy in order to look for the mucosal surface pattern. It is quick and easy to apply.

The reversal of mucosal changes after *H. pylori* eradication is still poorly understood. In this study, the accuracy of RAC pattern to predict *H. pylori* status in the group of patients with previous *H. pylori* treatment was 85.7% (95%CI: 71.5-94.6) compared with 71.1% (95%CI: 63.6-78.9) to the non-treated group. PPV was higher (78.9%; 95%CI: 54.4-93.9 *vs* 41.3%; 95%CI: 29.0-54.4), and NPV was similar (91.3; 95%CI: 72.0-98.9 *vs* 95.1%; 95%CI: 88.0-98.7). These findings could indicate that mucosal changes might be reversible in some cases.

Our study has some limitations. First, it is a single-institution study. It would be important to evaluate the interobserver agreement and to validate these findings in a multicenter study. On the other hand, our study supports the concept of first screening patients for the presence of RAC and deferring biopsy in patients positive for RAC.

Table 6 Studies associating loss of regular arrangement of collecting venules with the presence of *Helicobacter pylori*

Ref.	Country	*n*	RAC +	Technology	Sensitivity	Specificity	PPV	NPV
Machado *et al*[16], 2008	Brazil	99	60	SD	96.9	88.1	-	-
Cho *et al*[15], 2013	Korea	617	254	S-HD	93.3	89.1	92.	90.6
Yagi *et al*[17], 2014	Japan	38	26	S-HD	79	52	70	63
Garcés-Durán *et al*[14], 2019	Spain	140	47	S-HD	100	48.9	47.3	100
Ebigbo *et al*[22], 2021	German	200	-	S-HD	80.7	57.4	40.0	89.4
Glover *et al*[21], 2021	United Kingdom	153	108	S-HD	78.4	64.3	40.0	90.7
Jang *et al*[18], 2020	Korea	115	-	NF + NBI	86.5	84.1	84.1	88.3
Yagi *et al*[11], 2002	Japan	557	161	ME	93.8	96.2	-	-
Nakagawa *et al*[12], 2003	Japan	92	23	ME	66.7	100	100	82.4
Anagnostopoulos *et al*[10], 2007	United Kingdom	95	64	ME	100	92.7	83.8	100
Yagi *et al*[17], 2014	Japan	49	30	ME + NBI	91	83	88	86
This study	Brazil	187	105	NF	87.2	70.7	50.0	94.3

RAC: Regular arrangement of collecting venules; S-HD: Standard high definition; ME: Magnification endoscopy; SD: Standard definition; NF: Near focus; PPV: Positive predictive value; NPV: Negative predictive value.

CONCLUSION

In conclusion, the presence of RAC at the NF-HD exam and the absence of erythema in the gastric body at S-HD were predictive of *H. pylori* negative status. On the other hand, the loss of RAC had a poor association with the presence of *H. pylori*.

ARTICLE HIGHLIGHTS

Research background

In recent years, many advances in endoscopic imaging have surged, allowing for better characterization of gastric mucosal patterns. In 2001, Yao and Oishi described the characteristics of normal gastric mucosa with image magnification (ME). In the following year, Yagi *et al* described the differences between the magnified view of normal gastric mucosa from the pattern seen in patients with *Helicobacter pylori* (*H. pylori*)-associated gastritis. Although there are many studies correlating the findings of ME and *H. pylori* status, only a few validated these findings with high definition (HD) endoscopes without ME. Moreover, most of these studies were conducted in Asian countries, in centers with high expertise with magnifying images.

Research motivation

While magnification endoscopy is well incorporated in Asian countries, in Western countries most upper endoscopes devices are not equipped with this feature.

Research objectives

The aim of this study is to access the association between mucosal surface pattern under near focus HD (NF-HD) technology and *H. pylori* infection status in a western population.

Research methods

This was a cross-sectional study including all patients referred to routine upper endoscopy. Endoscopic exams were performed using standard HD (S-HD) followed by NF-HD examination. Presence of erythema , erosion, atrophy, and nodularity were recorded during S-HD, and surface mucosal pattern was classified using NF-HD in the gastric body, based on the classification proposed by Anagnostopoulos *et al*. Biopsies were taken for rapid urease test and histology.

Research results

One hundred and eighty-seven patients were included in the study, of those, 47 (25.1%) were *H. pylori* +. In the examination with S-HD, erythema had the best sensitivity for *H. pylori* detection (80.9%). On the other hand, the absence of erythema was strongly associated with *H. pylori*- (negative predictive value = 92%). With NF-HD, the loss of the regular arrangement of collecting venules (RAC) presented 87.2% sensitivity for *H. pylori* detection and 94.3% negative predictive value, indicating that loss of RAC was suboptimal to confirm *H. pylori* infection, but when RAC was seen, *H. pylori* infection was unlikely.

Research conclusions

Presence of RAC at the NF-HD exam and the absence of erythema in the gastric body at S-HD were predictive of *H. pylori* negative status. The loss of RAC had a poor association with the presence of *H. pylori*.

Research perspectives

Our study supports the concept of first screening patients for the presence of RAC and deferring biopsy in patients positive for RAC.

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CASE REPORT

Endoscopic treatment of periampullary duodenal duplication cysts in children: Four case reports and review of the literature

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Author contributions: Bulotta AL, Stern MV and Alberti D conceptualized and designed the study; Bulotta AL, Stern MV, Parolini F, Boroni G and Alberti D were involved in medical care of the patients; Bondioni MP performed radiological investigations; Missale G and Moneghini D performed endoscopic treatment; Stern MV, Bulotta AL and Parolini F collected the clinical data from patients and from literature; All authors contributed equally to preparation of the manuscript and reviewed and approved the final manuscript as submitted.

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Abstract

BACKGROUND

Duodenal duplications are rare congenital anomalies of the gastrointestinal tract. As the periampullary variant is much rarer, literature is scant and only few authors have reported their experience in diagnosis and treatment, particularly with operative endoscopy.

CASE SUMARY

To report our experience with the endoscopic treatment in a series of children with periampullary duodenal duplication cysts, focusing on the importance of obtaining an accurate preoperative anatomic assessment of the malformations. The pediatric periampullary duodenal duplication cyst literature is reviewed. We conducted a systematic review according to the PRISMA guidelines. The PubMed database was searched for original studies on "duodenal duplication", "periampullary duplication" or "endoscopic management" published since 1990, involving patients younger than 18 years of age. Eligible study designs were case report, case series and reviews. We analyzed the data and reported the results in table and text. Fifteen eligible articles met the inclusion criteria with 16 patients, and analysis was extended to our additional 4 cases. Median age at diagnosis was 13.5 years. Endoscopic treatment was performed in 10 (50%) patients, with only 2 registered complications.

CONCLUSION

Periampullary duodenal duplication cysts in pediatric patients are very rare. Our

according to the PRISMA 2009 Checklist.

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experience suggests that an accurate preoperative assessment is critical. In the presence of sludge or stones inside the duplication, endoscopic retrograde cholangio-pancreatography is mandatory to demonstrate a communication with the biliary tree. Endoscopic treatment resulted in a safe, minimally invasive and effective treatment. In periampullary duodenal duplication cyst endoscopically treated children, long-term follow-up is still necessary considering the potential malignant transformation at the duplication site.

Key Words: Periampullary duodenal duplication cyst; Duodenal duplication; Endoscopic ultrasound; Endoscopic treatment; Double wall sign; Case report

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Core Tip: Periampullary duodenal duplications are extremely uncommon in children. The authors report a series of 4 patients and provide a detailed literature review.

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INTRODUCTION

Duodenal duplications (DD) are rare congenital anomalies of the gastrointestinal tract, which usually arise during the first decade of life[1-3]. Due to variability of location and size, DD do not display pathognomonic clinical presentation, but they can manifest with a variety of complications including pancreatitis, bleeding, perforation and duodenal obstruction[1]. Unfortunately, little is reported about the anatomical details of DD, which can be divided into two groups: periampullary and non-periampullary duplication cyst. Periampullary duodenal duplication cysts (PADDC) are defined as cysts located near the major papilla and the biliary-pancreatic ampulla, sometimes with a small aberrant pancreatic duct drained into the cyst[4]. As the periampullary variant is much rarer, literature is scant and only few authors have reported their experience in diagnosis and treatment. Moreover, the recent introduction of operative endoscopy for DD treatment in adults has also been extended to the pediatric population with promising results[5-10].

The aim of this paper is to report our experience with the endoscopic treatment (ET) in a series of children with PADDC, focusing on the importance of obtaining an accurate preoperative anatomic assessment of the malformations. The pediatric PADDC literature is reviewed.

CASE PRESENTATION

All consecutive children with PADDC managed at our tertiary-level institution from 2015 to 2020 were retrospectively reviewed. A written consent was obtained from all patients. All data were retrospectively collected and recorded according to the Declaration of Helsinki.

Chief complaints

Case 1, 2 and 4: Abdominal pain.

Case 3: Abdominal pain and vomiting.

History of present illness

Case 1: A 14-year-old boy was admitted with a 1-year history of recurrent pancreatitis. The abdominal computed tomography (CT) scan, previously performed at another

center, showed a cyst within the duodenal lumen.

Case 2: A 16-year-old girl was admitted to our emergency room with abdominal pain.

Case 3: A Chinese 11-year-old girl was admitted for 1-year history of epigastric pain with vomiting and weight loss.

Case 4: An 11-year-old girl was admitted to our unit with abdominal pain and vomiting.

History of past illness

Case 1: His previous history was unremarkable.

Case 2: In the past 2 years she had suffered from recurrent abdominal pain due to pancreatitis.

Case 3: The girl was previously examined in her country, and a CT scan showed a cyst in the second part of the duodenum.

Case 4: Unremarkable.

Personal and family history

Unremarkable.

Physical examination upon admission

Case 1: On inspection, the abdomen was distended with tenderness in epigastrium upon superficial and deep palpation.

Case 2: Physical examination at admission showed a mild distended abdomen and diffuse tenderness upon superficial and deep palpation.

Case 3: Physical examination showed mild diffuse abdominal tenderness upon superficial and deep palpation.

Case 4: Physical examination showed severe tenderness upon superficial and deep palpation of the upper abdomen.

Laboratory examination

Case 1: Laboratory values revealed an increased serum levels of lipase (1077 UI/L; normal value (n.v.) 70-280 UI/L), amylase 514 UI/L (n.v. 15-53 UI/L) and C-reactive protein 168 mg/dL (n.v. < 5 mg/L), while gamma glutamyl transferase 69 U/L (n.v. 6-42 UI/L), count of blood cells, white cell count, total and conjugated bilirubin, alkaline phosphatase level, aspartate aminotransferase and alanine aminotransferase were normal.

Case 2: Blood samples revealed increased serum levels of lipase (2365 UI/L; n.v. 70-280 UI/L); the full panel of liver tests including cholestasis indexes were normal. US showed the presence of an anechoic cystic lesion within the pancreatic head. Intrahepatic and extrahepatic biliary ducts were normal.

Case 3: Laboratory values revealed increased serum levels of lipase (43440 UI/L; n.v. 70-280 UI/L). The full panel of liver tests was normal.

Case 4: Biochemical investigation revealed hyperlipasemia (5497 UI/L; n.v. 70-280 UI/L) and increased levels of aspartate aminotransferase (5.3 x n.v.), alanine aminotransferase (9.2 x n.v.) and gamma-glutamyl transferase (169 UI/L, n.v. 6-42).

Imaging examination

Case 1: The radiological workup first included an abdominal ultrasound (US) that showed a heterogeneous hyperechogenicity of the whole pancreas and an intraluminal duodenal cyst (5.8 cm x 4.5 cm x 4.0 cm in size) near the pancreas head. An 8.5 mm dilatation of the main common bile duct (CBD) was also detected. Intrahepatic biliary ducts and gallbladder were normal.

A magnetic resonance imaging (MRI) on HASTE T2-w sequence showed a homogeneously hyperintense cyst below the pancreatic head, located within a partially occluded duodenum (Figure 1A). On cholangiographic reconstruction the intrahepatic bile ducts were normal, the cystic duct appeared dilated with a tortuous course and the common hepatic duct presented saccular dilation. CBD had a caliber at

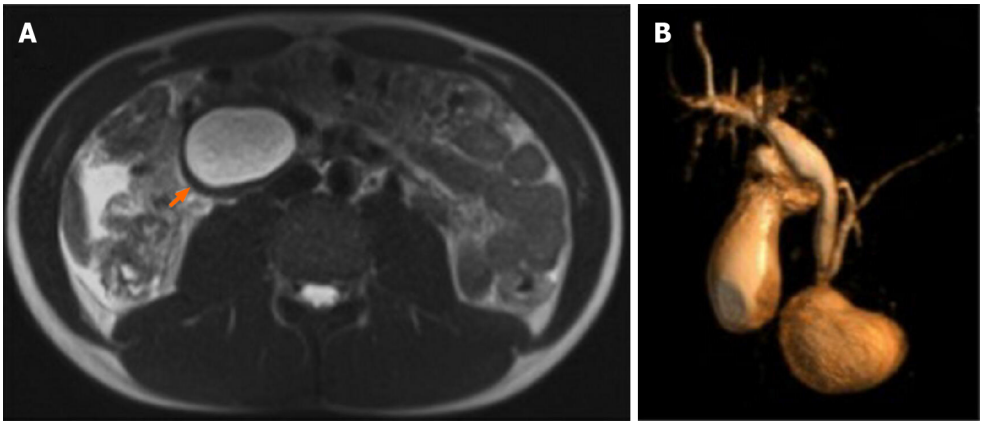

Figure 1 Magnetic resonance imaging on HASTE T2 w sequence. A: Homogeneously hyperintense cyst located within the duodenum, which was partially occluded (arrow); B: On 3D cholangiographic reconstruction, intrahepatic bile ducts were normal, cystic duct was dilated with tortuous course and common hepatic duct presented saccular dilation. Common bile duct had a caliber at the upper limits of the normal range with a regular course and was in communication with periampullary duodenal duplication cysts.

the upper limits of the normal range with a regular course; the Wirsung duct was normal (Figure 1B).

Case 2: An MRI on HASTE T2 w sequence revealed (Figure 2) a round homogeneous hyperintense lesion on the pancreas uncinate process, determining a major compression of the second portion of the duodenum. At cholangiographic reconstruction, the intra- and extrahepatic biliary tree along with the pancreatic ductal system were normal (Figure 2B).

Case 3: An MRI on HASTE T2 w sequence showed an oval heterogeneous hyperintense lesion, measuring 4.5 cm x 3.5 cm, containing multiple stones and located in the second part of the duodenum. Cholangiographic reconstruction indicated a normal/physiologic gallbladder as well as intra- and extrahepatic bile ducts. The lesion, irregularly hyperintense, was located below the gallbladder and laterally to the CBD and pancreatic duct (Figures 3 and 4).

Case 4: US examination found a cyst (2.5 cm × 2.5 cm × 1.6 cm) sharing bowel wall stratification with the second part of the duodenum and full of hyperechogenic debris. An MRI on HASTE T2 sequence detected an oval mass, located below the gallbladder and laterally to the CBD and pancreatic duct (Figure 5), adjacent to the pancreatic head. The cyst was filled with fluid and multiple stones. Cholangiographic reconstruction indicated a normal gallbladder and intra- and extrahepatic bile ducts.

FINAL DIAGNOSIS

Case 1

Endoscopic ultrasound (EUS) showed a bulging in the second duodenal portion, covered with normal mucosa, next to the Vater's papilla and filled with biliary sludge (Figure 6). The lesion preserved a five-layer wall consisting with the typical echoendoscopic feature for the gastrointestinal wall consistent with a PADDC, and ET was proposed to parents.

Case 2

A EUS showed an anechoic cystic lesion within the second duodenal portion, characterized by normal echographic bowel wall stratification and containing multiple hyperechoic stones; the cyst was not in communication with the CBD, and thereby PADDC was diagnosed.

Case 3

A EUS revealed an anechoic cystic lesion characterized by a normal echographic bowel wall stratification and containing biliary sludge.

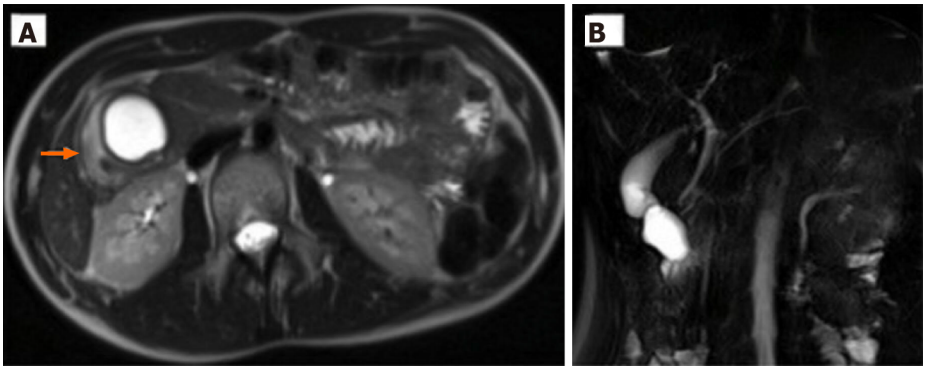

Figure 2 Magnetic resonance imaging of case 2. A: Round homogeneously hyperintense lesion at the level of uncinate process of the pancreas determined a major compression on the second portion of duodenum (arrow); B: At cholangiographic reconstruction, the intra- and extrahepatic biliary tree and pancreatic ductal system were normal.

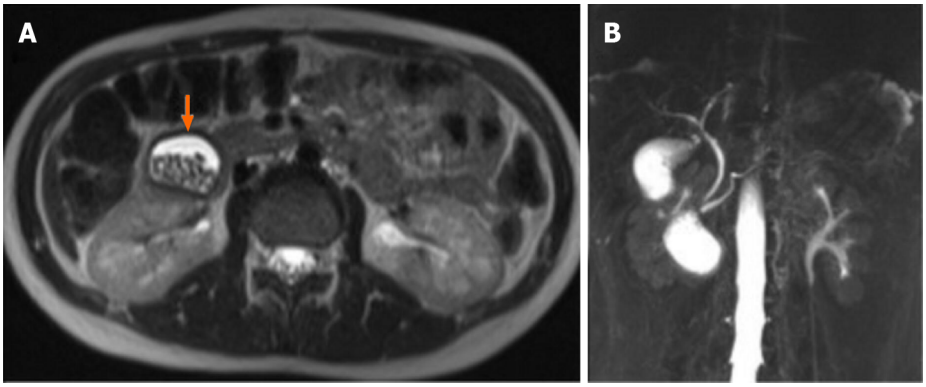

Figure 3 Magnetic resonance imaging of case 3. A: An oval heterogeneously hyperintense lesion containing multiple stones and located in the second part of the duodenum; B: Cholangiographic reconstruction showed normal gallbladder and intra- and extrahepatic bile ducts.

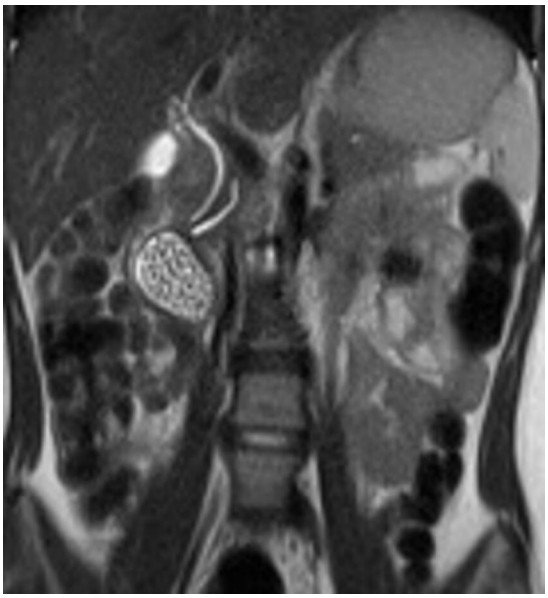

Figure 4 Magnetic resonance imaging showed periampullary duodenal duplication cysts filled with stones.

Case 4

Duodenoscopy revealed an intraduodenal cyst, next to the papilla of Vater and not in communication with the duodenal lumen.

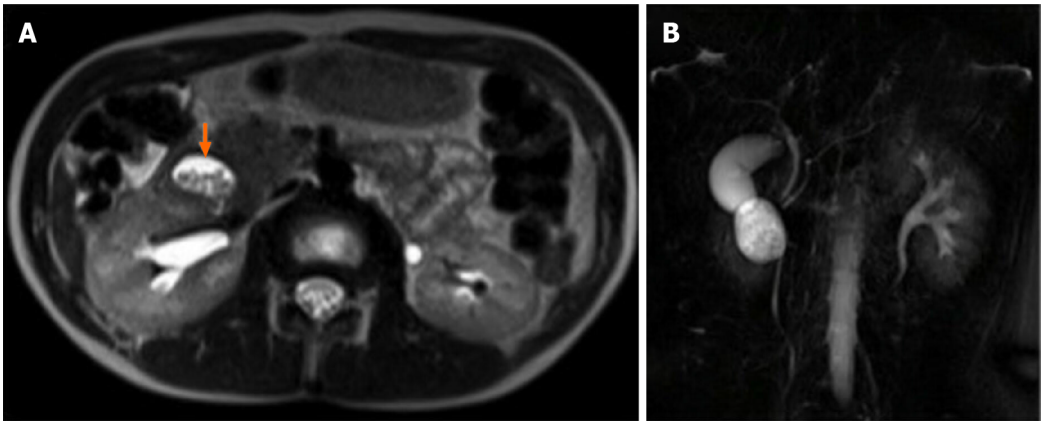

Figure 5 Magnetic resonance imaging. A: Oval mass is located below the gallbladder and lateral to the common bile duct and pancreatic duct, adjacent to the pancreatic head. The cyst was filled with fluid and multiple stones; B: Cholangiographic reconstruction showed normal gallbladder and intra- and extrahepatic bile ducts.

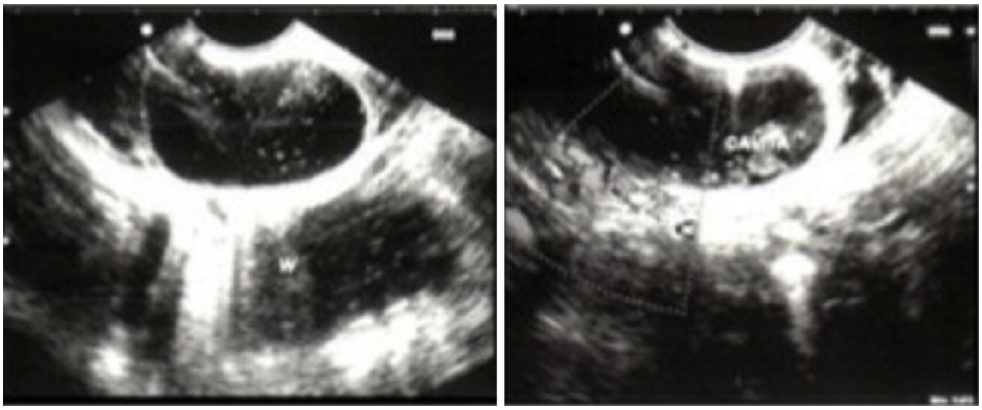

Figure 6 Endoscopic ultrasound. The probe is inside the duodenum, and the common wall separates the duodenum and the duodenal duplication.

TREATMENT

Case 1

Upon endoscopic retrograde cholangio-pancreatography (ERCP), elective cannulation of the CBD showed a direct communication with the cyst and multiple stones in its lumen. A sphincterotome incision of the wall cyst, laterally to the papilla, was performed, and the stones were removed.

Case 2

Upon ERCP, a small orifice on the lateral surface of the cyst was cannulated; a contrast injection failed to demonstrate any communication with the CBD. Intracystic stones were confirmed. The DD wall was incised with sphincterotome,, and stones were removed.

Case 3

ERCP showed a regular main pancreatic duct; after distal papillotomy, contrast was injected, and it filled the PADDC (Figure 7). Marsupialization of the cyst with sphincterotome was then performed.

Case 4

ERCP showed a normal pancreatic duct, dilation of CBD (20 mm diameter) without a detectable communication with the cyst. Cyst marsupialization was performed with subsequent extraction of biliary microstones (Figure 8).

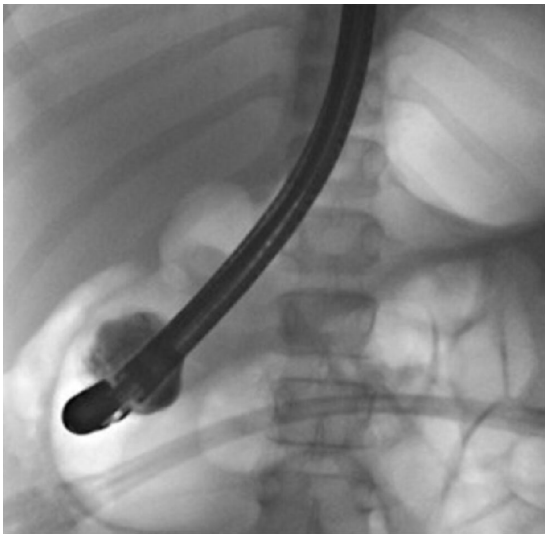

Figure 7 Endoscopic retrograde cholangio-pancreatography. After distal papillotomy, contrast filled the periampullary duodenal duplication cysts.

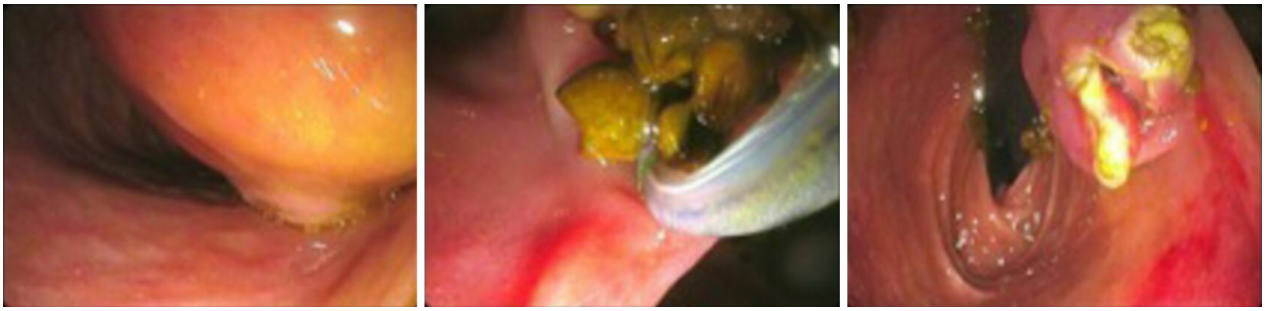

Figure 8 Cyst marsupialization was performed with subsequent extraction of biliary microstones.

OUTCOME AND FOLLOW-UP

Case 1

The patient had an uneventful postoperative course and was discharged home 8 d later with a quick resolution of the abdominal pain and normalization of serum pancreatic enzymes. Ursodeoxycholic acid therapy and a hypolipic diet were continued until the next follow-up. At the 3 mo follow-up, magnetic resonance cholangiopancreatography (MRCP) control after ET, PADDC was no longer detected (Figure 9). At the 10-year follow-up the patient is doing well, without any therapy or further episodes of pancreatitis.

Case 2

The patient had an uneventful recovery and was discharged home 2 d after the procedure with low fat meals. The 9 mo follow-up MRCP did not show any residual duplication (Figure 10), and at 8 years follow-up no further pancreatitis episodes were reported.

Case 3

The postoperative course was complicated by severe melena on day 3, which required packed red cell transfusion. Esophagogastroduodenoscopy detected bleeding at the cyst section site. Endoscopic metallic clip placement was effective for bleeding control. The patient showed a progressive normalization of the serum lipase, and she was discharged home with ursodeoxycholic acid therapy and a low-fat diet. MRCP, done 2 mo later, did not show any duodenal cyst or intra- or extrahepatic bile and pancreatic duct dilatation. At the 4-year follow-up, she was well, and no further episodes of abdominal pain were reported.

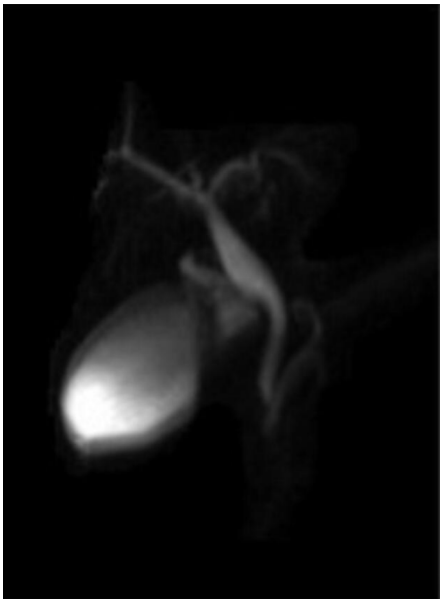

Figure 9 Magnetic resonance cholangiopancreatography performed 3 months after the endoscopic treatment did not show periampullary duodenal duplication cysts.

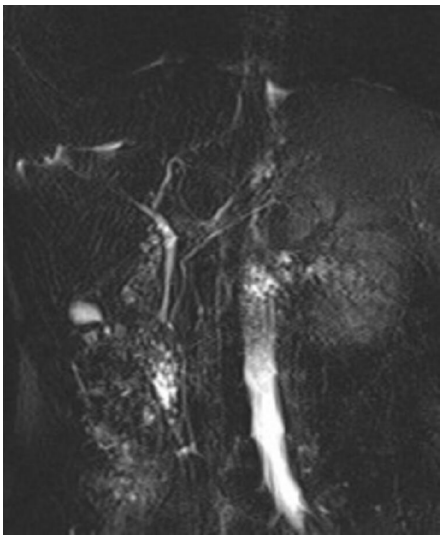

Figure 10 Magnetic resonance cholangiopancreatography performed after 9 mo endoscopic treatment did not show periampullary duodenal duplication cysts.

Case 4

The patient had an uneventful recovery and was discharged home 10 d after the procedure, with an ursodeoxycholic acid therapy and low-fat meals for 3 mo.

At the 2-year follow-up, she was totally asymptomatic, abdominal US was normal, and she eats a free diet.

Literature search

This literature review was performed according to preferred reporting items for systematic reviews and meta-analyses (PRISMA) guidelines[11] (Figure 11). The PubMed database was searched for original studies on "duodenal duplication," "periampullary duplication" or "endoscopic management" published since 1990, involving patients younger than 18 years of age. Eligible study designs were case reports, case series and reviews. We omitted reports in which abstracts indicated an adult population (> 18 years) and improper reporting of the diagnosis and treatment methods. We then evaluated the full text of the selected articles and consider PADDC only where that diagnosis was confirmed by authors.

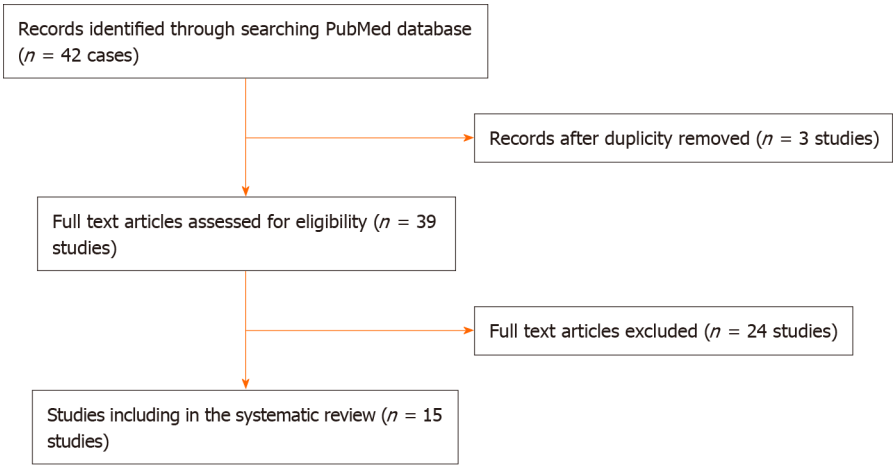

Figure 11 PRISMA 2009 flow diagram.

According to Tröbs *et al*[4], PADDC were defined as cysts located near the major papilla and the biliary-pancreatic ampulla that can have a small aberrant pancreatic duct drained into the cyst. We excluded all patients with a diagnosis of biliary/gallbladder disease (including acute acalculous cholecystitis) or with a diagnosis of duodenal duplication not located near the major papilla.

The date of the last search was December 2020. For each study, data were extracted for two primary outcomes (diagnostic assessment and type of treatment) and several secondary outcomes (including sex and age at presentation, clinical presentation, pathological examination and outcome). Analysis was extended to our additional 4 cases.

Research results

The initial PubMed search yielded 42 potentially relevant studies. Eventually, 16 eligible articles met the inclusion criteria, involving a total of 17 children with PADDC [1,3,4,6-9,12-20] (Table 1 and Figure 11). All selected studies were case reports (class of evidence III and rating scale of evidence E) and clearly reported the two primary outcomes.

The patients' median age at diagnosis was 14 years (range: 3-18 years), and PADDC was reported in 10 males and 8 females. For 3 patients, data were not available. Clinical presentation was unspecific, with abdominal pain reported in all cases. Recurrent pancreatitis was the most common complication and was observed in 14 cases (70%), followed by cholestasis, jaundice and intussusception.

All patients underwent abdominal ultrasound, followed by abdominal CT scan in 18 cases (90%), ERCP in 13 (65%), MRCP in 7 (35%) and EUS in 8 (4%); 1 patient was only examined with ERCP (5%) (Table 1).

Endoscopic treatment was performed in 10 patients (50%), with two reported complications, namely bleeding at the duplication incision site, which were treated with packed red cell transfusion and endoscopic clipping of the bleeding site in one case and with local injection of epinephrine in the other case (Table 1) [9]. The median follow-up was 22.5 mo (range: 4-108 mo); all endoscopically treated patients are doing well with disappearance of the duplication on imaging. No case of malignancy was reported.

DISCUSSION

Duodenal duplications are uncommon congenital anomalies of the gastrointestinal tract, which usually present during the first decade of life[4,5]. They represent 5%-7% of all gastrointestinal duplications and result from disturbances in the embryonic development, probably due to duodenal epithelial pinching during the outgrowth of the dorsal pancreatic bud or secondary to an epithelial sequestration[4]. The majority of them are cystic, adherent and located on the mesenteric side of the second or third portion of the duodenum, with an epithelial mucosal lining and a smooth muscle layer [10,21]. A communication with the duodenal lumen has been reported in up to 25% of cases[1], and some authors have also described the possibility of a pancreato-biliary

Table 1 Data of included studies

Ref.	Year	Age	Sex	Clinical	Laboratory data	US	MR/CT	EUS	ERCP	Description	Treatment and complications
Mattioli *et al* [13]	1999	11 yr	F	Abdominal pain	NA	Yes	Yes (CT)	No	Yes	Periampullary duplication	Surgical resection
Zamir *et al*[16]	1999	17 yr	M	Abdominal pain, duodeno-jejunal intussusception	AST/ALT, 50/140; ALP 250, GGT 400	Yes	Yes (CT)	No	No	Periampullary duplication	Surgical cyst marsupialization
Niehues *et al* [18]	2005	16 yr	M	Abdominal pain, jaundice	Lipase 3343	Yes	Yes (CT and MRCP)	No	Yes	Periampullary duplication	Surgical resection and cholecystectomy
Guarise *et al* [2]	2006	18 yr	M	Abdominal pain, pancreatitis	NA	Yes	Yes (CT and MRCP)	Yes	Yes	Periampullary duplication	Surgical resection
Chryssostalis *et al*[8]	2007	17 yr	-	Abdominal pain Recurrent pancreatitis	NA	Yes	Yes (CT)	No	Yes	Periampullary duplication	Endoscopic excision of the cyst
Ozel *et al*[14]	2008	8 yr	F	Abdominal pain, pancreatitis	Amylase 1287	Yes	Yes (CT)	No	No	Periampullary duplications	Surgical resection
Chen *et al*[3]	2009	8 yr	F	Abdominal pain, pancreatitis	Amylase 155; lipase 109	Yes	Yes (CT and MRCP)	No	Yes	Periampullary duplication	Surgical cyst marsupialization
Tröbs *et al*[4]	2009	8 yr	M	Abdominal pain, pancreatitis, hepatitis	Lipase 3000	Yes	Yes (CT and MRCP)	No	No	Periampullary duplication	Surgicalcyst marsupialization
Tekin *et al*[7]	2009	18 yr	F	Abdominal pain, pancreatitis	NA	Yes	Yes (CT)	No	Yes	Periampullary duplication	Endoscopic sphincterotomy and stent implantation
Criblez *et al* [17]	2011	17 yr	M	Abdominal pain	Lipase 5400	Yes	Yes (CT)	No	Yes	Periampullary duplication	Endoscopic cyst marsupialization and sphincterotomy
Romeo *et al*[9]	2011	-	-	Recurrent pancreatitis	NA	Yes	Yes (CT and MRCP)	Yes	Yes	Periampullary duplication	Surgical resection of common wall
		-	-	Recurrent pancreatitis	NA	Yes	Yes (CT and MRCP)	Yes	No	Periampullary duplication	Endoscopic cyst wall resection
Meier *et al*[6]	2012	9 yr	M	Abdominal pain	Amylase 270 U/ml; Lipase 824 U/ml	Yes	Yes (CT and MRCP)	No	Yes	Periampullary duplication	Endoscopic opening of cyst wall
Koffie *et al*[12]	2012	13 yr	M	Abdominal pain, hepatitis and pancreatitis	Lipase 1363; Amylase 401, direct bilirubin 9.1	Yes	Yes (CT and MRCP)	No	No	Periampullary duplication	Surgical resection
Taghavi *et al* [15]	2017	17 yr	M	Recurrent pancreatitis	NA	Yes	Yes (MRCP)	No	No	Periampullary duplication	Surgical resection, sphincteroplasty of terminal pancreatic duct and stent positioning.
Salazar *et al* [19]	2018	3 yr	M	Abdominal pain, pancreatitis	NA	Yes	Yes (MRCP)	Yes	No	Periampullary duplication	Endoscopic cyst marsupialization
This case	2019	14 yr	M	Recurrent pancreatitis and abdominal pain	Lipase 1077, Amylase 514 GGT 69	Yes	Yes (CT in another center, MRCP)	Yes	Yes	Periampullary duplication	Endoscopic distal papillotomy and cyst incision
		16 yr	F	Recurrent pancreatitis and abdominal pain	Lipase 2365	Yes	Yes (CT in another center, MRCP)	Yes	Yes	Periampullary duplication	Endoscopic cyst incision
		11 yr	F	Recurrent pancreatitis, abdominal pain	Lipase 43440	Yes	Yes (CT in another center,	Yes	Yes	Periampullary duplication	Endoscopic cyst incision (bleeding treated with metallic

			and weight loss			MRCP)				clips placement and blood transfusion)
	11 yr	F	Pancreatitis	Lipase 5497, AST/ALT 315/532; GGT 169	Yes	Yes (MRCP)	Yes	Yes	Periampullary duplication	Sphincterotomy

Unit used were as follows: amylase (UI/L), lipase (UI/L), bilirubin (mg/dL), alkaline phosphatase (UI/L), aspartate aminotransferase (UI/L), alanine aminotransferase (UI/L) and gamma-glutamyl transferase (UI/L). US: Ultrasound; CT: Computed tomography; EUS: Endoscopic ultrasound; ERCP: Endoscopic retrograde cholangio-pancreatography; NA: Not available; ALP: Alkaline phosphatase level; AST: Aspartate aminotransferase; ALT: Alanine aminotransferase; MRCP: Magnetic resonance cholangiopancreatography; GGT: Gamma-glutamyl transpeptidase; MR: Magnetic resonance; F: Female; M: Male.

involvement in 30% of patients, although this cannot always be the only explanation of pancreatitis[5,6].

Three different mechanisms have been reported as responsible for pancreatitis: (1) External papilla obstruction by duplication enlargement; (2) Presence of an aberrant pancreatic duct within the duplication, which can become obstructed by mucus and debris; and (3) Migration of biliary sludge and/or microstones from the cyst into the bilio-pancreatic duct[3,4]. Migration of biliary sludge and/or microstones from the cyst to the bilio-pancreatic duct is possible only due to a communication between the duplication and the bilio-pancreatic duct with stone formation due to the bile stasis within the duplication seeing as its peristalsis is intermittent[2]. For this reason, the presence of stones or biliary sludge inside a duodenal mass do not ruled out the possibility of a DD.

DD can be divided into two subgroups: periampullary (PADDC) and non-periampullary duplication cyst. According to Tröbs *et al*[4] periampullary duodenal duplication is defined as a duplication cyst located near the major papilla and the biliary-pancreatic ampulla, sometimes with a small aberrant pancreatic duct drained into the cyst[4].

Our experience suggests the possibility of communication between PADDC and the CBD and pancreatic duct, which explains both the possibility of observing sludge or calculi in the cyst and the pancreatitis. Unfortunately, detailed descriptions of the relationships between duplication and major papilla and/or pancreatic ampulla are lacking, and our review found that only 17 out of 49 pediatric patients reported a detailed description of the DD that can be classified as periampullary type (Table 1).

PADDC cases have been reported in childhood with a median age of diagnosis of 14 years (range: 3-18 years); this was consistent also in our series (Table 1).

The first radiological tool for diagnosis was US, which is highly suggestive for a DD when peristalsis and pathognomonic "double wall sign," consisting of an outer hypoechoic muscular layer, an internal echogenic mucosal layer and corpuscular fluid inside the lesion, are found[22]. However, this finding should be confirmed with a more exhaustive radiological work-up by abdominal CT scan or preferably by MRCP [23], which provides more information about the location, size, enhancement and multilayered duplication cyst wall as well as anatomical details of the biliary and pancreatic ductal system. Furthermore, ionizing radiation should be limited as much as possible in childhood.

Moreover, we suggest performing an EUS in children with a cystic lesion next to the papilla. In our experience, EUS offered two major advantages: (1) Endoscopic vision allowed a better definition of the intraluminal duodenal lesion and an accurate localization of the papilla; and (2) US vision highlighted the presence of an anechoic structure surrounded by a five layer wall, consisting with the typical echo-endoscopic feature for the gastrointestinal wall, distinguishing DD from the other cystic and neoplastic duodenal or pancreatic masses, including cystic dystrophy of the duodenal wall, pseudocysts, cystic lymphangiomas, mesenteric cysts and choledochocele[4,24].

In particular, the performance of EUS to identify the presence of normal echographic bowel wall stratification at the DD allowed us to make differential diagnosis with choledochocele, where that hallmark is absent, but which represents the most frequent and challenging differential diagnosis. Furthermore, although many authors consider biopsy as the gold standard for the differential diagnosis between DD and choledochocele, duodenal type mucosa has been reported in choledochocele[25-27]. Sarris and Tsang reported 15 cases of choledochocele with duodenal mucosa at pathological examination[27,28].

Eventually, EUS can well indicate the relationships between the duplication and biliary-pancreatic duct. Therefore, when a PADDC is suspected, we suggest considering radiological (EUS) and anatomic criteria appropriate to confirm the diagnosis. Only 4 out of the 16 patients (25%) that were included in our literature review, underwent a preoperative EUS evaluation (Table 1), but this is partly explainable by the recent EUS availability in pediatrics.

Despite having carried out the EUS, before proceeding with the endoscopic duplication unroofing, ERCP would have to be mandatory in order to obtain a detailed anatomic view of the bilio-pancreatic system and to detect a possible communication between the duplication and the biliary and/or pancreatic duct, particularly in patients with stones or sludge inside the cyst.

Endoscopic treatment of children with PADDC was first described in 2007[8], and a later meta-analysis of the pediatric population confirmed the safety, feasibility and effectiveness of this approach in this population[10]. Our review revealed that 10/20 patients with PADDC (50%) underwent ET[6-9,17,19].

Two postoperative complications occurred (bleeding) and were both endoscopically treated; this point stresses the importance of ensuring a careful coagulation of the severed edges of the duplication. When planning an ET we thereby advise that a thorough preoperative radiological imaging encompassing EUS be mandatory, and our experience suggests that the real incidence of PADDC is underestimated because of incomplete preoperative imaging.

The anatomic location of the PADD and the possible communication with the biliary and/or pancreatic ductal system makes an open surgical approach highly demanding and not necessarily safer than ET. Furthermore, surgery has several disadvantages over ET, including worse postoperative pain, higher risk of postoperative complications, visible scars and longer hospitalization time.

Endoscopic cyst marsupialization was highly effective in relieving symptoms and cyst disappearance even at long-term follow-up.

Undoubtedly endoscopic management of PADDC requires a skilled multidisciplinary team, and the still limited use of the endoscopic strategy in a pediatric setting is probably explained, other than the rarity of PADDC, by the unavailability of a trained ERCP endoscopic team.

We suggest considering ET as a first line approach after a complete EUS study and reserving a surgical approach only when it is impossible to understand the relationship between PADDC and the pancreato-biliary tree.

ET provides marsupialization or incision of PADDC, therefore it is rare, but possible, to leave ectopic gastric or pancreatic tissue with potential risk of malignant degeneration.

Eventually, although DD (PADDC included) are generally benign lesions and only a few cases of malignant transformation have been reported in literature[5,29,30], a long-term follow up is mandatory in endoscopically treated patients, even in asymptomatic ones.

CONCLUSION

PADDC in pediatric patients are very rare. Our experience suggests that an accurate preoperative assessment with EUS is essential to differentiating the duplication from other duodenal lesions. In the presence of sludge or stones inside the duplication, ERCP is mandatory to demonstrate a communication with the biliary tree. ET is a safe, minimally invasive and effective treatment in children with PADDC. Long-term follow-up of this population throughout adulthood is mandatory and necessary considering that malignant degeneration of duodenal duplication has been described [5,29,30].

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CASE REPORT

Small bowel perforation from a migrated biliary stent: A case report and review of literature

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Abstract

BACKGROUND

Bowel perforation from biliary stent migration is a serious potential complication of biliary stents, but fortunately has an incidence of less than 1%.

CASE SUMMARY

We report a case of a 54-year-old Caucasian woman with a history of Human Immunodeficiency virus with acquired immunodeficiency syndrome, chronic obstructive pulmonary disease, alcoholic liver cirrhosis, portal vein thrombosis and extensive past surgical history who presented with acute abdominal pain and local peritonitis. On further evaluation she was diagnosed with small bowel perforation secondary to migrated biliary stents and underwent exploratory laparotomy with therapeutic intervention.

CONCLUSION

This case presentation reports on the unusual finding of two migrated biliary stents, with one causing perforation. In addition, we review the relevant literature on migrated stents.

Key Words: Biliary stent; Biliary stent migration; Small bowel perforation; Endoscopic retrograde cholangiopancreatography; Case report

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Core Tip: Bowel perforation from biliary stent migration is a serious potential complication of biliary stents, but fortunately has an incidence of less than 1%. From this review of literature, we can see that most common types of migrated stents entailing bowel perforation are the plastic stents and the most common site of perforation is duodenum. A significant finding is the mortality after bowel perforation

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from biliary stent which is as high as 10.3%. The main treatment is surgical stent removal, but a growing body of literature shows that endoscopic removal and mucosal repair is feasible in select cases. This has still not been accomplished in the mid portion of the bowel.

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INTRODUCTION

Endoscopic biliary stents placement is a well-established therapeutic intervention in the era of modern medicine. It has been used either for temporary or permanent decompression of biliary system, for benign or malignant diseases. Biliary stents are classified by material into two categories: plastic and metallic stents, with the former being less expensive and easier to remove or change[1]. However, this technologically advanced treatment has not been free from complications. The complication rate ranges between 8% and 10% and serious common complications are stent occlusion, cholangitis, bleeding, pancreatitis, duodenal perforation and stent migration[2]. Biliary stent migration is well known with a rate of 5%-10% and can be either proximal or distal[2].

A serious potential consequence of stent migration is bowel perforation which can happen at any part of the small or large bowel, but fortunately has an incidence of less than 1%[3,4]. The majority of the case reports with bowel perforation secondary to migrated biliary stent describe duodenal or colonic perforations, with very few cases of small bowel perforations. Herein we report a case of a patient with multiple comorbidities and surgical interventions, who presents with two migrated biliary stents, one of which was perforating through the small bowel. Both stents were removed uneventfully with laparotomy and a single small bowel resection.

CASE PRESENTATION

Chief complaints

Diffuse abdominal pain.

History of present illness

We present the case of a 54-year-old Caucasian female, who presented in the emergency department of our hospital with diffuse abdominal pain for one week, which had become severe in the last day.

History of past illness

She initially presented in October 2019 with hyperbilirubinemia. At the time she had an ultrasound that showed gallstones as well as a dilated common bile duct of 10 mm. She underwent an magnetic resonance cholangiopacreatography (MRCP) which showed an 8mm duct, but no definite filling defects. Following this she underwent a diagnostic ERCP, at which time a distal stricture was noted, and a plastic stent [7 French (Fr) 7 cm single external and single internal flap] was placed. A second ERCP was done in February 2020, at which time choledocholithiasis was identified and felt to be the cause of the stricture. At that time a new plastic stent was placed (8.5 Fr 7 cm). The original stent was not seen at that time. In August 2020 she went for another ERCP at which time she had a normal cholangiogram, and the stent was not seen at that time. She presented to our Emergency Department in November 2020.

Personal and family history

Her past medical history was significant for human immunodeficiency virus (HIV) infection with acquired immunodeficiency syndrome, chronic obstructive pulmonary

disease, alcoholic liver cirrhosis, and portal vein thrombosis. Her past surgical history was significant for colectomy with end ileostomy for toxic megacolon from Clostridium difficile, followed later by a re-exploration and ileorectal anastomosis with proximal diverting loop ileostomy, which was still in place.

Physical examination

On initial evaluation the patient had temperature 98.2 °F (36.7 °C), pulse 87 per minute, blood pressure 115/83 mmHg. Her clinical examination revealed diffuse abdominal tenderness and focal peritonitis in the left lower quadrant of the abdomen.

Laboratory examinations

From laboratory evaluation the patient had WBC 6.1 k/μL and total bilirubin 0.7 mg/dL.

Imaging examinations

Computed tomography (CT) scan of the abdomen and pelvis with intravenous contrast showed two migrated biliary stents. The first was in an ileal loop and was perforating through the bowel wall into the mesentery (Figure 1A) and a second stent within a mid-jejunal loop (Figure 1B, C). The CT scan showed significant surrounding inflammatory phlegmon, but no free air or focal abscess was noted. After discussion with the patient, it was decided to proceed with surgical treatment of the bowel perforation and removal of both biliary stents.

MULTIDISCIPLINARY EXPERT CONSULTATION

The gastroenterology team was consulted, and they agreed with surgical exploration.

FINAL DIAGNOSIS

Small bowel perforation from a migrated biliary stent.

TREATMENT

The patient underwent a laparotomy at which time extensive adhesions were noted. The bowel was cocooned in most of the abdomen, with multiple interloop adhesions, as well as adhesions to the abdominal wall. The segment of bowel with the perforation was planned for resection due to the extensive inflammation. The second stent was milked within the bowel lumen to the area of the first stent, and both stents were removed in a single resection, after which a primary anastomosis was done. As a result of the extensive adhesions, and the urgent nature of the surgery, the right upper quadrant was not explored at this time. On detailed examination of the specimen, the resected small bowel had hypertrophic changes of the luminal mucosa at the internal opening of the perforation track (Figures 2, 3).

OUTCOME AND FOLLOW-UP

The patient had an uneventful recovery and she was discharged eight days later to a rehab facility.

DISCUSSION

Endoscopic placement of stents in common bile duct of pancreatic duct has been an important scientific achievement of modern medicine and is a frequently employed method to relieve either benign or malignant stenosis/obstruction of biliary or pancreatic tract. It was first described in 1980 by Soehandra *et al*[5] as an alternative method of decompressing the biliary system for high risk or inoperable cases instead of surgical choledochoduodenostomy. After the first description of endoscopic biliary

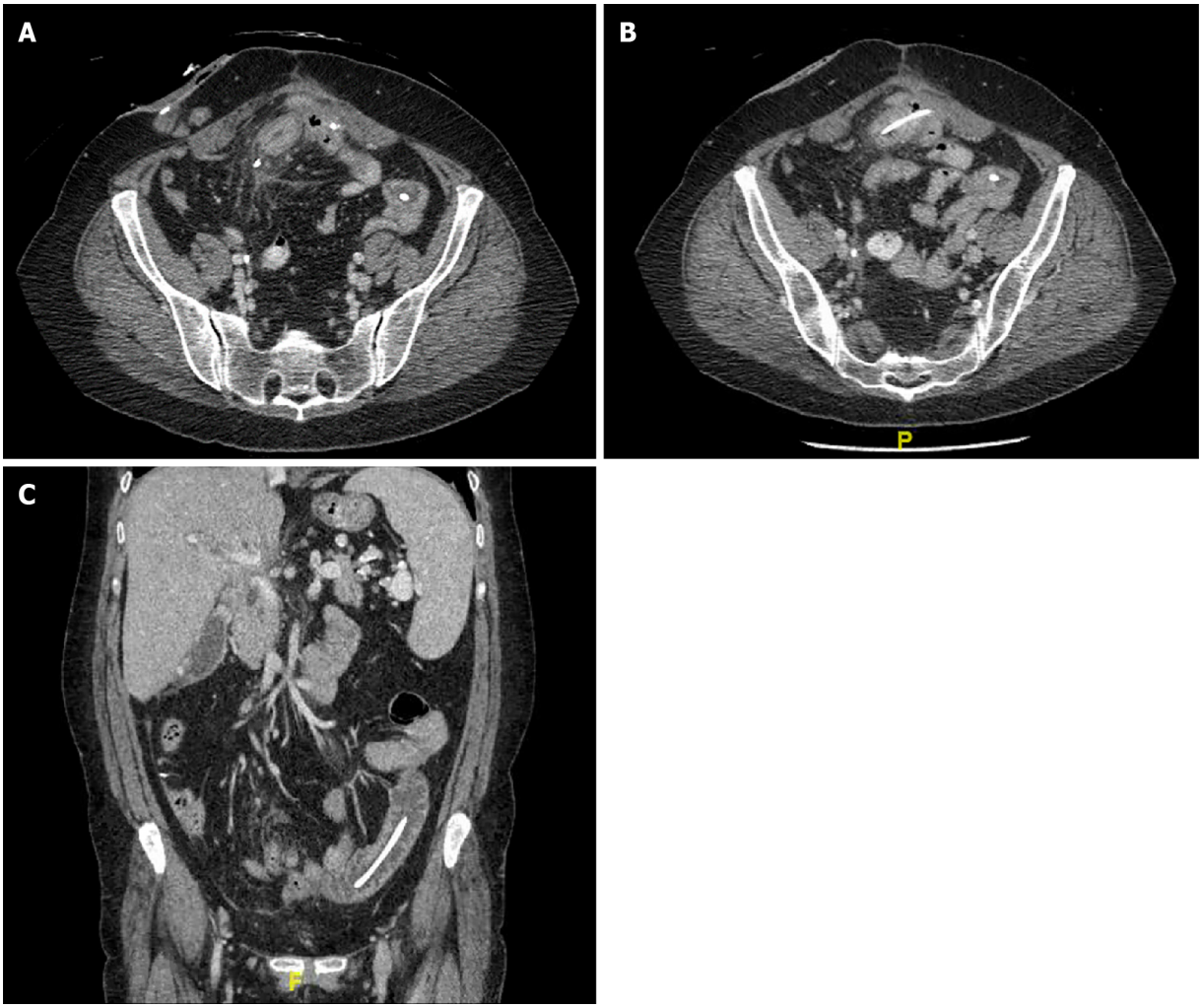

Figure 1 Computed tomography scan. A: Small bowel perforation by migrated biliary stent (Axial view); B: Second migrated biliary stent (Axial view); C: Second migrated biliary stent (Coronal view).

stent placement, the whole procedure and the available stents have been significantly improved and the popularity of this technique is gradually increasing as it constitutes a less morbid intervention comparing to a surgical operation[6]. Despite its clear benefit and the significant improvements in this field, there is always the risk of significant complications during or after endoscopic procedures like upper endoscopy and biliary tract cannulation.

Well described complications of biliary stent placement include stent occlusion by clogging with possible subsequent cholecystitis or cholangitis, pancreatitis from duct manipulation, hemorrhage, stent fracture and stent migration[1,2,6,7]. The total rate of biliary stent complications varies among different institutes because of different level of experience, different available equipment and different etiologic reasons for the intervention. According to Arhan *et al*[2] the complication rete for biliary stents is between 8% and 10%. Stent migration rate ranges from 5% to 10%, with the migration rates in plastic stents higher compared to others[2,7,8]. Biliary stent migration can be further categorized into proximal and distal migration. Distally migrated stents usually pass through the bowel without any complication[1,9]. In our case the patient had multiple previous laparotomies which led to adhesions, thereby making the bowel less mobile. This led to an increased likelihood that the stent would get impacted and not pass. In general, most institutions have policies in place to make sure all stent patients are called back for stent removal, including our own. At the last ERCP there was a normal cholangiogram and the stent was no longer in place. It was felt to have migrated, but without symptoms the impression was that it had completely passed through and eliminated from the GI tract safely. In retrospect an X-ray or further imaging at that time would have been helpful.

Bowel perforation from a migrated stent is a serious complication, which can occur in any part of the small or large bowel. The vast majority of reported cases with bowel

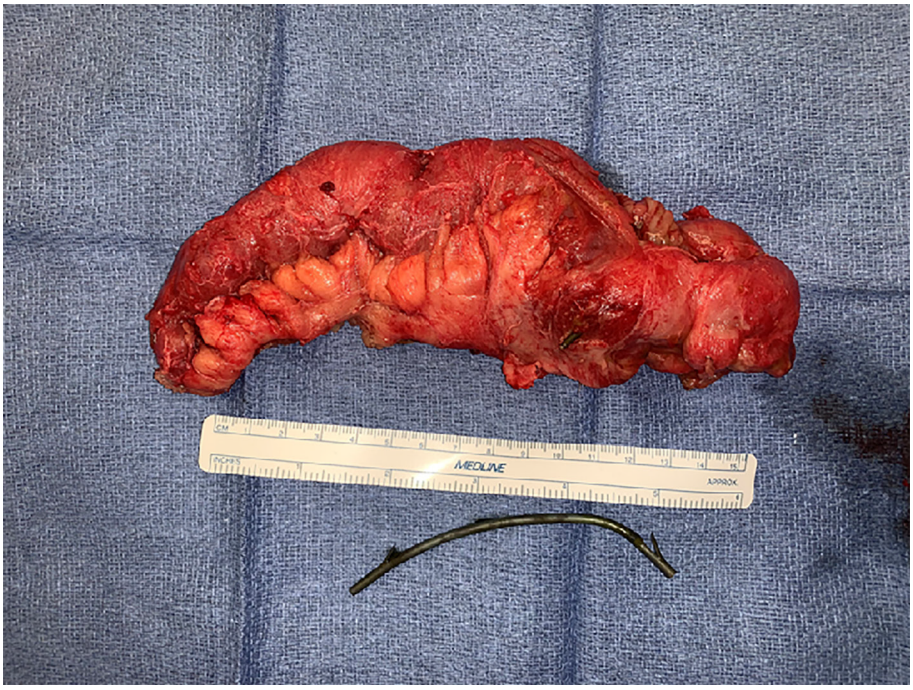

Figure 2 Small bowel segment with stent perforating through it, together with second migrated stent.

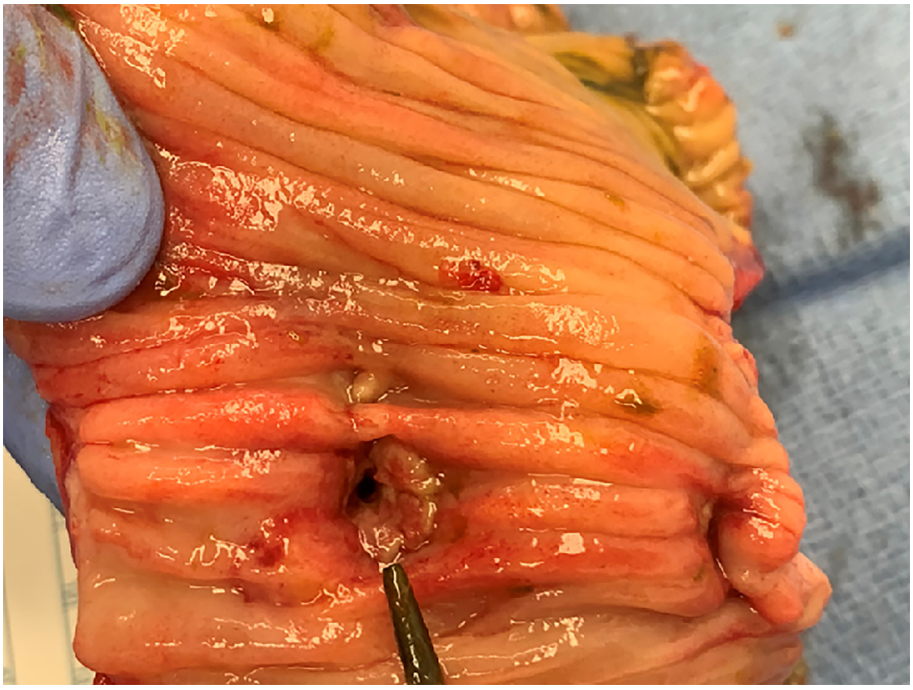

Figure 3 Internal opening of perforation.

perforation from migrated biliary stent describe either duodenal perforation or large bowel perforation, with very few cases of small bowel perforation. Most patients with perforation will present with diffuse peritonitis and signs of sepsis. In our patient, we believe the amount of infection was limited by the perforation happening slowly over time, and her septic response was also blunted by her HIV with a low CD4 count.A growing body of literature exists on this topic and different treatment approaches have been proposed. Diller *et al*[10] reported a case series of stent migration necessitating surgical intervention in 2003. The size of the stents varied between 7 and 14 Fr and the lengths ranged from 7 to 12 cm. Two patients had Polyurethane stents, one patient had Teflon stent placement and the other two patients had metallic stents. The diagnosis was biliary obstruction from acute pancreatitis in 4 patients and the fifth patient

received a prophylactic stent after liver transplantation. One of those five patients died from postoperative respiratory failure. In this study they reported a stent migration rate of 3.7% among 987 patients. Namdar *et al*[1] reported a case of rectal perforation from migrated biliary stent and review of literature with 12 cases in total and 7 cases from 2000. Several studies have shown that downstream migration is more frequent in benign than in malignant biliary disease, with the possible explanation being the resolution of the stenosis after regression of inflammation[1]. In addition, they state that any migrated biliary stent should be removed immediately regardless of the patient's clinical status[1]. An early growing body of literature describes endoscopic techniques for treatment of bowel perforation from migrated stent, but the majority focus on duodenal perforation or distal large bowel perforation. Bureau *et al*[11] recently described a case series of six patients with lateral duodenal wall perforation from displaced plastic biliary stent that were treated with over-the-scope clip. Given that in our case the bowel perforation was in a mid-jejunal loop, the endoscopic approach was less feasible. In addition, there was already significant inflammation seen around the bowel on CT scan, and we were concerned that an endoscopic mucosal repair would not hold. As such, we proceeded directly to surgery.

We performed a systematic review of literature from 2000 until 2020 for bowel perforation from migrated biliary stents and we found 81 cases (Table 1). Eligible articles were identified by a search of MEDLINE bibliographical database (last search: July 4th, 2021) using the following search algorithm: (("intestinal perforation"[MeSH Terms] OR ("intestinal"[All Fields] AND "perforation"[All Fields]) OR "intestinal perforation"[All Fields] OR ("bowel"[All Fields] AND "perforation"[All Fields]) OR "bowel perforation"[All Fields]) AND ("migrate"[All Fields] OR "migrated"[All Fields] OR "migrates"[All Fields] OR "migrating"[All Fields] OR "migration"[All Fields] OR "migrational"[All Fields] OR "migrations"[All Fields] OR "migrator"[All Fields] OR "migrators"[All Fields]) AND "biliary"[All Fields] AND ("stent s"[All Fields] OR "stentings"[All Fields] OR "stents"[MeSH Terms] OR "stents"[All Fields] OR "stent"[All Fields] OR "stented"[All Fields] OR "stenting"[All Fields])) AND (2000:2020[pdat]). Further search was performed in the references of related articles and relative articles with our topic were included. Manuscripts with full text available online were used and E-Videos, E-pictures and not English manuscripts were excluded. Cases were also excluded if there was not full text available online. Wang *et al*[3] in 2020 reported three cases of duodenal perforation due to biliary stent migration and performed a review of literature of duodenal perforation from migrated stents. In this study they reported that duodenal perforation from migrated biliary stents are mainly caused by distal stent migration[3]. Kawaguchi *et al*[12] studied 396 patients with bile duct stenosis between June 2003 and March 2009, retrospectively examined the frequency of stent migration and analyzed the patient factors and stent characteristics. They found that potential risk factors for stent migration are stent with large diameter, straight-type stents, stent duration > 1 mo, and common bile duct diameter > 10 mm[12].

In our review of literature (Table 1) there were 39 (50%) of male gender, 35 (44.9%) of female gender and 4 (5.1%) patients with missing data. The mean age of the total population was 66 (± 15.5) and the median 67 (IQR-56-77.5). The majority of patients had a plastic stent (93.6%). The stent length ranged from 5 to 15 cm and the stent size from 5 to 14 Fr. However, the majority of patients (50%) had a stent of 10 Fr or 12 Fr size. From the total population 35 patients (44.9%) had duodenal perforation, 23 patients (29.5%) had large bowel perforation, 18 patients (23.1%) had small bowel perforation, one patient had bile duct perforation and the last patient had no available information regarding the site of perforation. From the whole cohort, 47 patients (60.3%) had surgical intervention, 27 patients (34.6%) had endoscopic removal of the stent and 3 patients (3.8) had percutaneous removal of the stent. The overall mortality among the 54 patients was 8 patients (10.1%). Finally, the distribution of case reports was 38 (48.7%) from Europe, 21 (26.9%) from Asia-Middle East, 12 (15.4%) from the United States, 5 (6.4%) from Australia and 2 (2.6%) from South America.

CONCLUSION

From this review of literature, we can see that most common types of migrated stents entailing bowel perforation are the plastic stents and the most common site of perforation is duodenum. A significant finding is the mortality after bowel perforation from biliary stent which is as high as 10.3%. The main treatment is surgical stent removal, but a growing body of literature shows that endoscopic removal and mucosal repair is feasible in select cases. This has still not been accomplished in the mid portion

Table 1 Systematic review of literature from 2000 until 2020 for bowel perforation from migrated biliary stents

No	Year	Age, yr	Gender	Type of stent[1]	Site of perforation	Treatment	Country	Mortality	Stent length	Stent size	Ref.
1	2000	81	M	P	SB	ST	Norway	Y	6.5	10 Fr	[13]
2	2000	86	M	P	LB	ST	Norway	N	5	7 Fr	[13]
3	2000	74	M	P	DU	ET	Spain	N	15	10 Fr	[14]
4	2001	58	M	P	DU	ET	Italy	N	12	10 Fr	[15]
5	2001	43	F	P	DU	ET	India	N	NA	10 Fr	[16]
6	2001	NA	NA	P	SB	ST	United States	N	12	11.5 Fr	[17]
7	2001	88	F	P	DU	ST	Germany	N	10	7 Fr	[18]
9	2001	31	F	NA	BD	ST	Denmark	N	NA	NA	[19]
10	2001	47	M	P	LB	ST	Spain	N	10	10 Fr	[20]
11	2002	72	F	P	SB	ST	Italy	N	NA	12 Fr	[21]
12	2002	NA	NA	P	SB	ST	United States	N	7	8.5 Fr	[22]
13	2003	85	F	P	LB	ST	Germany	N	NA	NA	[23]
14	2003	86	M	P	DU	ET	Italy	Y	15	10 Fr	[24]
15	2003	27	F	P	SB	ST	Germany	N	12	12 Fr	[10]
16	2003	58	M	P	LB	ET-ST	Germany	N	10	7 Fr	[10]
17	2003	60	F	P	SB	ST	Germany	N	12	14 Fr	[10]
18	2003	64	M	M	LB	ST	Germany	Y	7	10 Fr	[10]
19	2003	65	M	M	NA	ST	Germany	N	7	10 Fr	[10]
20	2003	62	F	P	LB	ST	Argentina	N	NA	8 Fr	[25]
21	2003	62	F	P	SB	ST	Argentina	N	NA	5.5/10 Fr	[25]
22	2003	80	F	P	LB	ST	Australia	N	10	10 Fr	[26]
23	2004	65	F	P	LB	ST	United States	N	NA	NA	[27]
24	2005	69	M	M	DU	ST	United States	N	NA	NA	[28]
25	2006	55	M	P	DU	ET	Greece	Y	NA	NA	[29]
26	2006	74	M	P	DU	ST	India	NA	10	7 Fr	[30]
27	2006	54	F	P	SB	ST	United Kingdom	N	7	10 Fr	[31]
28	2006	85	M	P	DU	ST	Italy	N	10	9 Fr	[32]
29	2007	65	F	P	LB	ST	Germany	N	10	12 Fr	[1]
30	2008	75	M	P	DU	ST	Taiwan	N	NA	NA	[33]
31	2008	52	F	P	DU	ST	Turkey	N	10	8.5 Fr	[34]
32	2008	67	M	P	DU	ST	Australia	Y	NA	5/10 Fr	[35]
33	2008	43	M	P	DU	ET	Belgium	N	NA	NA	[36]
34	2008	71	F	P	SB	ST	Belgium	N	NA	NA	[36]
35	2009	77	M	P	LB	PI	United States	N	12	10 Fr	[37]
36	2009	76	F	P	SB	PI	United States	N	NA	10 Fr	[38]
37	2009	59	F	P	SB	ST	Turkey	N	7	11 Fr	[39]
38	2011	58	M	P	DU	PI	United Kingdom	N	10	8.5 Fr	[40]
39	2011	65	F	P	LB	ST	Germany	N	10	10 F Fr	[41]
40	2011	73	NA	P	LB	ST	France	N	5	10 Fr	[42]

41	2011	75	M	P	SB	ST	United Kingdom	N	NA	NA	[43]
42	2011	70	M	P	DU	ET	China	N	NA	8.5 Fr	[44]
43	2011	82	F	P	LB	ET	United Kingdom	N	7	7 Fr	[45]
44	2012	55	M	P	DU	ET	South Korea	N	7/5	5 Fr	[46]
45	2012	27	F	P	DU	ST	United Kingdom	N	12	7 Fr	[47]
46	2012	87	F	P	DU	ET	United States	N	15	8.5 Fr	[48]
47	2012	73	M	P	LB	ET	Spain	N	12	10 Fr	[49]
48	2012	50	NA	P	LB	ET	Belgium	N	NA	NA	[50]
49	2013	51	M	P	DU	ST	S. Arabia	N	10	10 Fr	[51]
50	2013	66	M	P	LB	ET	United Kingdom	N	NA	NA	[52]
51	2013	50	M	M	SB	ST	India	N	NA	NA	[53]
52	2014	67	M	P	DU	ST	United States	Y	12	10 Fr	[54]
53	2014	73	M	P	LB	ST	Australia	N	5	10 Fr	[55]
54	2014	66	F	P	DU	ET	The Netherlands	N	15	NA	[56]
55	2015	48	M	P	DU	ET	United States	N	NA	NA	[57]
56	2015	NA	F	P	LB	ST	Italy	N	12	12 Fr	[58]
57	2015	NA	F	P	LB	ET	Italy	N	12	12 Fr	[58]
58	2015	52	F	P	SB	ST	Turkey	N	NA	NA	[7]
59	2015	NA	M	P	LB	ST	United Kingdom	Y	NA	NA	[59]
60	2016	85	F	P	SB	NA	Turkey	Y	NA	NA	[6]
61	2017	75	F	P	LB	ST	Greece	N	NA	NA	[60]
62	2018	57	M	P	DU	ET	United States	N	15	8.5 Fr	[61]
63	2018	79	F	P	DU	ET	United States	N	12+15	7+10 Fr	[62]
64	2018	87	M	P	DU	ST	Greece	N	15	10F	[63]
65	2018	20	M	P	SB	ST	Turkey	N	NA	NA	[64]
66	2019	71	M	P	DU	ET	France	N	12	8.5 Fr	[65]
67	2019	50	M	P	DU	ET	South Korea	N	10	10F	[66]
68	2019	78	M	P	DU	ET	South Korea	N	10	7 Fr	[66]
69	2019	72	M	P	DU	ET	South Korea	N	12	10 Fr	[66]
70	2019	84	F	P	DU	ET	South Korea	N	12	10 Fr	[66]
71	2019	73	F	P	DU	ET	South Korea	N	15	10 Fr	[66]
72	2019	63	F	P	DU	ST	Jordan	N	10	10 Fr	[67]
73	2019	65	F	P	LB	ST	Portugal	N	5	10 Fr	[68]
74	2019	79	F	P	LB	ST	United States	N	10	7+10 Fr	[69]
75	2020	90	F	P	SB	ST	Australia	N	9	10 Fr	[70]
76	2020	84	F	P	SB	ST	Australia	N	7	10 Fr	[71]
77	2020	72	M	P	DU	ET	China	N	9	8.5 Fr	[3]
78	2020	84	M	P	DU	ET	China	N	12	7 Fr	[3]
79	2020	52	M	P	DU	ET	China	N	9	8.5 Fr	[3]

[1]Time interval from stent placement to complication in days.
P: Plastic; M: Metallic; BD: Bile duct; DU: Duodenum; SB: Small bowel; LB: Large bowel; ST: Surgical treatment; ET: Endoscopic treatment; PI: Percutaneous intervention; NA: Not available.

of the bowel, however this might be an area for future innovation and research.

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ORIGINAL ARTICLE

Observational Study

Needle-based confocal endomicroscopy in the discrimination of mucinous from non-mucinous pancreatic cystic lesions

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Abstract

BACKGROUND

Pancreatic cystic lesions (PCLs) are considered a precursor of pancreatic cancer. Needle-based confocal endomicroscopy (nCLE) is an imaging technique that enables visualization of the mucosal layer to a micron resolution. Its application has demonstrated promising results in the distinction of PCLs. This study evaluated the utility of nCLE in patients with indeterminate PCLs undergoing endoscopic ultrasound fine-needle aspiration (EUS-FNA) to distinguish mucinous from non-mucinous lesions.

AIM

To evaluate the accuracy of nCLE in indeterminate PCLs undergoing EUS-FNA to distinguish mucinous from non-mucinous lesions.

METHODS

Patients who required EUS-FNA between 2015 and 2017 were enrolled prospectively. During EUS-FNA, confocal imaging, analyses of the tumor markers carcinoembryonic antigen and amylase, and cytologic examination were

patient from the study.

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conducted. All patients were followed for at least 12 mo and underwent laboratory testing and computed tomography scanning or magnetic resonance imaging. nCLE videos were independently reviewed by 6 observers to reach a final diagnosis (mucinous *vs* non-mucinous) based on criteria derived from previous studies; if there was disagreement > 20%, a final diagnosis was discussed after consensus re-evaluation. The sensitivity, specificity, and accuracy of nCLE were calculated. Adverse events were recorded.

RESULTS

Fifty-nine patients were included in this study. Final diagnoses were derived from surgery in 10 patients, cytology in 13, and imaging and multidisciplinary team review in 36. Three patients were excluded from final diagnosis due to problems with nCLE acquisition. Fifty-six patients were included in the final analysis. The sensitivity, specificity, and accuracy of nCLE were 80% [95% confidence interval (CI): 65-90], 100% (95%CI: 72-100), and 84% (95%CI: 72-93), respectively. Post-procedure acute pancreatitis occurred in 5%.

CONCLUSION

EUS-nCLE performs better than standard EUS-FNA for the diagnosis of indeterminate PCL.

Key Words: Needle-based confocal endomicroscopy; Pancreatic cystic lesion; Pancreatic adenocarcinoma; Endoscopic ultrasound; Endoscopic ultrasound fine-needle aspiration; Intraductal papillary mucinous neoplasm; Serous cyst adenoma

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Core Tip: Pancreatic cystic lesions are considered a precursor of pancreatic cancer. Needle-based confocal endomicroscopy is an imaging technique that enables visualization of the mucosal layer to a micron resolution. Endoscopic ultrasound with fine-needle aspiration is the most accurate procedure for identifying pancreatic cystic lesions, as it combines cytology with analysis of intracystic carcinoembryonic antigen level, although its accuracy is low. Needle-based confocal endomicroscopy has demonstrated promising results.

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INTRODUCTION

Pancreatic cancer is the 10th most common cancer in men and 9th most common cancer in women. Compared to other cancers, pancreatic cancer has the lowest survival, with a 5-year survival rate of 9% and an estimated 56000 new cases per year according to the Surveillance, Epidemiology, and End Results database[1]. Pancreatic cystic lesions (PCLs) are considered a precursor of pancreatic cancer, as some have malignant potential and therefore should be evaluated carefully. However, other PCLs exhibit benign behavior with no surveillance required[2-4].

Currently, endoscopic ultrasound (EUS) with fine-needle aspiration (FNA) is the most accurate procedure for identifying the nature of a pancreatic cyst, as it combines cytology with analysis of intracystic carcinoembryonic antigen (CEA) level. The specificity, sensitivity, and overall accuracy of CEA in the discrimination of mucinous from non-mucinous is 98%, 48%, and 79%, respectively. However, in the absence of an associated solid component, pancreatic cyst fluid is frequently acellular or paucicellular, with resultant low diagnostic yield[5,6].

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Confocal laser endomicroscopy is an innovative imaging technique that enables visualization in real-time, to a micron resolution, of the mucosal layer. Luminal confocal exploration has demonstrated excellent results in distinguishing neoplastic from benign tissue. Needle-based confocal endomicroscopy (nCLE) is a subtype of confocal laser imaging, in which a mini-probe is inserted through a 19-gauge EUS-FNA needle under EUS guidance. The first three clinical trials (total of 126 patients) described the correlation between nCLE and histological features, and established the criteria for characterizing the most frequent type of cysts; however, they did not evaluate the performance of these criteria[7-9]. Moreover, some concerns were raised about the safety of the procedure and interobserver agreement (IOA)[10,11]. Recently, two papers were published evaluating the impact of nCLE on surgical outcome[12, 13]; the results were very promising, with some interesting economic consequences for follow-up costs[14].

We present the results of a multicenter prospective study evaluating the diagnostic accuracy of EUS-guided nCLE in differentiating mucinous from non-mucinous PCLs compared to standard of care, by analysis of intracystic CEA and amylase level and/or cytology *vs* surgical pathology.

MATERIALS AND METHODS

Study design and inclusion criteria

From November 2015 to December 2017, all consecutive patients referred for EUS-FNA for undetermined PCLs were prospectively enrolled and underwent EUS associated with both FNA and nCLE at four centers (AOU-Modena; Ospedale Le Molinette-Torino; Istituto Nazionale Tumori-Milano; Ospedale Maggiore, Crema, Italy). The inclusion criteria were as follows: age > 18 years; ability to provide informed consent; and, had a single undetermined pancreatic cyst > 20 mm without evidence of communication with the main pancreatic duct (PD) in previous imaging investigations. Exclusion criteria were as follows: Known fluorescein allergy; pregnancy; worrisome features or high-risk stigmata according to Fukuoka Guidelines [15]; or, any contraindication to performing EUS (Figure 1). The study was carried out in accordance with the Declaration of Helsinki and was approved by the Ethical Committee of Baggiovara Hospital in Modena (Prot. 16/11/2015 prat n 4327; Baggiovara, Italy).

Study aims

The primary goal of the study was to determine the accuracy of nCLE in discriminating mucinous from non-mucinous PCLs. The secondary goals were to determine the feasibility of nCLE by evaluating the rate of procedure completion and by rating the ease of the procedure as easy, moderate, or difficult, and to assess the safety of the procedure by recording the immediate and 30-d complication rates (bleeding, infection, perforation, or acute pancreatitis (AP) classified as mild, moderate, or severe according to the European Society of Gastrointestinal Endoscopy guidelines)[16].

Procedures

EUS and EUS-FNA: All EUS procedures were performed by five operators with experience in biliopancreatic EUS (> 200/year) and nCLE (> 15/per operator). Antibiotic prophylaxis was administered 1 h before the procedure and continued for 3 d after[3]. The procedures were performed under deep sedation using a linear array echoendoscope (Olympus®, Tokyo, Japan or Hitachi-Pentax®, Hamburg, Germany) to evaluate the following PCL characteristics: site; morphology; cyst diameter; diameter of the main PD; communication with a duct (main or branch); thickness of the cyst wall; presence of septa and/or wall nodules; and, contrast medium to evaluate the enhancement of any septa or nodule. Once the cyst was visualized, it was punctured from the stomach or duodenum with a 19-gauge needle (Expect™; Boston Scientific, Boston, MA, United States) that was preloaded with the AQ-flex 19 miniprobe (Mauna Kea Technologies®, Paris, France). Then 2.5 mL of 10% fluoresceine was intravenously injected, the probe was gently advanced in contact with the cyst wall, and nCLE imaging was performed. After nCLE imaging acquisition, the probe was retrieved from the EUS-FNA needle and the cyst was completely aspirated. The cyst fluid was sent for analysis of CEA and amylase, and cytologic examination.

nCLE classification and diagnosis: Before patient enrollment, 6 investigators received nCLE training to learn technical tips and agreement for imaging interpretation,

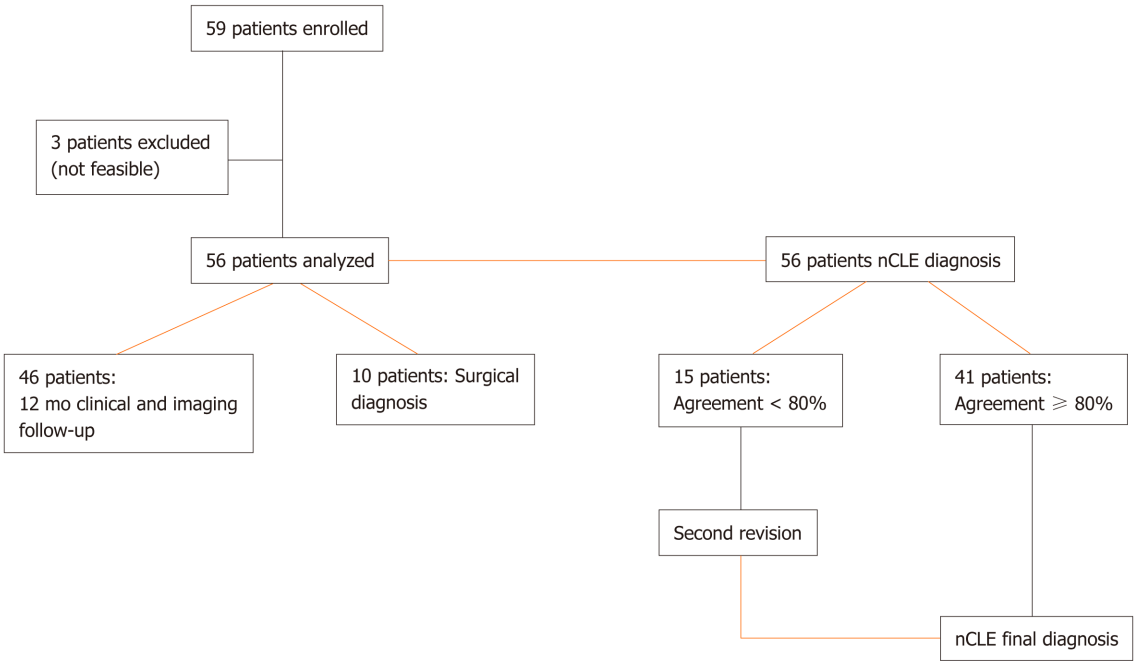

Figure 1 Flow chart. nCLE: Needle-based confocal endomicroscopy.

highlighting the high specificity of nCLE for the diagnosis of serous cystadenoma (SCA), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN) and for the differentiation of mucinous from non-mucinous lesions, with a 20-video review. The criteria used in this study were derived from previously validated criteria from publications by Napoleon *et al*[8,9] as well as studies on papillary projections in IPMN[7,17] (Figure 2A), the superficial vascular network in SCA[9] (Figure 2B), MCNs in which the epithelial cyst border appears as a gray band delineated by a thin dark line[9] (Figure 2C), pseudocysts identified by bright gray and black particles[9] (Figure 2D), and cystic pancreatic neuroendocrine tumors (PNETs) characterized by dark irregular clusters of cells surrounded by gray matter[9].

After the conclusion of follow-up, all nCLE videos were independently and blindly reviewed by the 6 observers; no clinical or imaging information was provided at this time. After video review, each investigator provided a final diagnosis of mucinous (mucinous cystadenoma or IPMN) or non-mucinous (SCA, pseudocyst, PNET) neoplasia, according to the criteria described above. In cases of disagreement between > 20% of observers, videos were discussed together to reach a final nCLE consensus diagnosis. In the event of persistent disagreement between the investigators, the videos were considered false negatives.

Final diagnosis: The final diagnosis was based on histological analyses of the surgical specimen and/or when FNA results were diagnostic on cell block sections or smears. Otherwise, all patients were followed up at 6 mo with magnetic resonance imaging (MRI) or computed tomography (CT) scan or EUS, and the final diagnosis was based on a consensus of EUS findings plus analysis of CEA level with at least 12 mo follow-up.

IOA

The extent of agreement among raters of nCLE diagnosis was performed with Gwet's agreement coefficient (AC) [95% confidence interval (CI)]. Gwet's AC provides a more stable interrater reliability coefficient than Cohen's kappa. It is also less affected by prevalence and marginal probability than Cohen's kappa, and therefore should be considered for use with interrater reliability analyses. For all measures of agreement, the following guideline provided by Landis and Koch[19] for the interpretation of kappa was used: < 0.00, poor; 0.00 to 0.20, slight; 0.21 to 0.40, fair; 0.41 to 0.60, moderate; 0.61 to 0.80, substantial; and 0.81 to 1.00, almost perfect[18,19].

Statistical analyses

The categorical variables are expressed as absolute numbers and percentages, while

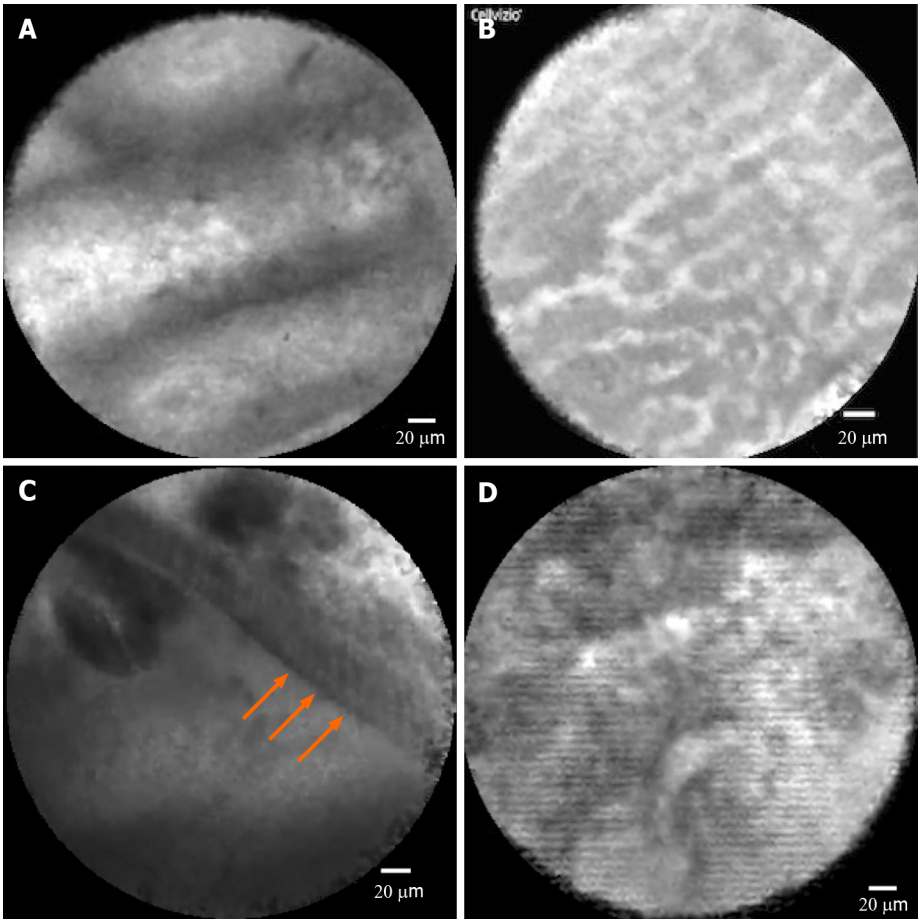

Figure 2 Confocal images of pancreatic cyst subtypes. A: Intraductal papillary mucinous neoplasm, showing papillary projections; B: Serous cystadenoma, showing superficial vascular network; C: Mucinous cystic neoplasm, in which the epithelial cyst border appears as a gray band delineated by a thin dark line; D: Pseudocyst, showing gray and black particles.

the continuous variables are expressed in the case of normal distribution as mean and standard deviation and relative 95%CI, or in the case of non-normal distribution, as median and interquartile range. The study was approved by the local Ethical Committee of Baggiovara Hospital in Modena (Prot. 4327/2016) and subsequently by the Ethical Committees of all centers involved.

RESULTS

Baseline patient characteristics

From November 2015 to December 2017 a total of 59 patients were referred for EUS-FNA of PCLs, and were prospectively enrolled in the study to undergo EUS-guided FNA and nCLE during the same session. Patient demographics and PCL features are listed in Table 1. The mean patient age was 64-year-old, and 41 patients were female (70%). The majority of patients at the time of EUS were asymptomatic (n = 45; 76%); a history of AP was identified in 3 (5%) and concurrent symptoms potentially attributable to PCL were reported in 11 (19%), all of whom had abdominal pain. Previous cross-sectional abdominal imaging reports for PCL evaluation were available in all cases (n = 33 CT, n = 43 MRI).

The PCLs were distributed as follows: head of pancreas in 13 patients (22%); uncinate process in 8 (13%); neck in 6 (10%); body in 26 (45%); and tail in 6 (10%). The median cyst size was 32 mm (range: 22-45 mm). The majority of lesions were multilocular (n = 27, 46%). The main PD communication was considered exclusion criteria if found during CT or MRI. However, in 1 case, a communication was detected by EUS. No PD dilation (≥ 5 mm) was identified. Solid components or intramural nodules were present in 3 patients (5%). Intracystic CEA was available in 53 cases (95%), with a level > 192 ng/mL in 28 patients (47%) and < 5 ng/mL in 14 cases (24%).

Table 1 Patients demographics and pancreatic cystic lesions features

Characteristic	Enrolled, *n* (%)
Patients, *n*	59
Age	64 ± 13
Sex, female	41 (70)
Clinical presentation	
Asymptomatic	45 (76)
Abdominal pain	11 (19)
Pancreatitis	3 (5)
Site of lesion	
Head	13 (22)
Uncinate process	8 (13)
Neck	6 (10)
Body	26 (45)
Tail	6 (10)
Cyst diameter mm	32 (22-45)
Morphology	
Unilocular macrocyst	31 (52)
Multilocular microcyst	27 (46)
Microcyst	1 (2)
Main pancreatic duct diameter > 3 mm	5 (8)
Communication with a duct	1 (2)
Cyst wall diameter > 1 mm	20 (34)
Septa and/or wall nodules	35 (59)
CEA > 192 ng/mL	21 (35)
Amylases ≥ 50 UI/L	53 (90)

CEA: Carcinoembryonic antigen.

Final diagnosis

Final diagnosis was made of 11 mucinous cystadenomas, 34 branch-duct IPMNs, 13 SCAs, and 1 cystadenocarcinoma (Table 2). Final diagnosis was derived from surgery in 10 patients (17%), cytology in 13 patients (22%), and a team discussion of the review of all CT/MRI/EUS images and intracystic CEA level in the remaining cases.

Feasibility

The procedure was technically feasible in 56 patients; therefore, the feasibility rate was 95%, with a rating of easy in 48 patients (82%), moderately difficult in 7 patients (11%), and difficult in 4 patients (7%). The median nCLE scanning time was 3 min and did not exceed 4 min in any case.

Comparison of CEA and nCLE

The analysis of "intention to treat" showed sensitivity, specificity, and accuracy for diagnosing mucinous lesions and intracystic CEA > 192 ng/mL of 58% (95%CI: 43-72), 100% (95%CI: 73-100), and 67% (95%CI: 53-78), respectively. The sensitivity, specificity, and accuracy of nCLE were 80% (95%CI: 65-90), 100% (95%CI: 72-100), and 84% (95%CI: 72-92), respectively, in distinguishing mucinous from non-mucinous lesions (Table 3).

Table 2 Final diagnosis

Final diagnosis	*n* (%)
Serous cystoadenoma	13 (22)
Cystoadenocarcinoma	1 (2)
Branch-duct IPMN	34 (58)
Mucinous cystoadenoma	11 (18)

IPMN: Intraductal papillary mucinous neoplasm.

Table 3 Diagnostic yield of carcinoembryonic antigen and needle-based confocal laser endomicroscopy in mucinous *vs* non-mucinous lesions

	Sensitivity (%)	Specificity (%)	Accuracy (%)
CEA > 192 ng/mL	58.0	100.0	67.0
nCLE mucinous *vs* non-mucinous	80.0	100.0	84.0

CEA: Carcinoembryonic antigen; nCLE: Needle-based confocal laser endomicroscopy.

IOA

IOA for nCLE diagnosis was 0.76 (range: 0.65-0.86). In 15 cases (26%), there was disagreement in more than 20% of the observers, so a second revision was necessary. After the second review, the sensitivity, specificity, and accuracy were calculated for 56 patients in whom nCLE was technically feasible.

Adverse events

Six adverse events (10%) were registered: 2 cases of self-limited intracystic bleeding (in 1 SCA and 1 IPMN); 3 cases of AP (in 3 IPMNs); and 1 case of abdominal pain (in 1 IPMN). AP was classified as interstitial edematous pancreatitis according to Atlanta classification[20] and required patient hospitalization; none developed infected pancreatic necrosis or walled-off necrosis.

DISCUSSION

PCLs are a heterogeneous family of lesions; some show benign behavior and others have unequivocal malignant potential and thus are considered a precursor of pancreatic cancer. The increased use of cross-sectional imaging, CT and MRI, has increased the reporting of incidental PCLs by up to 45%[2]. A key element of optimal clinical management of PCLs is identification of the small minority of cysts with early invasive cancer or high-grade dysplasia, and possibly the prediction of patients who will develop them in the future. A major challenge is that commonly used diagnostic tools, such as CT, MRI, and EUS-FNA cytology, and intracystic CEA analysis have suboptimal sensitivities and specificities for identifying patients at high risk, especially in cases of overlapping EUS features or borderline CEA intracystic level[5].

Recently a new technique, nCLE, has demonstrated promising results in visualization of the epithelial lining of the cyst wall, and consequently in the distinction of cyst type with accuracy and specificity that has not previously been described in PCLs. However, only limited studies on this technique with limited patients are available from three select centers: one from Europe[8] and two from the United States[7,11]. Consequently, optimal results could be related to the selected cases more than to the technique's performance.

The strength of our study was that the performance of nCLE was evaluated in four different centers with high EUS volume, by experts with previous experience in confocal endomicroscopy imaging, in a non-selected group of patients referred for EUS-FNA for undetermined PCLs without PD communication as determined by previous imaging. We also excluded worrisome features and high-risk stigmata as well as solid masses to avoid biased study results. The diagnostic yield of confocal

endomicroscopy in our study has been optimal with a specificity of 100%. In a clinical setting, these data confirm the potential of this technique to classify PCLs as high and low risk of progression, and consequently, to modulate the surveillance program for these patients.

The feasibility of EUS-guided nCLE has been a subject of debate due to the use of a large needle[7]. This study showed that the feasibility of the technique is excellent in experienced hands. Our study also confirmed the safety of nCLE; indeed, the rate of post-procedure AP was slightly higher (5%) than that described by Palazzo *et al*[14] but was lower than that in another report[15]. The cases of AP were mild, and none evolved to walled-off necrosis. We postulated that prolonged examination of the cyst wall could be related to an increased risk of bleeding or debris that could enhance the risk of AP; however, this was not statistically significant.

At the time of study onset, data derived from the two recently published papers by Napoleon *et al*[12] and Krishna *et al*[13] were not available; therefore, the performance of this technique is still considered under investigation. Our results support the recently published data, showing the potential of nCLE to be used in selected patients in a clinical setting as proposed by Napoleon *et al*[12], to evaluate multiple PCLs before surgery in order to guide partial *vs* total pancreatectomy, or to assess single lesions in young women where, in case of SCA, surveillance could be discontinued.

The limitation of our study was that it was conducted in a limited study population; thus, only small numbers of final surgical diagnoses were available. This has been frequently described in PCL studies due to the surveillance approach suggested by various international guidelines, even in lesions with a high risk of progression (mucinous cystadenoma and IPMN > 3 cm)[21].

CONCLUSION

In conclusion, a few years after the first publication on nCLE in PCLs[7], this study confirms that the diagnostic yield of EUS-guided nCLE is higher than any available technique for PCL characterization, and as such is a valuable tool in PCL management.

ARTICLE HIGHLIGHTS

Research background

Some pancreatic cystic lesions (PCLs) have unequivocal malignant potential, but the precise determination of the risk of progression with endoscopic ultrasound (EUS), fine-needle aspiration (FNA), analysis of carcinoembryonic antigen (CEA) level, and cytology is still challenging. Among the novel tools for assessing PCLs, needle-based confocal endomicroscopy (nCLE) has been identified as one of the most sensitive, but some concerns have been raised about its safety and reproducibility.

Research motivation

The first clinical trials published described a correlation between nCLE and histological features, and established the criteria for characterizing the most frequent type of cysts. However, no multicenter prospective studies have been performed at the time of study conception to evaluate the safety of the procedure and interobserver agreement (IOA).

Research objectives

The purpose of this multicenter prospective study was to evaluate the diagnostic accuracy of EUS-guided nCLE to differentiate mucinous from non-mucinous in PCLs compared to standard of care, by analysis of intracystic CEA and amylase level and/or cytology *vs* surgical pathology.

Research methods

The strength of the study is its observational design in high-volume centers compared to the single-center studies previously published. All nCLE videos were independently reviewed by 6 observers blind to clinical or imaging information; each investigator provided a final diagnosis, and if the disagreement between reviewers was > 20%, videos were discussed together in order to reach a final nCLE consensus diagnosis. In the event of persistent disagreement among investigators, the videos were considered

false negatives.

Research results

A total of 59 patients were enrolled in this study to receive EUS-FNA and nCLE. The procedure was technically feasible in 95% of patients; nCLE sensitivity, specificity, and accuracy for the diagnosis of mucinous lesions were 80% [95% confidence interval (CI): 65-90], 100% (95%CI: 72-100), and 84% (95%CI: 72-92), respectively, and for distinguishing mucinous from non-mucinous lesions compared to intracystic CEA > 192 ng/mL were 58% (95%CI: 43-72), 100% (95%CI: 73-100), and 67% (95%CI: 53-78), respectively. IOA for nCLE diagnosis was 0.76, and 10% of adverse events were recorded.

Research conclusions

Our study confirmed the feasibility of nCLE and its excellent performance in the discrimination of mucinous *vs* non-mucinous lesions. This new finding confirms the possibility of an accurate pre-operative diagnosis. The strength of the study was the multicenter, prospective observational design and the selection of a study group of real undetermined pancreatic cysts without pancreatic duct communication and free of worrisome features; this was also a weakness due to the low number of cases with surgical/histological diagnosis. The excellent performance of nCLE opens various possible scenarios for the management of undetermined PCLs.

Research perspectives

Future research should include fine-needle biopsies with biopsy forceps to improve pathological diagnosis without surgery.

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CASE REPORT

Acute upper gastrointestinal bleeding caused by esophageal right bronchial artery fistula: A case report

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Abstract

BACKGROUND

Fistula between the esophagus and bronchial artery is an extremely rare and potentially life-threatening cause of acute upper gastrointestinal bleeding. Here, we report a case of fistula formation between the esophagus and a nonaneurysmal right bronchial artery (RBA).

CASE SUMMARY

An 80-year-old woman with previous left pneumonectomy and recent placement of an uncovered self-expandable metallic stent for esophageal adenocarcinoma was admitted due to hematemesis. Emergent computed tomography showed indirect signs of fistulization between the esophagus and a nonaneurysmal RBA, in the absence of active bleeding. Endoscopy revealed the esophageal stent correctly placed and a moderate amount of red blood within the stomach, in the absence of active bleeding or tumor ingrowth/overgrowth. After prompt multidisciplinary evaluation, a step-up approach was planned. The bleeding was successfully controlled by esophageal restenting followed by RBA embolization. No signs of rebleeding were observed and the patient was discharged home with stable hemoglobin level on postoperative day 7.

CONCLUSION

This was a previously unreported case of an esophageal RBA fistula successfully managed by esophageal restenting followed by RBA embolization.

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Core Tip: Esophageal bronchial artery fistula is an extremely rare cause of upper gastrointestinal bleeding. Here, we describe a previously unreported case of fistula formation between the esophagus and a nonaneurysmal right bronchial artery (RBA), in the setting of palliative esophageal metallic stenting and previous left pneumonectomy. Hemostasis was achieved by the use of esophageal restenting followed by RBA embolization.

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INTRODUCTION

Acute upper gastrointestinal bleeding (UGIB) is a potentially life-threatening emergency with a reported incidence of about 100 per 100000 persons per year[1,2]. Its etiology has been divided into variceal and nonvariceal bleeding. The most common causes of acute UGIB include peptic ulcer disease and esophageal varices, followed by Mallory–Weiss syndrome and neoplasms[1-3]. Acute UGIB caused by esophageal bronchial artery fistula is extremely rare. To date, only a few cases of fistula formation between the esophagus and the right bronchial artery (RBA) have been reported worldwide. Here, we describe a previously unreported case of a fistula between the esophagus and a nonaneurysmal RBA, in the setting of palliative esophageal metallic stenting and previous left pneumonectomy.

CASE PRESENTATION

Chief complaints

An 80-year-old woman was admitted to our bleeding unit due to severe anemia (hemoglobin 7.1 g/dL) and hematemesis with signs of hemodynamic instability.

History of present illness

One episode of hematemesis with presyncope occurred 1 h prior to hospital admission.

History of past illness

The patient underwent left pneumonectomy with adjuvant chemoradiotherapy for lung cancer 6 years before. An uncovered self-expandable metallic stent (SEMS) had been placed 3 mo prior at another institution for the palliation of a locally advanced esophageal adenocarcinoma.

Personal and family history

The patient denied further medical history. There was no family history of GI cancer.

Physical examination

On presentation, the patient was hemodynamically unstable (pulse 115 bpm, blood pressure 90/60 mmHg). She was afebrile, with respiratory rate 17 breaths/min and oxygen saturation 94%. On general physical examination, she looked pale and dehydrated. Abdominal examination revealed nondistended, nontender abdomen

with normal bowel sounds. The rectal examination exhibited melena.

Laboratory examinations

Complete blood count analysis was notable for hemoglobin of 7.1 g/dL and hematocrit of 23.6%. All remaining laboratory examinations, including liver enzymes, coagulation studies and renal function tests, were within normal limits.

Imaging examinations

After blood transfusion and hemodynamic stabilization, emergent computed tomography (CT) angiography was performed showing no active GI bleeding with the esophageal stent correctly placed. The RBA appeared tortuous, dilated and tightly adherent to the thickened middle esophagus wall. Although no contrast extravasation was noted, the tissue planes between the RBA and the esophagus appeared obliterated (Figure 1).

MULTIDISCIPLINARY EXPERT CONSULTATION

After prompt multidisciplinary evaluation, involving a GI endoscopist, surgeon, and a diagnostic and interventional radiologist, a minimally invasive step-up approach with esophageal restenting followed, if necessary, by RBA embolization was planned.

FINAL DIAGNOSIS

Fistula formation between the esophagus and a nonaneurysmal RBA, in the setting of palliative esophageal metallic stenting and previous left pneumonectomy.

TREATMENT

Under fluoroscopic and direct endoscopic guidance, an over-the-guidewire partially covered SEMS was placed through the previously inserted uncovered SEMS. Immediately thereafter, diffuse esophageal bleeding controlled by the partially covered SEMS was endoscopically noted (Figure 2). On postoperative day (POD) 1, hematemesis with severe anemization (hemoglobin 5.7 g/dL) and hemodynamic instability occurred. After blood transfusion and hemodynamic stabilization, emergent CT angiography was repeated, showing the esophageal stents correctly placed with unmodified previous findings and no GI active bleeding. Esophagogastroduodenoscopy (EGD) revealed fresh blood within the esophagus and a large amount of dark blood under the partially covered SEMS, in the absence of identifiable active bleeding sites (Figure 3). Thus, operative angiography was performed. Selective RBA arteriography showed contrast extravasation within the esophagus and RBA was successfully embolized with microcoils (Figure 4).

OUTCOME AND FOLLOW-UP

Postoperative stay was complicated by the occurrence of pulmonary edema responsive to medical therapy. No rebleeding was observed and the patient was discharged home with stable hemoglobin level (9.1 g/dL) on POD 7. The patient died at home 1 mo postoperatively, in the absence of overt GI rebleeding or anemization.

DISCUSSION

Arterioesophageal fistulas (AEFs) are pathological communications between an arterial system and the esophagus, which may lead to exsanguination from massive UGIB if not recognized promptly. They develop most commonly due to aortic fistulization caused by foreign bodies, aortic aneurysm, or esophageal neoplasms[4-6]. Nonaortic AEFs have been less frequently reported, with the bronchial artery being the most commonly involved vessel. Etiology includes foreign bodies, vascular surgery and thoracic arterial malformations, and chemoradiotherapy in esophageal cancer

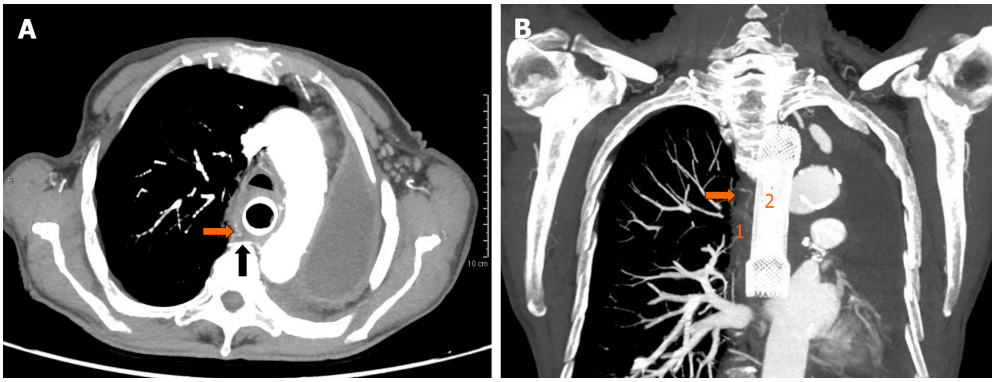

Figure 1 Arterial phase contrast-enhanced computed tomography. A: Axial view showing the tortuous and dilated right bronchial artery (orange arrow) originating from the right third posterior intercostal artery (black arrow); B: Coronal view showing delation of the tissue planes between the right bronchial artery (orange arrow) and the thickened middle esophageal wall (1), with correct placement of the esophageal metal stent (2).

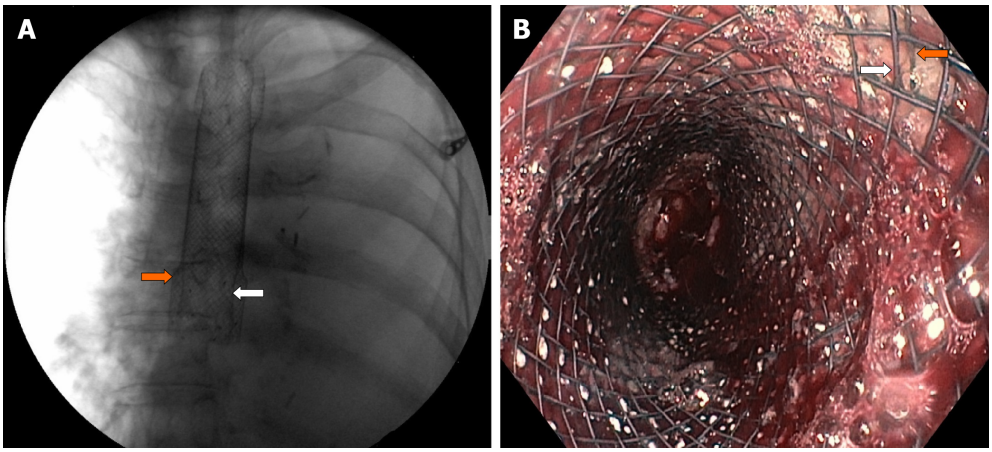

Figure 2 Placement of partially covered self-expandable metal stent (white arrow) through the previously inserted uncovered metal stent (orange arrow). A: fluoroscopic view; B: Endoscopic view showing esophageal bleeding controlled by the partially covered metal stent.

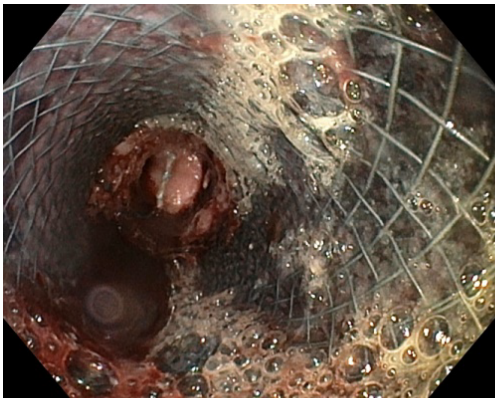

Figure 3 Second upper endoscopy showing fresh blood within the esophageal lumen and a diffuse amount of dark blood under the partially covered metal stent, in the absence of active bleeding sites.

patients with invasion of the aorta[7,8].

Although extremely rare, an esophageal RBA fistula is a potentially life-threatening condition. To date, only a few cases of fistula formation between the esophagus and a bronchial artery aneurysm have been reported. Shaer and Bashist[9] first reported a fatal case of massive UGIB due to a bronchial artery aneurysm with an esophageal fistula (BAAEF). Later on, two cases of BAAEFs successfully treated with RBA coil embolization have been reported[10,11]. In 2018, Nakada *et al*[12] reported a case of

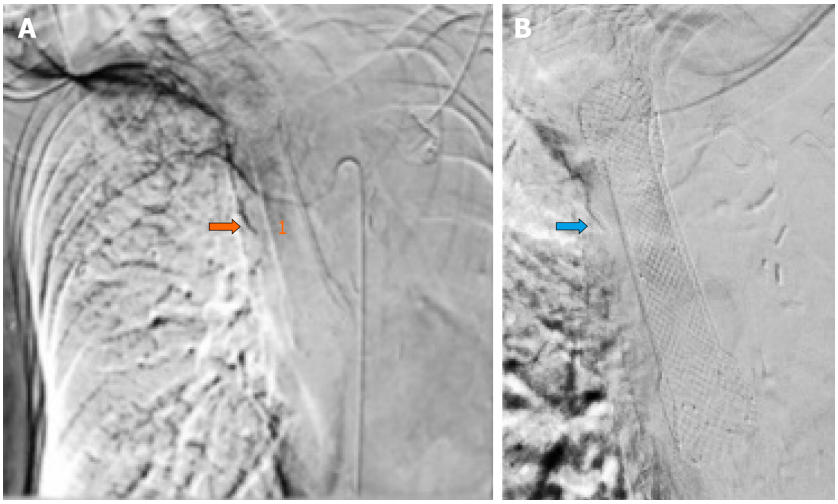

Figure 4 Operative angiography. A: Selective arteriogram of the right bronchial artery (orange arrow) showing contrast extravasation within the esophageal lumen (1); B: Right bronchial artery coil embolization (blue arrow).

BAAEF caused by bronchial arterial embolization. Due to the unfeasibility of transcatheter coil embolization, hemostasis was achieved by emergent thoracic endovascular aortic repair. Subsequently, aneurysmotomy, debridement and pedicled omental flap repair were successfully performed. Finally, a case of fistula between the esophagus and a RBA pseudoaneurysm secondary to an endobronchial ultrasound-guided transbronchial needle aspiration has been recently reported. This was successfully managed by endoscopic clipping followed by transcatheter coil embolization[13].

Moreover, only four cases of esophageal fistulas with a nonaneurysmal RBA have been reported, including three patients with locally advanced esophageal cancer and one with Mallory–Weiss tear refractory to endoscopic hemostasis. In all cases, the esophageal bleeding was successfully controlled by means of transcatheter arterial embolization[14-16].

However, to our knowledge, this is the first reported case of a fistula between the esophagus and a nonaneurysmal RBA, in the setting of palliative esophageal metallic stenting and previous left pneumonectomy.

In our case, emergent CT showed no active GI bleeding with the esophageal stent correctly placed. Although no direct signs of fistulization were observed, the RBA appeared tortuous, dilated and tightly adherent to the thickened middle esophagus wall, with obliteration of the tissue planes between the RBA and the esophagus. Subsequent emergent EGD confirmed the absence of active bleeding without identifiable bleeding sources. After prompt multidisciplinary evaluation, a minimally invasive step-up approach with esophageal restenting followed, if necessary, by RBA embolization was planned. However, after esophageal restenting, rebleeding occurred. Thus, operative angiography was performed. Selective RBA arteriography showed contrast extravasation within the esophageal lumen and RBA embolization was performed.

CONCLUSION

Digestive endoscopists should be aware of this critical, albeit extremely rare, cause of UGIB, in order to provide prompt diagnosis and treatment. In our opinion, early diagnosis, multidisciplinary evaluation and prompt tailored treatment seem to be crucial for the proper management of an esophageal RBA fistula.

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REVIEW

Choledochoscopy: An update

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Abstract

Choledochoscopy, or cholangioscopy, is an endoscopic procedure for direct visualization within the biliary tract for diagnostic or therapeutic purposes. Since its conception in 1879, many variations and improvements are made to ensure relevance in diagnosing and managing a range of intrahepatic and extrahepatic biliary pathologies. This ranges from improved visual impression and optical guided biopsies of indeterminate biliary strictures and clinically indistinguishable pathologies to therapeutic uses in stone fragmentation and other ablative therapies. Furthermore, with the evolving understanding of biliary disorders, there are significant innovative ideas and techniques to fill this void, such as nuanced instances of biliary stenting and retrieving migrated ductal stents. With this in mind, we present a review of the current advancements in choledochoscopy with new supporting evidence that further delineates the role of choledochoscopy in various diagnostic and therapeutic interventions, complications, limitations and put forth areas for further study.

Key Words: Choledochoscopy; Cholangioscopy; Indeterminate biliary strictures; Difficult bile stones; Primary sclerosing cholangitis; Cholangiocarcinoma

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Core Tip: The role of choledochoscopy (for extrahepatic biliary procedures) and cholangioscopy (for intrahepatic biliary procedures) is one and a half centuries old. It is a reliable tool in the visualization of indeterminate strictures and subsequent biopsy for diagnostic purposes. Furthermore, it serves as the "safety net" in therapeutic measures where endoscopic retrograde cholangiopancreatography cannot manage, such as biliary stone fragmentation and retrieving migrated equipment. With the advent of new

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techniques and adjuncts, its potential has further evolved to improve the procedure's accuracy. We provide a comprehensive update on the current and future potential of choledochoscopy.

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INTRODUCTION

Choledochoscopy, or cholangioscopy, refers to an endoscopic procedure for direct visualization within the biliary tract for diagnostic or therapeutic purposes. Attempts to directly visualize the bile duct lumen began as early as 1879. However, it was only with the Wildegans choledochoscope in 1953 that choledochoscopes started having some interventional capabilities. Other milestones in choledochoscopy include developing a flexible choledochoscope by Shore and Lipman in 1965, improved imaging quality with the Hopkins rod lens system in 1975, and cameras attached to the choledochoscopes to televise images for simultaneous viewing in 1985[1].

Regarding currently available choledochoscopes, peroral choledochoscopy was introduced in 1976 using the dual-operator "mother-baby" scope. Subsequently, single-operator choledochoscopes such as the direct peroral choledochoscopes (D-POC) and SpyGlass Direct Visualisation system choledochoscopes (Boston Scientific Corporation, Natick, MA, United States) were introduced[2]. Table 1 enlists technical specifications and details of commonly available choledochoscopes. Spurred by an improved understanding of biliary disorders and innovative technological advances, choledochoscopy remains an evolving field. Choledochoscopy and cholangioscopy are used interchangeably in the literature. However, for this review, choledochoscopy refers to the extrahepatic biliary tree procedure, and cholangioscopy refers to the intrahepatic biliary tree procedure. This review aims to update the technical advances in choledochoscopy, new evidence that further delineates the role of choledochoscopy in various diagnostic and therapeutic interventions, complications, limitations, and put forth areas for further study.

LITERATURE RESEARCH

An electronic search of PubMed was conducted in February 2021 for literature published in English. The following terms were used, and relevant articles were considered: [(choledochoscopy) OR (cholangioscopy)]. The last date of the search was 28th February 2021.

TYPES OF CHOLEDOCHOSCOPY

Choledochoscopy can be performed by peroral, percutaneous transhepatic, percutaneous transenteric *via* access loop, intra-operative transcystic, or intra-operative transcholedochal access (Figure 1). Table 2 summarizes types of choledochoscopy according to access routes, with each route's advantages and limitations. Peroral and percutaneous transhepatic access are the most widely discussed in the literature and are further elaborated on in this section.

Peroral choledochoscopes (POC) are further categorized into dual-operator or single-operator systems. Dual-operator systems require two endoscopists to operate "mother-baby" scopes, where a choledochoscope is inserted through the instrumentation channel of a duodenoscope. This includes original fibreoptic scopes and newer videocholangioscopes with Narrow Band Imaging (NBI) capacity. The original fibreoptic scopes were necessary for peroral choledochoscopy but have limited use currently due to its disadvantages: requires two endoscopists, low image quality with fibreoptic imaging, suboptimal working or irrigation channels, poor maneuverability

Table 1 Technical specifications of commonly discussed choledochoscopes

Type of choledochoscope	Fibreoptic or digital-based imaging systems1	Outer diameter (mm)	Accessory working channel diameter (mm)	Tip deflections
Percutaneous				
CHF-CB30 L/S (Olympus Medical Systems, Tokyo, Japan)[13]	Digital	2.8	1.2	2-way (up-down)
Peroral – dual-operator				
Mother-baby[4]	Fibreoptic	"Mother": 12.6 mm "Baby": 2.8–3.4 mm	0.8 – 1.2	2-way (up-down)
Short-access-mother-baby (Karl Storz, Tuttlingen, Germany)[4]	Fibreoptic	"Mother": 12.6 mm "Baby": 3.4 mm	1.5	2-way (up-down)
Videocholangioscope (CHF-B290; Olympus Medical Systems, Tokyo, Japan)[6]	Digital	3.3	1.3	2-way (up-down)
Peroral – Single-Operator				
SpyGlass Legacy 2007 (Boston Scientific Corporation, Natick, MA, United States)[5]	Fibreoptic	3.3	1.2	4-way (up-down, left-right)
SpyGlass Direct Visualisation 2015 (Boston Scientific Corporation, Natick, MA, United States)[5]	Digital	3.6	1.2	4-way (up-down, left-right)
SpyGlass Direct Visualisation II 2018 (Boston Scientific Corporation, Natick, MA, United States)	Digital	Data has not been published yet		
Direct peroral choledochoscopy using variety of ultra-thin endoscopes[5]	Digital	5.0 – 5.9	2.0	4-way (up-down, left-right)

Fibreoptic and digital catheters differ in the modality used to illuminate, acquire and transmit endoscopic images back to the camera. Fibreoptic catheters utlitise multiple individual fibre-optic bundles to reflect light off cable walls and into a camera. Digital catheters use imaging chips to convert reflected light into a digital signal, to produce a higher resolution digital image.

Table 2 Types of choledochoscopy

Type of choledochoscopy	Advantages	Disadvantages
Peroral (endoscopic)	Natural orifice	(1) Technical expertise; (2) Sedation or anesthesia; and (3) Not possible in patients with previous gastric resections or Roux-en-Y gastric bypass
Percutaneous transhepatic (interventional radiology)	(1) Shorter scope length; (2) Repeated with ease; and (3) Therapeutic interventions	(1) Need dilated intra-hepatic ducts; and (2) Risk of bleeding, bile leak, tumor seeding, biliary fistula and skin excoriation
Percutaneous transenteric *via* access loop (interventional radiology, surgical)	(1) Shorter scope length; (2) Repeated with ease; (3)Therapeutic interventions; (4) Ductal dilatation not necessary; and (5) In patients with RPC	(1) Previous access loop creation; and (2) Risk of small bowel injury, peritonitis, biliary fistula and skin excoriation
Intra-operative transcystic (surgical)	(1) Avoid CBD incision; (2) Therapeutic interventions; (3) Can document CBD clearance; and (4) It can be done laparoscopically	(1) The spiral valve of Heister; (2) Anatomy of the cystic duct; (3) Size of the cystic duct; (4) Need thin scopes (3 mm); (5) Technical expertise; and (6) Risks of bleeding, bile leak
Intra-operative transcholedochal (surgical)	Most direct access	(1) Need dilated extra-hepatic biliary system; (2) Risk of bleeding, bile leak; (3) Can put an internal stent; and (4) Can put T tube

RPC: Recurrent pyogenic cholangitis; CBD: Common bile duct.

with two-way tip deflection, and scope fragility[3,4]. In contrast, interest in video-cholangioscopes (CHF-B260, latest version: CHF-B290; Olympus Medical Systems, Tokyo, Japan) remains despite the need for two endoscopists. Advantages include using NBI for improved image quality, the stability of baby scope positioning in bile ducts, and a small outer diameter for use in intrahepatic bile ducts[5,6]. However, its role, especially considering the latest CHF-B290 model, is still being defined and is not currently available for clinical use.

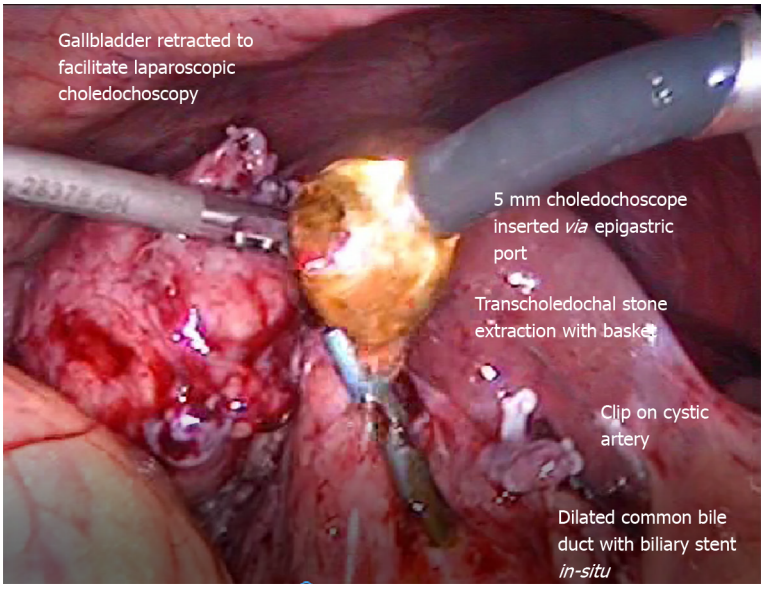

Figure 1 Laparoscopic transcholedochal common bile duct stone extraction by operative choledochoscopy.

To minimize drawbacks associated with the dual-operator technique, single-operator systems such as the SpyGlass Direct Visualisation peroral choledochoscopy system and D-POC using ultra-thin endoscopes were developed. Currently, three versions of SpyGlass are available – the first-generation SpyGlass Legacy 2007 (Fibre-optic) (FSOC), second-generation SpyGlass Digital System delivery, and access catheter 2015 (Digital) (DSOC) and third-generation SpyGlass Digital System II delivery and access catheter 2018 (Digital). Advantages of FSOC include a four-way deflectable tip for better maneuverability and a dedicated irrigation channel for continuous irrigation. It is limited by the inferior image quality and field-of-view (70˚), poor durability of the reusable fibreoptic probe, small therapeutic channel, and cumbersome setup[7]. Thus, DSOC improved on FSOC by having digital images with 400% greater resolution and 60% wider field-of-view (110˚), improved accessory channel, and easy "plug and play" set up[8]. The third-generation SpyGlass Direct Visualisation II delivery and access catheter 2018 (Digital) is touted to have 250% better resolution than DSOC and adjusted lighting to reduce flare. However, clinical data on its efficacy is not yet available[9].

D-POC utilizes a variety of ultra-slim endoscopes designed initially for pediatric and transnasal use. Key advantages are the variety of endoscopes already available, four-way deflectable tip, and the ability to use NBI for improved image quality. Disadvantages include relatively large outer diameters (5.0-5.9 mm), which may complicate scope insertion and advancement in smaller bile ducts, requiring prior large sphincterotomy to accommodate scope diameters gastric and duodenal looping [5].

Novel multi-bending choledochoscopes are developed to improve the ease of bile duct cannulation. This avoids accessory devices as two bending sections allow more acute angulation and control the choledochoscope while preventing choledochoscope dislodgement. Three prototype models exist. For the first two prototypes, freehand insertion had a 0% technical success rate in a study by Itoi *et al*[10] involving seven patients. Compared to the second prototype, the third prototype has more excellent distal tip angulation (200˚ *vs* 160˚) and a smaller outer diameter distal end (4.9 mm *vs* 5.2 mm) to improve the scope's pushability to minimize loop formation. This translated into improved technical success rates and shorter procedure time with reduced radiation exposure than conventional choledochoscopes and previous generations of multi-bending choledochoscopes. In a randomized controlled trial by Lee *et al*[11] involving 92 patients, while efficacy in diagnostic and therapeutic interventions was equivalent, multi bending choledochoscope had high technical success rates of freehand biliary insertion (89.1% *vs* 30.4%, $P < 0.001$) and shorter mean procedure time with reduced radiation exposure (3.2 ± 1.8 *vs* 6.0 ± 3.0 min, $P = 0.004$) than conventional D-POC.

Percutaneous transhepatic choledochoscopy (PTCS) is reserved for cases when peroral choledochoscopy is unsuitable, such as in complicated anatomy. This percutaneous approach permits shorter endoscopes with better maneuverability to

reach areas that are less accessible perorally[12]. A variety of endoscopes can be used, such as those used for other indications (*e.g.*, nephroscope, ureteroscope, bronchoscope) and those specifically designed for choledochoscopy (*e.g.*, CHF-CB30 L/S; Olympus Medical Systems, Tokyo, Japan)[13]. However, it remains second-line to peroral choledochoscopy due to the invasive and time-consuming need to create and mature a large-diameter percutaneous tract several days before choledochoscopy and complications such as bile leak and bleeding metastatic spread to the peritoneum or sinus tract[14].

CHOLEDOCHOSCOPE ADJUNCTS AND ACCESSORIES

This section will discuss the advancements in accessories that facilitate choledochoscope advancement, optimize view, improve image quality and efficacy in specific interventions.

Choledochoscope advancement

Devices are developed to guide the advancement of D-POC into bile ducts. An example is how in a study by Yang *et al*[15] involving 79 patients, the use of D-POC enabled high rates of scope insertion (72.0%). Another device to increase choledochoscope stability is a hybrid balloon catheter anchoring device using a 0.021-inch guidewire attached to a balloon catheter's distal end. In a single-center retrospective study by Li *et al*[16] involving 55 patients, this device-guided D-POC achieved significantly higher technical success rates compared to the conventional wire-guided method (92.7% *vs* 47.1%, $P < 0.05$). Another anchoring technique is advancing D-POC over a reusable guide probe of the Kautz device (MTW, Wesel, Germany), designed initially for non-transendoscopic placement of biliary stents. This method increases probe stiffness to prevent choledochoscope looping and had an 85% technical success rate[17].

Optimize view by medications

Ways to optimize view across various modes of choledochoscopy have been described. In D-POC, intraductal simethicone reduces the surface tension of gas bubbles and improves mucosal visualization by anti-foaming action. This is particularly useful in the presence of pneumobilia following a sphincterotomy for choledochoscope access [18].

Optimize view by structural modification

In percutaneous choledochoscopy, Demmert *et al*[19] devised a novel choledochoscopy expander using microwires to create a flexible whisk-like shape to distend the gallbladder lumen before visualization by choledochoscopy mechanically. A case report showed its use improved gallbladder visualization with reduced infolding of gallbladder lumen and minimal mucosal injury. Other accessories include a transparent cap to the choledochoscope in gallbladder-preserving surgery. According to Jian *et al*[20] in a retrospective study of 50 patients, the addition of a transparent cap for patients undergoing laparoscopic choledochoscopy significantly reduced gallbladder exploration time (12.04 ± 6.01 min *vs* 27.96 ± 12.24 min). Reasons put forth include eliminating blind spots as the transparent cap promoted distance between the lens and mucosa, allowing complete visualization. Other benefits include protection of the scope. Sometimes direct visualization by choledochoscopy is not possible due to complete ductal obstruction. In such instances, microcatheters made of the 3-French outer sheath of a basket catheter (MicroCatch; MTW Endoskopie, Düsseldorf, Germany) and 3-French endoscopic nasobiliary drainage tube (Daimon-PTCD set, Hanaco Medical, Saitama, Japan) can aid injection of contrast medium to facilitate guidewire manipulation[21].

Image-enhanced function systems

To improve direct visualization capabilities, choledochoscopy can harness various preexisting image-enhanced function systems, such as NBI, probe-based confocal laser endomicroscopy, i-Scan, chromocholangioscopy, and autofluorescence imaging. NBI utilizes filtered light to improve visualization of ductal mucosa and vessels compared to conventional white-light imaging. It is compatible with videocholangioscopes and D-POC[5]. NBI can improve visual differentiation of benign from malignant strictures [22]. However, improved visualization *via* NBI may not translate into improved rates of malignancy detection. Dysplasia detection rate did not increase even when 48%

more suspicious lesions were biopsied when using NBI in patients with primary sclerosing cholangitis (PSC)[23]. i-Scan, a computed virtual chromoendoscopy system, may also improve visualization of ductal mucosa and vasculature compared to conventional white-light imaging. While diagnostic accuracy using i-Scan was not significantly better, surface structure, surface microvascular architecture, and margins were significantly better visualized[24]. Probe-based confocal laser endomicroscopy captures microscopic images of living tissue for real-time histological tissue assessment under direct visualization. Compatibility with DSOC was demonstrated in a study by Tanisaka *et al*[25] involving 30 patients with indeterminate biliary strictures (IBS). While probe-based confocal laser endomicroscopy during DSOC had lower sensitivity compared to DSOC alone (94.1% *vs* 100%), higher specificity (92.3% *vs* 76.9%) and accuracy [93.3% (95%CI: 78.7%-98.8%) *vs* 90% (95%CI: 74.4%-96.5%)] was reported. Chromocholangioscopy can show differences between inflamed, ischaemic, and dysplastic biliary lesions based on different gross surface staining patterns using methylene blue injections during choledochoscopy[26]. However, data on the efficacy of chromocholangioscopy in IBS are limited. Lastly, autofluorescence imaging, which compares colors of lesions when blue excitation light and green and red field cameras, are utilized to distinguish between normal and neoplastic mucosa. Itoi *et al*[27] evaluated autofluorescence imaging as an adjunctive imaging technique during PTCS. Amongst 65 biliary tract lesions, PTCS with autofluorescence imaging had higher specificity (87.5% *vs* 52.5%) and accuracy (87.7% *vs* 70.8%) than PTCS alone, though sensitivity decreased (88% *vs* 100%).

Nevertheless, most image-enhanced function systems have not yet been validated for clinical use in choledochoscopy. Further studies need to evaluate different choledochoscopes with these current imaging systems and if better biliary visualization indeed translates into improved diagnostic and therapeutic accuracy.

Tissue diagnosis

For the acquisition of larger tissue samples, the SpyBite Max biopsy forceps acquire twice the amount of tissue than the SpyBite biopsy forceps[9]. This is particularly promising given how the diagnostic accuracy of biopsy samples of IBS obtained *via* the legacy SpyBite biopsy forceps has been hampered by inadequate tissue samples[28].

Stone retrieval and fragmentation

For stone retrieval, a variety of equipment is available for the retrieval of stones. Commonly, stone retrieval baskets are the foremost choice, as there are many variable shapes and sizes that can suit most situations. These include Dormia baskets, SpyGlass Retrieval Basket (SpyBasket), and SpyGlass Retrieval Snare (SpySnare)[29]. However, the baskets require expansion and retraction to securely surround the stones, which may be difficult due to limited space[13]. In those cases, open-ended graspers such as alligator forceps are an option.

When the stone is too large to fit into a retrieval basket or difficult to remove after securing the forceps, fragmentation of the stones is possible[30]. Lithotripsy, either electrohydraulic lithotripsy (EHL), extracorporeal shockwave lithotripsy (ESWL), or laser lithotripsy (LL), can aid fragmentation. Traditionally, mechanical lithotripsy is less commonly used due to its limitations in breaking large pigment stones and challenging maneuverability[31]. In addition, EHL has a higher risk of duct damage due to relative imprecision. Furthermore, the probe's caliber may be too large to enter more miniature endoscopes if needed[13]. LL probes are small caliber and allow accurate and precise fragmentation. Commonly, pulse and non-pulsed lasers are available depending on the penetration depth required. However, LL is notably more expensive than EHL.

Migrated hardware retrieval

Choledochoscopic visualization of the hepatobiliary ducts is also valuable for retrieving migrated hardware such as stents using SpyBasket and SpySnare[32], broken baskets[33,34], and migrated coils[35]. However, such instances have yet to be reported on a larger scale and currently lack power. With the garnering of more reported cases, it would then be possible to truly delineate the potential of choledochoscopy in therapeutic interventions and other instances.

Stricture ablation

Choledochoscopy can perform therapeutic interventions like ablation of cholangiocarcinoma (CCA) *via* photodynamic therapy or radiofrequency ablation. Choledochoscopy can confirm successful radiofrequency ablation administration and

immediate post-procedure complications. Novel choledochoscopy-guided balloon-radiofrequency ablation techniques demonstrated in animal models also show potential for clinical use[36]. Case reports by Chandrasekar *et al*[37] and Brunaldi *et al*[38] describe the use of digital cholangioscopy to evaluate photodynamic therapy.

Scope handling techniques

The use of different techniques when handling the choledochoscope has also been proposed in lithotripsy. For example, Zhang *et al*[39] proposed the J maneuver when performing choledochoscopy in a freehand technique, described as retroflection of the upper endoscope while in the second part of the duodenum, simultaneous rotation and retraction of the endoscope towards the papilla. Zhang *et al*[39] claimed that this maneuver would eliminate the need for surgical bile duct exploration.

CLINICAL APPLICATIONS

Choledochoscopy can be used for diagnostic and therapeutic indications (Table 3), with main indications in diagnosing IBS and lithotripsy. This section will discuss the efficacy of choledochoscopy compared to conventional methods and recent advances in various diagnostic and therapeutic indications.

IBS

IBS is defined as biliary strictures with aetiologies that cannot be established after standard diagnostic investigations such as laboratory tests, imaging (such as computed tomography or magnetic resonance cholangiopancreatography), or procedures (such as endoscopic retrograde cholangiopancreatography (ERCP)-guided tissue biopsy)[40]. This section will discuss the role of choledochoscopy in diagnosing IBS, specifically when along with the diagnostic algorithm it should be done, optimal choledochoscope choice, the two main ways choledochoscopy can be used, and factors affecting its diagnostic accuracy.

The imperative in biliary strictures is to exclude malignancies, where ERCP with brush cytology is the initial modality of choice. However, despite its high specificity with brush cytology (> 95%), sensitivity remains low. In a review of 16 studies involving 1556 patients, Burnett *et al*[41] reported that ERCP brush cytology had a sensitivity of 41.6% ± 3.2% (99%CI) and a negative predictive value (NPV) of 58.0% ± 3.2% (99%CI). Thus, adjunctive diagnostic modalities such as choledochoscopy are required. Per the 2018 Asia-Pacific ERCP Club consensus guidelines, choledochoscopy-guided biopsies are recommended to improve diagnostic accuracy in situations where conventional ERCP-based brush cytology and forceps biopsy are inconclusive despite clinical suspicion[42].

Choledochoscopy is a valuable diagnostic modality as it can affect the aggressiveness of management. In a multicentre study by Prat *et al*[43] involving 61 IBS patients, choledochoscopy prevented unnecessary surgical resection in 33 out of 57 patients with initially-suspected carcinoma, and significantly improved management adequacy rates ($P < 0.001$) than before choledochoscopy despite a moderate overall diagnostic sensitivity (52%-63.6%). Hence given differences in morbidity in surgical compared to conservative management, there is value in choledochoscopy for patients with unclear diagnoses.

Stricture location determines if choledochoscopy should be done at all and, if done, when along with the diagnostic algorithm after ERCP-based sampling[42]. Firstly, strictures can be intrinsic (*e.g.*, cholangiocarcinoma, periampullary bile duct cancer) or extrinsic to bile duct (*e.g.*, pancreatic cancer, gallbladder cancer, metastatic disease)[44]. Peroral choledochoscopy is more helpful in evaluating intrinsic than extrinsic strictures. The sensitivity for diagnosing malignancy in intrinsic strictures was higher than extrinsic strictures in both FSOC visual impression and FSOC-guided biopsy[44]. Secondly, strictures are either proximal or distal strictures. Martinez *et al*[45] recommend that peroral choledochoscopy can be used immediately after the first inconclusive ERCP-based sampling for proximal biliary strictures. On the contrary, for distal biliary strictures, peroral choledochoscopy is recommended only if both ERCP-based sampling and endoscopic ultrasound-guided fine-needle aspiration are negative.

Choledochoscopy should be used in both ways for the diagnosis of IBS – visual impression and choledochoscopy-guided biopsies. Direct visualization by choledochoscopy permits the identification of mucosal features suspicious for malignancy and targeted biopsies. In a recent meta-analysis by Wen *et al*[40] involving

Table 3 Diagnostic and therapeutic indications for choledochoscopy

Diagnostic indications	Therapeutic indications
Visual impression and visually-guided biopsies of: (1) Indeterminate biliary strictures (IBS); (2) Dominant strictures in primary sclerosing cholangitis (PSC); and (3) IgG4-related sclerosing cholangitis (IgG4-SC)	Stone fragmentation: (1) Electrohydraulic lithotripsy (EHL); and (2) Laser lithotripsy (LL)
Precise preoperative mapping of the extent of tumor involvement in CCA	Ablative therapies in cholangiocarcinoma (CCA): (1) Radiofrequency ablation; (2) Photodynamic therapy; (3) Nd:YAG laser ablation; and (4) Argon plasma coagulation
Choledochal cysts	Cystic duct stent placement
Intraductal papillary neoplasms of the bile duct	Guidewire passage through strictures, surgically altered anatomy
Cholangioadenoma	Resection of ductal masses
Biliary papillomatosis	Retrieval of migrated ductal stents
Eosinophilic cholangitis	Gallbladder stenting and drainage
Biliary varices	
Right Hepatic Artery Syndrome	
Congenital pancreaticobiliary maljunction	
Post-liver transplant ductal ischemia	
Tissue sampling and visual evaluation for infections: (1) Cytomegalovirus; and (2) HIV	
Evaluation of intrahepatic biliary tracts during minimally invasive surgery	

HIV: Human immunodeficiency virus.

356 patients across 11 studies, the visual impression was more sensitive than choledochoscopy-guided biopsy across DSOC, FSOC, and D-POC (95% *vs* 74%, 84.5% *vs* 60.1%, 83%-92% *vs* 43%-89.5%). However, specificity was higher in choledochoscopy-guided biopsy than visual impression across DSOC, FSOC and D-POC (98% *vs* 92%, 98% *vs* 82.6%, 97% *vs* 84%-92%)[40]. Furthermore, the lack of a standardized visual classification system necessitates that biopsy results confirm visual findings. Thus, it is insufficient to use either visual impression or biopsy findings alone.

Various choledochoscopes have been studied in the diagnosis of IBS. However, an ideal choledochoscope has not yet been established for IBS diagnosis in clinical practice. POC are more frequently used in IBS. However, PTCS can also be used when POC instability prevents adequate bile duct visualization[46]. When comparing POC without the use of image-enhanced function systems, DSOC has an excellent diagnostic yield in both visual impression and choledochoscopy-guided biopsies[40,47,48]. In a study by Mizrahi *et al*[47] involving 324 patients, DSOC had a significantly higher diagnostic yield of visual impression for malignancy than FSOC (78% *vs* 37%, $P = 0.004$). However, studies comparing the efficacy of different choledochoscopes when image-enhanced function systems are used are lacking. For instance, NBI, which is compatible only with videocholangioscopes and D-POC, may significantly improve the efficacy of these two choledochoscopes compared to others.

Several factors confound the diagnostic accuracy of choledochoscopy in IBS. This section will explore these confounders in visual impression and choledochoscopy-guided biopsies and advances made to mitigate them.

For both visual impression and biopsies, the diagnostic accuracy of choledochoscopy may decrease with increasing hyperbilirubinemia levels[49] and in specific patient populations such as patients with PSC[50]. This highlights the importance of patient optimization pre-procedure and identification of other confounding patient factors. Other factors include inadequate experience amongst endoscopists (< 25 cases performed)[49].

A major drawback of visual impression using choledochoscopy is the lack of a standardized visual classification system[40], especially because diagnostic accuracy is experience and operator-dependent. Several studies have proposed novel classification systems. However, there is a lack of comparative studies to standardize one classification system. Tumor vessels, which are dilated and tortuous vessels, are markers of malignancy that provide moderate diagnostic accuracy when coupled with biopsy

[51]. Other malignant characteristics include nodular mucosa, neovascularization, friability, and papillary characteristics[52]. More recently, in 2018, a new classification system by Robles-Medranda *et al*[53] classified lesions based on morphological and vascular characteristics (*i.e.*, polypoid, ulcerated, honeycomb, *etc.*). This had a high sensitivity (96.3%) and specificity (92.3%) amongst 106 patients. However, there was a discrepancy in an inter-observer agreement between experts and non-experts ($\kappa > 80\%$ and 64.7%-81.9% respectively). Better inter- and intra-observer agreement between both expert and non-expert operators ($\kappa > 80\%$; $P < 0.001$) was seen in the use of neovasculature morphology, defined as irregular or 'spider' vascularity as proposed by Robles-Medranda *et al*[53] in 2020. This had a sensitivity of 94%, a specificity of 63%, a positive predictive value (PPV) of 75%, NPV of 90% amongst the 95 patients studied[54]. In 2020, Sethi *et al*[55] proposed the Monaco Classification, which combined eight observable criteria (presence of stricture, lesion, mucosal features, papillary projections, ulcerations, abnormal vasculature, scarring, pronounced pit pattern). A fair diagnostic accuracy (70%) and inter-observer agreement ($\kappa = 0.31$, SE = 0.02) was reported, with ulceration (OR = 10.3, $P = 0.01$) and papillary projections (OR = 7.2, $P = 0.02$) being most associated with malignancy.

Two main issues limit the use of choledochoscopy-guided biopsies in IBS – challenges in analyzing small biopsy samples obtained during choledochoscopy and lack of consensus on the optimum number of sample sizes required.

Firstly, choledochoscopy-guided tissue samples are often too small for accurate offsite histopathological examination and thus decrease sensitivity. Adequate tissue acquisition is primarily limited by the technical ability of choledochoscopy forceps jaw [28]. Other factors include age less than 65 years old (OR = 0.170, 95%CI: 0.044–0.649, $P = 0.010$) and previous biliary stenting before POC (OR = 0.199, 95%CI: 0.053–0.756, $P = 0.017$)[56]. Thus, one approach improves the choledochoscopy forceps jaw's technical ability to acquire large tissue samples per bite, such as in the SpyBite Max biopsy forceps[57]. Alternatively, specimen processing techniques that can process smaller tissue samples have been proposed as adjuncts to conventional histopathological examination. One method is rapid onsite evaluation of touch imprint cytology (ROSE-TIC) during choledochoscopy-guided biopsies. Touch imprint cytology is useful as an adjunct in cases where clinical suspicion for malignancy is high, but offsite sampling is negative or indeterminate[58]. In a study by Varadarajulu *et al*[59] involving 31 FSOC- and DSOC-guided biopsy procedures, ROSE-TIC provided an additional opportunity for onsite specimen processing and demonstrated sensitivity (100%), specificity (88.9%), PPV (86.7%), NPV (100%), and diagnostic accuracy (93.5%). However, the use of ROSE-TIC in the context of choledochoscopy has yet to be validated in large-size trials. Another method already used for processing smaller specimens is cell block cytology. A study by Baars *et al*[60] involving 240 SpyBite specimens from the upper gastrointestinal tract in 10 patients found that cellblock cytology results in fewer crush artifacts and requires a significantly smaller specimen to achieve equivalent diagnostic accuracy (1.49 mm *vs* 2.02 mm, $P < 0.001$) compared to standard histopathology. However, as this comparative analysis was performed using gastrointestinal samples, a pilot study involving six IBS patients was performed. All 20 SpyBite samples were successfully processed by cell block cytology[60].

Secondly, the optimum number of biopsies to be taken during choledochoscopy remains unestablished. This may depend on specimen processing techniques (onsite *vs* offsite) and stricture location (intrinsic *vs* extrinsic). In a randomized control trial using DSOC by Bang *et al*[58] involving 62 patients, three biopsies were recommended for offsite specimen processing and one biopsy for onsite specimen processing to achieve equivalent diagnostic accuracy (90%). Additional biopsies for offsite specimen processing did not improve diagnostic accuracy. However, other retrospective studies by Onoyama *et al*[28] and Varadarajulu *et al*[59] recommend minimally four biopsies when using offsite and onsite[60] processing techniques, respectively. Furthermore, Varadarajulu *et al*[59] observed that extrinsic strictures required more biopsies than intrinsic strictures for onsite processing techniques.

PSC

Diagnosis of current studies on choledochoscopy in PSC has focused on identifying CCA in PSC strictures and subtyping PSC through visual impression and choledochoscopy-guided biopsies. While the accuracy of visual impression and choledochoscopy-guided biopsies have been well-studied in IBS, the same conclusions cannot simply be applied to PSC. Underlying ductal inflammation and scarring may mimic CCA visually and complicate the passage of choledochoscopes through bile ducts to evaluate strictures[61]. However, large-scale studies specifically on PSC patients are limited.

The ability to accurately exclude CCA in PSC is critical as PSC patients have an increased CCA risk[61]. Various investigations such as imaging and serological tumor markers such as carbohydrate antigen 19-9 are possible but lack sufficient sensitivity and specificity when used alone[62]. Tissue diagnosis is thus crucial in this workup. A meta-analysis by Njei *et al*[61] across 21 studies found that single-operator choledochoscopy-guided biopsies are the most accurate in diagnosing CCA in PSC patients as compared to brush cytology, fluorescence in situ hybridization, and probe-based confocal laser endomicroscopy, with a sensitivity of 65% (95%CI: 35%-87%) and specificity of 97% (95%CI: 87%-99%). A study by Majeed *et al*[63] involving 225 PSC patients found that the use of DSOC in addition to second brush cytology improved sensitivity than second brush cytology alone (100% *vs* 82%) in detecting CCA in PSC. However, another retrospective study by Kaura *et al*[64] involving 36 PSC patients found that the addition of SpyGlass choledochoscopy-guided biopsy to fluorescence in situ hybridization did not significantly increase sensitivity compared to brush cytology alone. Hence, there remains uncertainty on whether choledochoscopy with other diagnostic investigations can improve CCA detection in PSC.

Furthermore, choledochoscopy findings on visual inspection can subtype PSC into early or late stages of the disease. Sandha *et al*[65] proposed the novel Edmonton Classification, which categorizes PSC's visual impression features on FSOC and DSOC into three phenotypes – "inflammatory type", "fibrostenotic type", and "nodular or mass-forming type". Fujisawa *et al*[66] further correlated these findings with time course – "'inflammatory type" correlated to active phase and early-stage PSC, "fibrostenotic type" with chronic phase and late-stage PSC, and "nodular or mass-forming type" in either phase. Stratification into the disease stages is vital in informing each patient's disease and guiding targeted treatment[65].

In the management of PSC, the role of POC has also been considered, specifically when managing patients with dominant strictures. A dominant stricture is defined as a stricture of ≤ 1.5 mm in the common bile duct or ≤ 1 mm in the hepatic duct within 2 cm of the intrahepatic confluence. In a prospective study by Awadallah *et al*[67] involving 55 patients with PSC, POC was able to help with the diagnosis of PSC-associated biliary strictures and discovered the presence of choledocholithiasis, which was missed in 30.0% of similar patients undergoing cholangiography, improving therapeutic yield. In bacterial cholangitis superimposed, temporary drainage and flushing measures to keep the biliary ducts patent can be performed. This includes the use of naso-biliary tubes for drainage, biliary lavage for decanting and flushing[68], as well as percutaneous transhepatic cholangioplasty for relief of jaundice[69].

IgG4-sclerosing cholangitis

Choledochoscopy is primarily used to visually differentiate IgG4-related sclerosing cholangitis (IgG4-SC) from PSC and CCA. Accurate differentiation is essential as the prognosis and management of the three conditions differ[66]. A study by Itoi *et al*[70] using peroral videocholangioscopes on 33 patients found a significant discrepancy in the incidence of visual findings such as the presence of dilated and tortuous vessels, scarring, and pseudodiverticula between patients with IgG4-SC and PSC (P = 0.015, P = 0.001, P = 0.0007 respectively). There is a significant discrepancy in the incidence of partially enlarged vessels and dilated vessels between IgG4-SC patients and distal CCA (P = 0.004) and hilar CCA (P = 0.015)[70]. Another study by Ishii *et al*[71] using peroral videocholangioscopes on 17 IgG4-SC and 53 CCA patients reported that the use of vessel morphology seen on choledochoscopy could distinguish IgG4-SC patients from CCA patients with sensitivity (96%), specificity (89%), interobserver agreement (κ = 0.719), and the intraobserver agreement (κ = 0.768 and 0.754).

CCA

Choledochoscopy may be helpful in the precise preoperative mapping of CCA before surgical resection. This section will discuss the utility of choledochoscopy regarding its rate of adequate tissue acquisition, diagnostic accuracy in mapping the lateral extent of tumor involvement, ability to impact management, therapeutic interventions, and caveats to its use in CCA.

Choledochoscopy allows good access laterally along the bile duct to reach lateral margins of CCA. For example, in a study by Ogawa *et al*[72] involving 118 target sites along the extrahepatic bile duct, DSOC-guided mapping biopsies could reach 100% of target sites compared to fluoroscopy-guided mapping biopsy (78%).

Diagnostic accuracy of the preoperative mapping of CCA using choledochoscopy requires further validation, owing to the small sample sizes studied[73]. In a study by Pereira *et al*[74] involving 43 patients, the accuracy of DSOC-guided visual impression and DSOC-guided biopsy was 95% and 81% respectively in the diagnosis of CCA. To

further increase diagnostic accuracy in identifying the superficial spread of CCA based on visual impression, Fukasawa *et al*[75] proposed the novel Form-Vessel Classification (F-V scores), stratifying the form of biliary surface and vessel structure seen on peroral choledochoscopy into four and three grades, respectively. Amongst the 30 biopsy samples from 11 patients, higher F-V scores corresponded with a higher histological malignancy rate and frequency of mutant alleles[75].

Furthermore, choledochoscopy has been shown to alter management. Tyberg *et al*[76] reported that DSOC-guided mapping biopsy altered the surgical plan in 32 out 105 patients, where six patients required less extensive surgery, 12 had more extensive disease precluding surgery, and 14 were found to have the benign disease.

Caveats to the use of choledochoscopy in the preoperative mapping of CCA include suboptimal rates of successful biopsies attributable to inadequate sample size[72] and limited ability to visualize proximal tumor margin and submucosal tumor extension in all patients[77].

The use of choledochoscopy to perform therapeutic interventions in CCA has also been explored. As mentioned in the section on adjuncts to choledochoscopes above, the use of radiofrequency ablation, photodynamic therapy, and modalities like Nd-YAG laser ablation or Argon plasma coagulation in treating hemobilia have been explored in recent years[78]. However, further studies should be reported to broaden the currently lacking literature as therapies like photodynamic therapy are currently rarely used due to their complex logistical requirements and unclear role in managing biliary pathologies such as malignant biliary strictures[12].

Extrahepatic stones

The primary use of the choledochoscopy resides as an option in managing large or complicated extrahepatic stones in the biliary tree after endoscopic measures have been considered or found unsuitable. Endoscopic treatment *via* ERCP with standard sphincterotomy or endoscopic papillary large balloon dilatation (EPLBD) is currently recognized as the first-line treatment for extrahepatic bile duct stones, using a combination of basket or balloon catheterization for the exploration and then extraction[79].

Choledochoscopy can be considered for the removal of difficult extrahepatic bile stones. POC-guided clearance is was highly effective in clearing difficult bile stones defined as large stones ≥ 15 mm in diameter and with a prior attempt at stone clearance or impacted multiple stones[80]. Any stones in the hepatic duct or above a stricture were also considered difficult. Choledochoscopy has also been touted to have surpassed the previous second-line therapy of mechanical lithotripsy. In a study involving 32 patients with huge common bile duct stones, defined as stones not cleared by endoscopic sphincterotomy and EPLBD or not amenable to EPLBD, Angsuwatcharakon *et al*[81] claimed a higher success rate in choledochoscopy-guided laser lithotripsy over mechanical lithotripsy in the first session (63.0% *vs* 100%, $P < 0.01$) and lower radiation exposure (20989 *vs* 40745 mGycm^2).

Additionally, the use of EHL and LL assisted by POC also has excellent duct clearance rates. Both EHL and LL had higher ductal clearance rates when compared to ESWL in dealing with retained biliary stones[82]. However, complications and length of hospital say were similar between the two. In a meta-analysis of 49 studies, Korrapati *et al*[83] noted the accuracy of POC to be 89.0% (95%CI: 84%-93%) for the visualization of the pathology and a clearance rate of 88.0% (95%CI: 85%-91%).

The safety and reduced radiation exposure make choledochoscopy an excellent alternative to conventional management of extrahepatic biliary stones. In a study by Franzini *et al*[4] involving 100 patients, the use of choledochoscopy-guided EHL was non-inferior to ERCP with EPLBD in the removal of complex biliary stones (defined as > 15 mm, > 10 stones, the disproportion of ≥ 2 mm between stone and distal common bile duct or biliary stricture with a stone upstream)[84]. However, some still consider POC to be relatively complicated and time-consuming despite its safety and benefits compared to the conventional and more straightforward mechanical lithotripsy technique[85]. In a study by Buxbaum *et al*[86] consisting of 60 patients comparing POC-assisted lithotripsy and conventional therapy (defined as mechanical lithotripsy), the duration for lithotripsy procedure was significantly longer (120.7 *vs* 81.2 min, $P = 0.0008$). In contrast, Angsuwatcharakon *et al*[81] claimed that there was no significantly different procedure time (66 *vs* 83 min, $P = 0.23$) between POC-assisted lithotripsy and mechanical lithotripsy in stone management after the failure of EPLBD. While more trials with higher power should be performed to establish the significance of this disparity in procedural time, the efficacy and non-inferior complications rate of POC-assisted lithotripsy against manual lithotripsy in the management of large bile duct stones has been established. Therefore, it can be used as a standard of care after failing

endoscopic treatment with ERCP and sphincterotomy.

The efficacy of different types of POC in stone removal is also a consideration. In a retrospective study involving 32 patients who failed conventional ERCP for stone removal, Murabayashi *et al*[87] noted that both DSOC and videocholangioscope (CHF-B260) achieved a 100% complete stone removal with similar adverse event rates. However, DSOC was noted to have significantly shorter procedural time (67 ± 30 minutes *vs* 107 ± 64 min), and a lesser number of endoscopic sessions were needed (1.35 ± 0.49 *vs* 2.00 ± 0.85)[87].

Alternative therapeutic options like ESWL, where direct contact with the stone is unnecessary, are valuable when patients cannot undergo endoscopic therapy[88]. However, the risk of recurrence was notably higher when compared to POC. A prospective study of 58 patients by Aljebreen *et al*[89] compared ESWL and SpyGlass-guided EHL. Bile duct stone clearance rate was 100% in the SpyGlass-guided EHL group and 64.4% in the ESWL group. Historically, the role of chemical dissolution (such as methyl) of stones had been entertained by perfusing the common bile duct with solvents. However, the success rate remains low (66%-74%), with high complication rates (67%), including haemorrhage, duodenal ulceration, acute pancreatitis, and anaphylaxis[90].

Intrahepatic stones

The use of cholangioscopy for hepatolithiasis is limited due to relatively smaller hepatic ducts and strictures within the intrahepatic lumens[12]. Consequently, the literature is scarce, with few large patient studies. In a case series involving 190 patients, Cheng *et al*[91] reported a high intrahepatic stone clearance rate *via* POC (88.4%). However, a higher recurrence rate is reported with such an approach. In a retrospective study by Huang *et al*[92] of 245 patients undergoing PTCS to treat hepatolithiasis, recurrence rates was 63.2% overall, depending on the type of hepatolithiasis. Cholangioscopy *via* a percutaneous transenteric approach *via* access loop is another alternative for hepatolithiasis extraction. Access loops are preemptively created during hepaticojejunostomy for ease of future biliary interventions. This is particularly relevant for patients with intrahepatic strictures, predisposed to recurrent hepatolithiasis and cholangitis requiring repeated biliary intervention[93]. In cases with altered surgical anatomy, the use of cholangioscopy is valuable, allowing access to pathology sites without a choledochotomy, hence sparing the patient from a T-tube insertion. This helps lower complication rates and operative duration, and the length of hospital stay[94].

Other indications

In terms of diagnostic indications, choledochoscopy has also been used in diseases with a higher probability of malignant transformation, such as in the detection of dysplasia[95] and intraoperative determination of resection planes[96] in choledochal cysts, or diagnosis of malignant lesions such as intraductal papillary neoplasms of the bile duct[97]. In addition, recent reports demonstrate a role in the diagnosis of benign biliary pathologies such as cholangioadenoma[98], biliary papillomatosis[99], eosinophilic cholangitis[100], choledochal varices[101], right hepatic artery syndrome[102], congenital pancreaticobiliary maljunction[103], post-transplant ductal ischemia[104], infections such as cytomegalovirus and human immunodeficiency virus-associated cholangiopathy[105,106] and intraoperative evaluation for intrahepatic biliary duct injury during surgery[107].

For therapeutic interventions, choledochoscopy is useful in visualization and subsequent guidewire placement in the context of surgically altered anatomy. One example is PTCS in severe biliary-enteric strictures that have failed conventional fluoroscopic techniques[108]. Other examples include DSOC-guided direct visualization of late fibrotic strictures of anastomotic regions after deceased donor transplantation. This enabled guidewire placement, followed by subsequent dilation and stent placement[109,110]. Other surgically altered anatomy to which choledochoscopy is used successfully includes strictures in hepaticojejunostomy, afferent loop syndrome[111], and other complex biliary strictures that previously failed conventional guidewire placement[112]. Treatment of haemobilia has also been reported[78].

Choledochoscopy-assisted endoscopic transpapillary gallbladder stenting (ETGS) and subsequent drainage in acute cholecystitis is a potential use that has been recently explored. ETGS is an alternative for acute cholecystitis patients with significant comorbidity who are at prohibitive risk for cholecystectomy or even percutaneous cholecystostomy[113]. However, ETGS is commonly limited by poor cystic duct cannulation rates. In a retrospective study by Cao *et al*[114] of 226 patients with acute cholecystitis requiring ETGS, the use of single-operator choledochoscope guidance

increased the overall technical success of cannulation rates to 75%-86.4%.

COMPLICATIONS

Complications arising from choledochoscopy can be divided into procedure-related complications (including preparatory and intra-procedure complications) as well as technical complications of choledochoscopy. We will discuss a possible preventive measure that can be taken.

Procedure-related

For percutaneous choledochoscopy, complications occur during preparatory procedures such as percutaneous transhepatic biliary drainage and tract dilation than during choledochoscopy itself[115]. Regarding mild complications, a study by Wang *et al*[116] on 826 patients reported bleeding (1.9%), T-tube dislodgement (0.8%), infection (0.7%), basket incarceration (0.6%), and bile leaks (0.4%). Additionally, post-operative choledochoscopy could result in damage to T-tube systems, preventing extraction of retained stones, and causing bleeding and intestinal fistulas[117]. Severe complications include severe haemobilia, haemoperitoneum, sinus tract rupture, and ductal injury [115].

Peroral choledochoscopy is generally regarded as a low-risk procedure. Complications such as cholangitis, pancreatitis, haemobilia, bile leak, air embolization, bile duct perforation have been reported[44]. A meta-analysis by Korrapati *et al*[83] involving 2193 patients across 49 studies who underwent peroral choledochoscopy reported an overall adverse event rate of 7% (95%CI: 6%–9%), where complications primarily included cholangitis, followed by pancreatitis and perforation. However, Lenze *et al*[118], reported a 16.4% adverse event rate (pancreatitis, cholangitis, or significant bleeding) amongst 67 patients who underwent DSOC. While all complications in this study were successfully treated conservatively, it reinforces that choledochoscopy should only be used in patients failing conventional procedures.

Technical-related

Rates of adverse events arising from choledochoscopy have been compared against conventional procedures used in biliary disorders. A large retrospective study by Sethi *et al*[119] compared the adverse event rates occurring in 3475 ERCP procedures and 402 ERCP with additional choledochoscopy. It was found that the additional choledochoscopy contributed to a significantly higher rate of cholangitis than when the only ERCP was done (1.0% *vs* 0.2%; OR = 4.98; 95%CI: 1.06-19.67), which is postulated to be secondary to intermittent intraductal irrigation during choledochoscopy[119]. A caveat when comparing adverse events rates across procedures is the selection bias in patients undergoing choledochoscopy. They are likely to have failed conventional methods like ERCP, possibly due to underlying complicated anatomy or lesions, which in itself may predispose to complications[83].

Prevention of complications

Risks of complications can be mitigated. A retrospective multicentre study by Ang *et al*[120] analyzing 250 DSOC procedures found that prophylactic pre-procedural antibiotics significantly decreased the rate of cholangitis in patients who received antibiotics (n = 102) than those who did not (n = 148) (1% *vs* 12.8% respectively, P < 0.001).

Special considerations

Choledochoscopy has demonstrated good safety profiles in diverse patient groups – the elderly, pregnant women, and children. In a multicentre study by Bernica *et al*[121] across 209 patients, there was no significant difference in adverse events rates even in patients above 75 years old when compared with younger patients (7.30% for patients aged below 65 years, 6.98% for patients aged 65–75 years, and 7.79% for patients aged above 75 years; P < 0.17). Choledochoscopy is a promising alternative procedure for choledocholithiasis in pregnant women who require minimal radiation exposure. Pregnant women with choledocholithiasis have significant radiation exposure when treated conventionally *via* ERCP. A case report demonstrated the ability to completely reduce radiation exposure during choledocholithiasis identification and removal using DSOC. This combination of DSOC with ERCP was not associated with adverse maternal and fetal outcomes[122]. Case series have also reported successful choledochoscopy with no significant complications in children for indications such as

intrahepatic lithotripsy[123], evaluation of biliary strictures, and management before and after liver transplant[124]. While choledochoscopy in children is beyond the scope of this review, it can be extrapolated to be a safe and effective modality used in pediatric biliary pathologies such as Caroli disease, biliary atresia, and monitoring post-Kasai procedure.

In summary, choledochoscopy is generally a low-risk procedure that can be used even in the elderly, pregnant women, and children when indicated. However, given that patients undergoing choledochoscopy have a higher risk of complications than conventional biliary procedures, choledochoscopy should only be used in patients failing conventional procedures.

LIMITATIONS

Overall limitations of choledochoscopy include operator-dependency, cost, and technical limitations in choledochoscopes and accessories.

Firstly, the accuracy of choledochoscopy is highly operator-dependent and may be affected by insufficient endoscopy experience (< 25 cases performed)[49]. Increased choledochoscopy volume could result in a less steep learning curve. This is supported by the concept that repetition allows for accurate anatomical recognition and more straightforward instrumentation guidance[125]. Simulated training models are proposed to improve inter-operator discrepancy. A randomized control trial by Li *et al*[126] involving 20 resident trainees found that the use of physical three-dimensional printed models for simulated choledochoscopy led to significantly higher accurate anatomical structure identification ($P < 0.05$) and reduction in time taken to complete simulated choledochoscopy. Other training models include a three-dimensional printed model of a biliary tree integrated with augmented reality by Tang *et al*[127]. This allows for spatially accurate real-time simulated choledochoscopy. A training model for the freehand double-bending D-POC technique is also reported[128]. The advent of artificial intelligence to aid in customized, individualized learning should also be considered in surgery[129]. Larger studies are needed to validate these training models, determine optimum training time to achieve competency in choledochoscopy and compare if training translates to reduced inter-operator discrepancy in clinical practice.

Another limitation lies in the cost-benefit analysis of choledochoscopy compared to conventional procedures. High capital costs for the initial purchase of processors, scopes, and repair costs are cited as factors against choledochoscopy. For recurring costs for performing a single procedure, Loras *et al*[130] found that additional choledochoscopy use during ERCP in 2018 can increase procedural costs alone by $3662.71 and $2637.02 for stone extraction and stricture diagnosis, respectively. ERCP with choledochoscopy was the most expensive among advanced endoscopic procedures studied, even though ERCP alone was not more expensive than most other procedures[130]. However, there is an argument for cost-efficacy in choledochoscopy. Choledochoscopy may reduce the need to perform costlier procedures. In a study by Sandha *et al*[131] across 51 patients with difficult-to-access choledocholithiasis, choledochoscopy-guided lithotripsy circumvented the need for laparoscopic and open surgical bile duct exploration. This decreased costs per procedure by $1619 and $3210 respectively[131]. However, it is essential to consider the potential reusability of the equipment. While it is thought that reusable devices are more cost-effective and environmentally less damaging[132], the use of disposable equipment in other laparoscopic surgeries is noted to be associated with more significant intraoperative problems caused by technical difficulties[133]. Thus, proper handling and technical maintenance of reusable equipment should be emphasized and taught to benefit financially, economically, and technically.

Other limitations include the technical aspects of fiberoptics and accessories. Suboptimal image quality, size of therapeutic channels of current systems, ease of use, and various accessories still limit choledochoscopy use[12]. However, given how new technology could overcome previous models' limitations and develop new accessories quickly, it is promising that current technical limitations can similarly be overcome.

FUTURE DIRECTIONS

Future studies can develop quality indicators to prove the adequacy of choledochoscopy, validate technological advances, and identify factors affecting

choledochoscopy efficacy and methods to overcome limitations in specific indications such as IBS diagnosis and preferred management of complex bile stone disease.

First, future studies can focus on ways to improve the accuracy of choledochoscopy. Other than hyperbilirubinemia and endoscopists' experience, patient and procedural factors should be identified[49]. This can guide ways to optimize patients pre-procedure and improve the quality of choledochoscopy. Specifically, studies are still needed to determine the optimal number of biopsies for IBS diagnosis while considering technical improvements in choledochoscopy forceps jaws (*e.g.*, SpyBite Max). Regarding visual impression, many studies have developed novel visual classification systems such as the "tumor vessel sign"[51], characterization of mucosal and vascular features[52-54], and the Monaco Classification[55]. However, these are done using specific choledochoscopes like DSOC. Given how different choledochoscopes have variable imaging quality, studies need to determine if such visual classification systems can be accurately applied even when using choledochoscopes with lower imaging quality. Subsequently, comparative studies are needed to determine a standardized classification system with the highest accuracy and least inter-observer variability.

Secondly, there is a lack of quality indicators to demonstrate the biliary system's complete visualization in real-time during each choledochoscopy. Good advancement of the choledochoscope for complete visualization is often presumed[134]. Zimmer *et al*[134] proposed the visualization of the "bilio-papillary Z line" as a quality indicator. As it represents the distal-most end of the common bile duct at the bilio-papillary junction, visualization of the "bilio-papillary Z line" is thought to confirm visualization of the entire common bile duct. However, this marker is limited due to occasional difficult access and prolapsing papillary mucosa at this junction[134]. Future studies should evaluate this marker's accuracy and develop other quality indicators easily adaptable in clinical use.

Thirdly, studies can further clarify the role of novel enhanced imaging systems and new video display techniques. Some studies involving NBI and i-Scan reported no increase in diagnostic accuracy rate despite improved duct visualization[23,24]. Future studies need to explore if improved biliary visualization correlates to improved diagnostic or therapeutic efficacy.

To further improve image quality, studies can explore the use of new display techniques during choledochoscopy, which may negate any loss of three-dimensionality and poor spatial orientation associated with choledochoscopy. These include three-dimensional (3D) and two-dimensional-4K ultra-high definition (2D-4K), which has four-fold more pixels than two-dimensional high definition (2D-HD)[135]. While 3D and 2D-4K display techniques have not been studied in choledochoscopy, advantages are reported in laparoscopic surgery. The 3D display enables better laparoscopic performance compared to conventional 2D-HD monitors[136]. However, it is less clear whether 3D or 2D-4K display is better. Some studies demonstrated significantly better laparoscopic performance in 3D display than 2D-4K display, lower operative time, error rates[136], and increased precision in tasks[137]. Other studies found no significant difference in either operative time or error rates[138]. Nevertheless, given that 3D and 2D-4K displays may optimize scope-guided procedures, studies can consider evaluating these new display techniques in choledochoscopy.

Lastly, the role of artificial intelligence in chole-dochoscopy can be explored. Artificial intelligence has shown good accuracy in automating the detection of polyps, neoplasia, and blind spots and documentation of the procedure's technical details when used for colonoscopy and oesophagogastroduodenoscopy[139]. Given how it has shown potential in improving efficiency, particularly in gastrointestinal endoscopy, future studies may consider applying machine learning models to automate certain aspects of choledochoscopy.

CONCLUSION

Choledochoscopy (for extrahepatic biliary procedures) and cholangioscopy (for intrahepatic biliary procedures) is a dynamic instrument, adapting to a myriad of different circumstances. While the two phrases are used interchangeably, a distinction has to be acknowledged. It serves a diagnostic purpose in the evaluation of biliary pathologies and aids in histology sampling. It also serves a therapeutic purpose in stone fragmentation and extraction and manages malignant lesions in the biliary tree. Collectively, the utility of this instrument has advanced tremendously in recent years,

potentially overtaking conventional methods of diagnosis and treatment in the near future. Choledochoscopy is complementary to other endoscopic, interventional radiology, and operative techniques for biliary intervention as well. With the increasing ability of artificial intelligence to automate the detection of pathologies and individualise training for endoscopists, a future pioneered by choledochoscopy and cholangioscopy is promising.

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MINIREVIEWS

Composite intestinal adenoma-microcarcinoid: An update and literature review

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Abstract

Composite intestinal adenoma-microcarcinoid (CIAM) is a rare intestinal lesion consisting of conventional adenoma and small, well differentiated carcinoid [microcarcinoid (MC)] at its base. The incidence of CIAM is 3.8% in surgically resected colorectal polyps. While its pathogenesis is unknown, studies support the role of Wnt/β-catenin pathway in the tumorigenesis of CIAM. CIAMs have been primarily reported in the colon wherein they present as polyps with well-defined margins, similar to conventional adenomatous polyps. MC is usually found in adenomatous polyps with high-risk features such as large size, villous architecture, or high grade dysplasia. Histologically, the MC component is often multifocal and spans 3.9 to 5.8 millimeters in size. MC is usually confined within the mucosa but occasional CIAM cases with MC extending to the submucosa have been reported. MC of CIAM demonstrates bland cytology and inconspicuous proliferative activity. The lesional cells are positive for synaptophysin and 60% to 100% of cases show nuclear β-catenin positivity. MC poses a diagnostic challenge with its morphologic and immunohistochemical resemblance to both benign and malignant lesions, including squamous morules/metaplasia, adenocarcinoma, squamous cell carcinoma, sporadic neuroendocrine tumor and goblet cell adenocarcinoma. CIAM is an indolent lesion with a favorable outcome. Complete removal by polypectomy is considered curative. Awareness and recognition of this rare entity will help arrive at correct diagnosis and improve patient care. Currently, CIAM is not recognized as a subtype of mixed neuroendocrine-non-neuroendocrine neoplasm by WHO.

Key Words: Composite; Adenoma; Microcarcinoid; Composite intestinal adenoma-microcarcinoid; Wnt/β-catenin; Mixed neuroendocrine-non-neuroendocrine neoplasm

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Core Tip: Composite intestinal adenoma-microcarcinoid (CIAM) is a rare intestinal lesion consisting of adenoma and well differentiated microcarcinoid components. While it is a form of mixed neoplasm with both neuroendocrine and non-neuroendocrine elements, CIAM is currently not recognized as a distinct subtype of mixed neoplasm by WHO. It is found incidentally during the pathologic examination of adenomatous polyps. Altered Wnt/β-catenin pathway appears to play a role in its pathogenesis. Other benign and malignant lesions need to be distinguished from CIAM given differing therapeutic implications. CIAM is an indolent disease with a favorable outcome.

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INTRODUCTION

Composite intestinal adenoma-microcarcinoid (CIAM) is a rare intestinal lesion consisting of conventional adenoma and associated microscopic well-differentiated neuroendocrine cell clusters [microcarcinoid (MC)] at its base. The adenoma component presents as a typical polyp, which is removed either endoscopically or surgically[1-3]. The MC component does not form grossly evident nodules or masses [1,3] and is typically located at the base of the polyp, usually within the mucosa. Occasional cases of CIAM with the MC component extending into the submucosa have been reported[1,4,5]. As MC occupies only a minute area and forms small nests or clusters microscopically, the overall architecture of the polyp is preserved[2,3].

CIAM was first described by Moyana *et al*[6] in 1988. In this report, the authors described two adenomas co-existing with carcinoids: One was in the center of a dome-shaped polyp, and the other was at the base of a sessile villous adenoma. The authors also noticed a transition zone between the two components. It is unclear how much of the lesion was composed of carcinoid component in their report. However, based on the illustrations provided in the report, the carcinoid components do not appear subtle [6]. Since its first description, CIAM have been sporadically documented as case reports or small case series[2,5,7,8].

Although CIAM is a rare entity, endocrine cell "differentiation" is not uncommon in colorectal adenomas, wherein the cells of neuroendocrine phenotype are considered to originate from the endoderm[9,10]. For example, argyrophil cells have been reported in 59% to 85% of adenomatous polyps[10,11]. In Iwashita's study, argyrophil cells and argentaffin cells were found in 76.4% and 60.4% of 212 colorectal adenomas, respectively. These cells were usually located in the lower third portion of the adenomatous glands[9]. In 8% to 10% of these cases, the density of the neuroendocrine cells may be higher than usual[9,10]. Therefore, it is not surprising that endocrine cell neoplasia may arise within adenomas and that it localizes preferentially at the base of the adenoma[2].

CIAM is distinct from mixed neuroendocrine-non-neuroendocrine neoplasm (MiNEN). MiNEN is an umbrella term referring to a neoplasm with both neuroendocrine and non-neuroendocrine components[4,12]. It is required that each component constitutes at minimum 30% of the neoplasm to qualify for MiNEN[12-14]. The terms "low grade" MiNEN and mixed adenoma well-differentiated neuroendocrine tumor (MANET) have been interchangeably used in the literature for a subset of CIAM meeting the required criterion of 30% for each component[4,12]. However, not all CIAMs described in the literature are necessarily low grade MiNEN. Moreover, recent WHO did not officially endorse a composite tumor consisting of an adenoma (a precursor of invasive adenocarcinoma) and well-differentiated neuroendocrine tumor as a subtype of MiNEN in the gastrointestinal tract and hepatopancreatobiliary organs [14].

Although this rare entity is not recognized by the current WHO classification, its recognition will allow for more efficient pathological diagnosis and more detailed clinicopathologic studies, thus leading to better patient care. CIAM may be under-recognized given its rarity and occasional morphologic subtlety. Moreover, it can resemble other benign and malignant lesions and can be mis-diagnosed. Its prognosis is vastly different from that of malignant composite tumors with expansile growth. We summarize the current state of knowledge on CIAM and provide an overview on its pathogenesis, microscopic features, differential diagnosis, as well as prognosis and treatment options. The differences in terminologies–CIAM, collision tumor and MiNEN–are also briefly discussed.

DEMOGRAPHICS

CIAM is identified in middle-aged to elderly patients, with a reported mean age of 60 years[1-4]. Slight male predilection has been reported[1,4,15], while another study found no gender predilection[3]. It is unknown whether there is a demographic divergence between CIAM and typical adenomatous polyps.

INCIDENCE

Recently we reported that the incidence of CIAM is 3.8% in surgically resected colorectal polyps. Our cohort consisted of consecutive, surgically resected 158 colorectal polyps from one tertiary care center over a span of 16 years[1]. Its incidence in endoscopically removed polyps is unknown.

To date, the largest series of colorectal CIAM has been reported by Kim *et al*[3] in South Korea, consisting of 24 cases. In their series, the polyps were excised endoscopically (91.7%) or surgically (8.3%) over a span of 7 years[3]. In the United States, the largest series of intestinal (to include 4 cases in the duodenum) CIAM was reported by Estrella *et al*[15] in a Cancer Center, consisting of 25 cases over a span of nearly 18 years[15]. However, the incidence of CIAM was not reported in these studies.

ASSOCIATED CONDITIONS

Colorectal MC is likely exceedingly rare and no minimum size criterion is currently available. MC has been observed in patients with chronic colitis, such as diversion colitis[16] and inflammatory bowel disease (IBD), especially in ulcerative colitis[17-21]. Likewise, Weyant *et al*[22] described a case of colonic MC and diffuse neuroendocrine cell hyperplasia following long-term cystoplasty[22]. These associations suggest that MC may represent an exaggerated proliferative response of gut mucosa to chronic inflammation.

On the other hand, it is largely unknown whether these patients with inflammatory conditions actually have a higher incidence of CIAM. Most reported CIAMs are sporadic, and it appears to be a much rarer condition than solitary MC[3]. Sigel and Goldblum[17] described a well differentiated neuroendocrine tumor adjacent to high grade glandular dysplasia in the setting of IBD. The authors postulated that the neuroendocrine tumor might have originated from multipotential dysplastic cells in the adjacent mucosa[17]. Alternatively, the MC component may reflect a metaplastic phenomenon related to chronic injury of the overlying adenomatous component[7].

Genetic predisposition may account for some cases of CIAM. Carcinoids at the base of duodenal adenomas have been reported in association with familial adenomatous polyposis (FAP)[15,23]. These observations support a role of the adenomatous polyposis coli (APC)/β-catenin pathway in the pathogenesis of CIAM (to be discussed below), although the risk of CIAM is probably explained by the risk of adenoma in this cohort.

PATHOGENESIS

The mechanism for the development of MC component in CIAM is not well understood. Earlier, authors postulated that CIAM represents a form of collision

tumor wherein the two components arise from two different clones and they coincidentally occur adjacent to one another[8]. However, evolving knowledge regarding the multipotent stem cells in the gut and their role in tumorigenesis has shed light on the possible histogenesis of tumors with different histologic components such as CIAM. Indeed, *in vitro* studies of the ileal epithelial cells (IEC-18) of rat have shown that these cells can transform into differing cell types with one type showing neuroendocrine-like morphology and expressing serotonin receptor gene, and the other with adenoma-like mRNA transcription and protein expression[24].

Likewise, a morphologic "transition zone" has been observed in several studies of CIAM[2,4,6,25]. In Pulitzer *et al*[2]'s study, the MC appeared to arise directly from the basal epithelium of adenomatous crypts, penetrating the basement membrane and infiltrating the lamina propria[2]. La Rosa *et al*[4] also observed numerous cells with both morphologic and immunohistochemical neuroendocrine differentiation along the base of the adenomatous glands. In addition, these cells demonstrated the same mutational and microsatellite instability profile as the adenomatous components, further supporting the hypothesis that these two components most likely represent divergent differentiation of a common precursor[4]. Interestingly, unlike conventional adenomas without MC, no *KRAS* mutation was identified in either component of CIAM. These findings suggested that the adenoma component of CIAM may develop through an alternative *KRAS*-independent pathway[4].

The finding of CIAM in FAP patients suggests the involvement of the Wnt/β-catenin pathway in the tumorigenesis of CIAM, as expected based on the canonical pathway by which normal mucosa becomes adenomatous. The MC components of CIAMs frequently display strong and diffuse nuclear β-catenin reactivity by immunohistochemistry[1,2,7,15]. In Estrella *et al*[15] study, the level of nuclear β-catenin expression was higher in the MC component of CIAM when compared with either the sporadic neuroendocrine tumors without associated adenoma, or neuroendocrine carcinomas associated with adenoma. Moreover, there was no difference in the level of β-catenin expression between CIAM patients with and without FAP[15].

This plausible hypothesis, though, requires confirmation by additional molecular studies as neither the presence nor absence of nuclear β-catenin expression by immunohistochemistry appears to be a true reflection of an activated Wnt signaling pathway[15,26-29]. For example, Su *et al*[29] found that carcinoid tumors can show nuclear β-catenin immunohistochemical staining without mutations in the *β-catenin* and *APC* genes[29].

In summary, CIAM appears to represent a true composite tumor with a common origin for the MC and adenoma components, and is not a collision tumor. Further molecular studies are needed to better understand the mechanisms driving its tumorigenesis.

PRESENTATION

CIAMs have been reported in the stomach, duodenum, ileum, colon, and rectum[4]. They are predominantly found in the colon, usually in the cecum and right colon[1-3]. They present as polyps with well-defined margins, similar to conventional adenomatous polyps. The reported mean size of the polyps is 2.4 cm[3]. As the MC component is microscopic, it is incidentally found during the pathologic examination of otherwise typical adenomatous polyps.

To the best of our knowledge, no definite clinical symptoms related to the MC component of CIAM have been established, however, one case report of rectal "collision tumor" consisting of adenoma and carcinoid tumor presented with carcinoid syndrome (elevated serum serotonin and chromogranin A, elevated urine 5-hydroxyindoleacetic acid level, and moderate tricuspid regurgitation). The patient's symptoms subsided following the endoscopic removal of the polyp with wide margins[30]. It is unclear whether this case represents a composite tumor (CIAM) or a collision tumor, as the author did not provide detailed histologic examination and classified the lesion as "collision" tumor[30].

MICROSCOPIC EXAMINATION AND IMMUNOHISTOCHEMISTRY

Adenomas with a MC component are usually high-risk adenomas (size ≥ 10 mm, villous components and/or high grade dysplasia)[1,3,5,7,15]. Therefore, the adenomatous components of CIAM tend to be large. For example, the mean size of

polyps was 24 mm in Kim *et al*[3]'s study. In our study, the average size of the polyps was 42 mm (probably because our cohort consisted of surgically removed polyps that were deemed endoscopically unresectable), all of the adenomas showed villous components and 50% had high grade dysplasia (Figure 1). However, no statistically significant differences in terms of polyp size, polyp location (right *vs* left) or the frequency of associated high grade dysplasia between the adenomas with and without MC were found[1]. In contrast, in Kim *et al*[3]'s study where most of CIAMs were detected in endoscopically resected polyps, 86% of CIAMs had conventional adenoma with low grade dysplasia[3]. In Salaria *et al*[7]'s study, high grade glandular dysplasia was seen in 4 (36%) of 11 CIAMs[7].

Microscopically, the MC component is found at the base of full-thickness adenomatous glands. The background lamina propria is myxoinflammatory with sometimes conspicuous eosinophils. The MC components are oftentimes connected to the overlying glandular components[3]. These small nests, irregular cords or clusters of neuroendocrine cells are sparsely distributed and do not form grossly evident nodules or masses (Figure 1). Occasional acinar structures may be seen[1-3,7].

In Salaria *et al*[7]'s study, the MC component extended over an average length of 3.9 mm. Also 64% (7/11) of the MCs were multifocal[7]. In Kim *et al*[3]'s and La Rosa *et al*[4]'s studies, the mean size of the MC components was 4.7 mm and 3.2 mm, respectively[3,4]. In our study, MCs were distributed over a mean area of 5.8 mm and were multifocal in 83% of the cases. In a majority of CIAMs, the MC components are confined within the mucosa, though extension into the submucosa can be seen[1,4,15] (Figure 2).

Cytologically, the neuroendocrine cells constituting MC are bland and monotonous (Figure 1). The cells show scant to abundant granular or eosinophilic cytoplasm and round central nuclei with salt and pepper-pattern chromatin. They are devoid of nuclear atypia, hyperchromasia, nuclear pleomorphism, conspicuous mitotic activity, and apoptosis. In other words, they are typical well-differentiated neuroendocrine cells.

By immunohistochemistry, the MC components are positive for synaptophysin (Figure 2B), supporting their neuroendocrine differentiation[1,3,15]. Chromograinin-A and CD56 show variable staining[4,5]. Variable immunolabeling with squamous markers such as p63 and CK5/6 can be seen[1,7]. They are well-differentiated with a low Ki-67 proliferation index (usually < 1%-2%) (Figure 2D), although sometimes the total number of neuroendocrine cells in MC may be insufficient (< 500 cells in total) for reliable Ki-67 index measurement[1,3,7]. The MC component shows nuclear β-catenin positivity (Figure 2C) in 60% to 100% of the cases, suggesting the role of Wnt/β-catenin pathway in the CIAM tumorigenesis[1,7,15].

MOLECULAR ANALYSIS

La Rosa *et al*[4] carried out mutational analysis for *KRAS, BRAF, PIK3CA* and microsatellite instability analysis on 6 CIAMs. No mutations were identified, and all cases were microsatellite stable in both adenoma and MC components[4].

DIFFERENTIAL DIAGNOSIS

MCs in CIAM may pose diagnostic challenge and may lead to misdiagnosis or overdiagnosis. MC can resemble squamous morules/metaplasia, invasive adenocarcinoma, squamous cell carcinoma (SCC), sporadic neuroendocrine tumor, and goblet cell adenocarcinoma (GCA). Awareness and recognition of this entity is crucial for accurate diagnosis and patient care.

Squamous morules/metaplasia

Squamous morules/metaplasia is an incidental histologic lesion that can be seen in colorectal adenomas[13,31]. The reported incidence of squamous morules in colonic adenoma is about 0.4%[11,32,33]. In our study, the incidence of squamous morules was 5.1% in surgically resected large colonic polyps[1].

Microscopically, squamous morules are characterized by a proliferation of immature squamoid or spindled cells forming nests and nodules without definitive keratinization or intercellular bridges[11,13,32]. Usually the nests protrude into the lumen of adenomatous glands (Figure 3), or may be identified at the base of the polyps especially in the cases of torsion and prolapse[1,13,32]. Immunohistochemically,

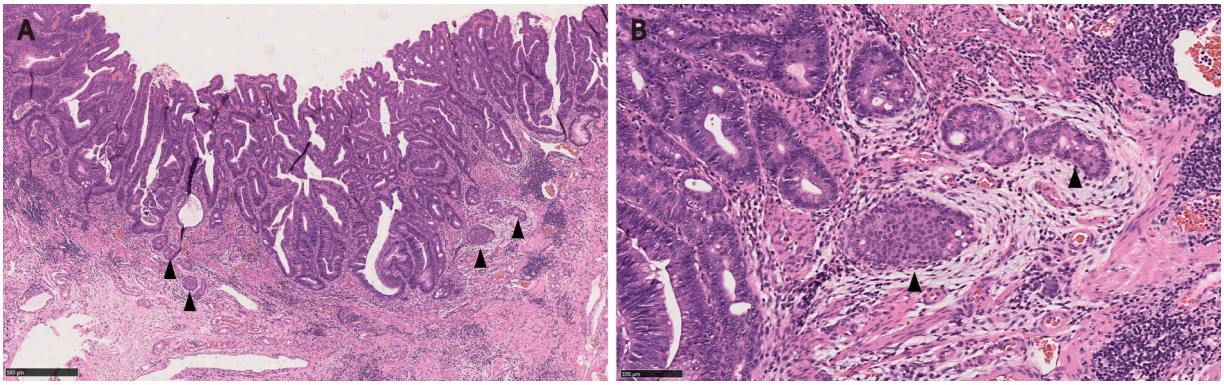

Figure 1 Composite intestinal adenoma-microcarcinoid consisting of tubulovillous adenoma with high grade dysplasia and microcarcinoid components (arrowheads) at its base. A: The overall polyp architecture is preserved (Hematoxylin and eosin, 50 ×); B: Microcarcinoid component shows bland cytology, within edematous stroma with conspicuous eosinophils, resembling desmoplasia (Hematoxylin and eosin, 200 ×).

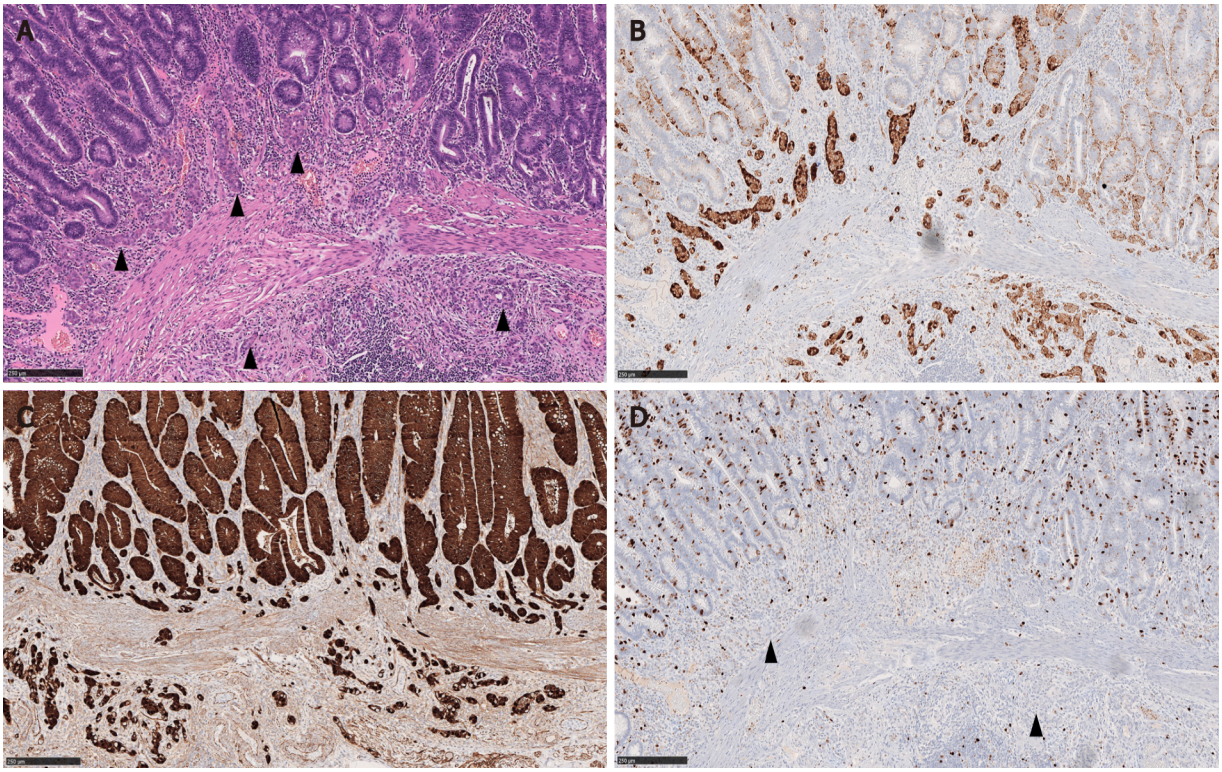

Figure 2 Composite intestinal adenoma-microcarcinoid with submucosal invasion of the microcarcinoid component. A: The microcarcinoid (MC) components (arrowheads) form small nests that are sparsely distributed at the polyp base. No nodules or masses are grossly evident (Hematoxylin and eosin, 100 ×); B-D: The MC components are positive for synaptophysin and beta-catenin (nuclear stain) with low proliferative rate (arrowheads) (B: Synaptophysin immunostain, 100 ×; C: Beta-catenin immunostain, 100 ×; D: Ki 67 immunostain, 100 ×).

squamous morules are positive for pan cytokeratin, CK5/6, cyclin D1 and β-catenin (nuclear staining)[1,13,34,35] (Figure 4) and show variable staining for p63[15,32]. Focal synaptophysin and chromogranin positivity can be seen[32].

There can be significant histomorphologic overlap between the MC component of CIAM and squamous morules**.** Both can present as solid nests around the bottom of adenomatous glands or myxoinflammatory stroma[1,32]. Indeed, in Kim *et al*[3]'s study, 6 CIAM cases were initially diagnosed as adenoma with squamous morules/metaplasia[3]. In Pulitzer *et al*[2]'s study, one CIAM was originally interpreted as adenoma with focal squamous metaplasia owing to the presence of abundant eosinophilic cytoplasm in MC[2]. In Salaria *et al*[7]'s study, MC was initially interpreted as squamous morules in 5 of 10 CIAMs[7].

In addition, there is immunophenotypic resemblance between the MC component of CIAM and squamous morules. Squamous morules may show focal positivity for

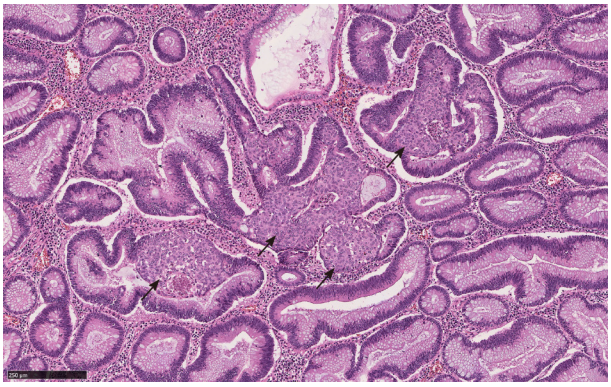

Figure 3 Squamous morules (arrows) with associated tubulovillous adenoma (Hematoxylin and eosin, 100 ×).

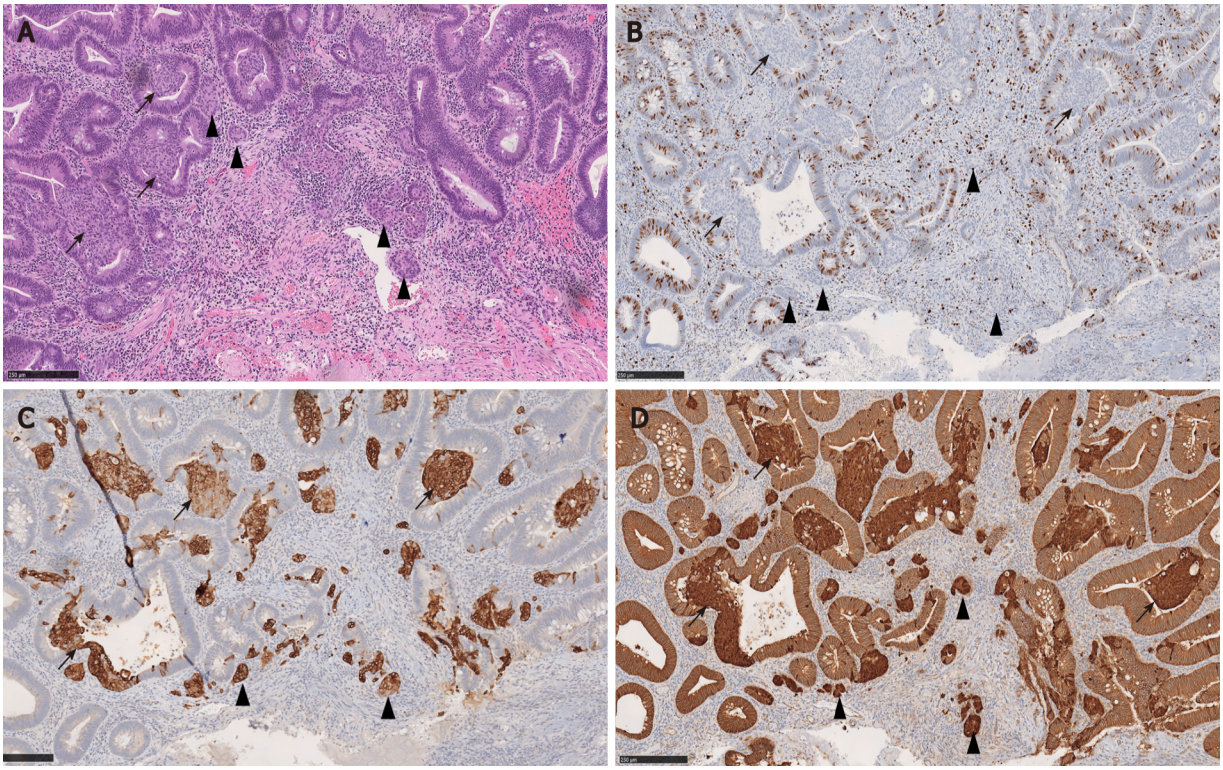

Figure 4 Composite intestinal adenoma-microcarcinoid with associated squamous morules (arrows). Both microcarcinoid (arrowheads) and squamous morules (arrows) show low proliferative rate and positivity for CK5/6 and beta-catenin (nuclear staining), suggestive of a shared pathogenesis. A: Hematoxylin and eosin, 100 ×; B: Ki 67 immunostain, 100 ×; C: CK5/6 immunostain, 100 ×; D: Beta-catenin immunostain, 100 ×.

neuroendocrine markers such as synaptophysin and chromogranin[32]. Conversely, the MC components of CIAM are variably immunoreactive with p63 and/or CK5/6 (Figure 4), suggesting squamous differentiation. In Salaria *et al*[7]'s study, 2 of 6 MC were focally positive for p63, and 5 of 6 MC were positive for CK5/6[7].

Given the morphologic and immunohistochemical overlap between squamous morules and the MC component of CIAM, we hypothesized that these two entities may be related. Interestingly, 33.3% (2 of 6) of CIAM showed concurrent squamous morule (Figure 4), compared to 4.0% (6 of 152) of adenomas without MC in our cohort, suggesting shared pathogenesis between the two ($P < 0.05$)[1]. Similarly, Estrella *et al* [15] reported that 4 (16%) of 25 CIAMs had squamous metaplasia in the adjacent adenomatous component[15].

Nevertheless, given that squamous morules/metaplasia is benign and the MC of CIAM is likely indolent, misdiagnosing MC as squamous morules/metaplasia may not have a significant clinical impact. In fact, it may be nearly impossible to distinguish these two in some cases.

SCC

As stated above, 16 to 33% of CIAMs can co-exist with squamous morules/metaplasia [1,15]. Moreover, MC components can demonstrate squamous differentiation with variable p63 and/or CK5/6 immunoreactivity (Figure 4) in a myxoinflammatory background mimicking desmoplasia. Therefore, SCC is considered a differential consideration for MC component of CIAM.

Primary colorectal SCC is a rare malignancy with an incidence of 0.1%-0.25%[36]. To date, less than 100 cases of colorectal SCC have been reported in the literature[37].

Usually, SCC of colon presents late in the disease course and shows an aggressive behavior with early metastasis and poor overall survival[38,39]. Thus, it is important not to overdiagnose the MC of CIAM as SCC. It will be helpful to be aware that MC can show immunohistochemical squamous differentiation to avoid this misinterpretation.

Invasive adenocarcinoma

MC components of CIAM may be misdiagnosed as invasive adenocarcinoma or tumor budding. Possible and reasonable explanations for this are: First, MC may show infiltrative or single-cell patterns at the polyp base, mimicking invasive disease[2] (Figure 5). Second, the background myxoinflammatory lamina propria associated with MC may resemble the edema and fibroblastic proliferation of desmoplasia that is usually associated with invasive disease[5,7]. Third, MC is commonly found at the base of full-thickness adenomatous mucosa frequently with high grade glandular dysplasia[1,5]. In fact, one of the CIAM cases reported by Lin *et al*[5] had been initially misinterpreted as adenocarcinoma[5].

Awareness of this entity and the recognition of bland cytoarchitecture and negligible mitotic activity of MC will be helpful to avoid misclassification[2]. Confirming neuroendocrine differentiation can be a useful diagnostic tool in challenging cases[7] (Figure 5).

Conventional sporadic neuroendocrine tumor

CIAMs and sporadic neuroendocrine tumors are treated differently. The MC components in CIAMs are usually situated at the polyp base in the mucosa, therefore complete polypectomy may suffice to remove the MC component with negative margin. On the other hand, the usual epicenter of sporadic neuroendocrine tumors is the submucosa. Therefore, additional surgery may be required to achieve complete resection with negative margin when the initial endoscopic biopsy shows sporadic neuroendocrine tumor[3].

For example, sporadic rectal neuroendocrine tumors are relatively common and oftentimes present as nodules or polyps on endoscopy[14,40-43]. They are usually small (over 50% of the cases < 1.0 cm in diameter), low grade, and located in the mucosa or submucosa[14] (Figure 6). Moreover, 79% to 84% of rectal neuroendocrine tumors are L-cell type that is known to be associated with rather indolent biologic behavior[44,45]. Therefore, rectal neuroendocrine tumors have an excellent overall prognosis especially after an endoscopic resection[41,42,45]. However, tumor stage and grade are still important prognosticators[41,43,46]. Large tumor size [(≥ 1.0 cm), high grade (WHO grade 2 to 3)], and the presence of muscular and lymphovascular invasion are often associated with metastatic disease, requiring aggressive treatment [43].

Nevertheless, MCs of CIAMs may also invade the submucosa[1,4,5,15]. Thus, to ensure complete removal of the MC component, further surgery may still be required following polypectomy[47]. Therefore, from a management standpoint, the tumor size and depth appear to be more relevant than their classifications.

Few studies have explored the biological differences between the MC components in CIAMs and sporadic intestinal carcinoid tumors without associated adenomatous components. Estrella *et al*[15] observed significantly higher β catenin expression score in CIAMs compared with sporadic neuroendocrine tumors, suggesting that CIAM may develop *via* a distinct pathway from the latter (*i.e.*, the adenoma pathway). In this study the overall 3- and 5-year survival of CIAM patients was significantly lower than those with sporadic NET[15]. This likely is due to the co-existing adenoma in CIAM as no CIAM patients died of neuroendocrine tumor in this study.

GCA

GCA, previously known as goblet cell carcinoid, adenocarcinoid, crypt cell carcinoma and microglandular carcinoma, is a subtype of appendiceal neoplasm. GCA is a mixed tumor with both glandular and neuroendocrine elements, and contains goblet cells

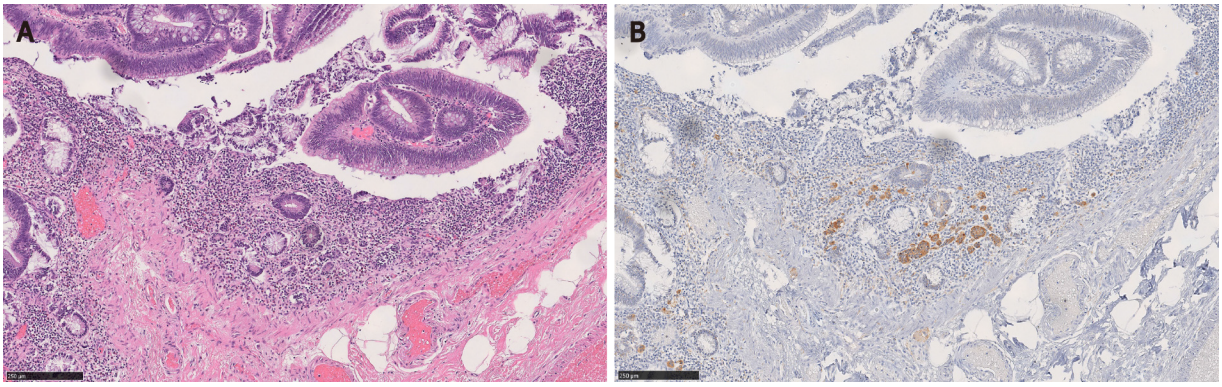

Figure 5 Microcarcinoid component of composite intestinal adenoma-microcarcinoid may mimic invasive adenocarcinoma. A: The microcarcinoid component is found at the base of full-thickness adenomatous glands (Hematoxylin and eosin, 100 ×); B: However, the constituting cells are positive for synaptophysin immunostain (Hematoxylin and eosin, 100 ×).

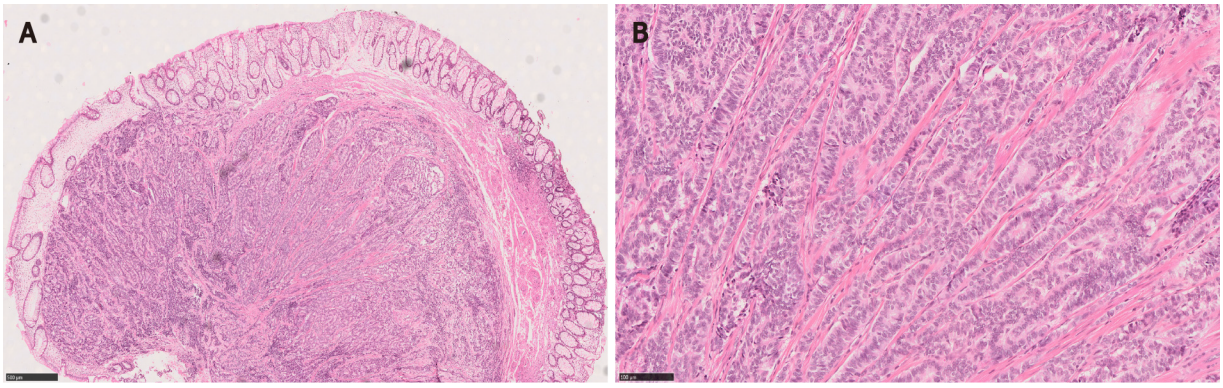

Figure 6 Rectal neuroendocrine tumor forming a nodule/polyp. A: The epicenter of the tumor is in the submucosa and the tumor extends to the deep margin (Hematoxylin and eosin, 40 ×); B: High magnification view shows typical trabecular growth pattern (Hematoxylin and eosin, 200 ×).

(Figure 7). The tumor nests stain positively for neuroendocrine markers and mucin [14]. Despite its mixed phenotype, GCA is officially recognized as a subtype of adenocarcinoma in the current WHO given its aggressive biologic behavior that is akin to adenocarcinoma[14,48]. GCA may co-exist with adjacent cecal adenoma[49]. Therefore, it is possible that cecal adenoma with underlying GCA may be interpreted as CIAM. Indeed, based on the provided illustrations, some authors raised a possibility that one of Lin *et al*[5]'s CIAM cases with lymph node metastasis may represent GCA with overlying adenoma[3,50]. GCA is an aggressive tumor and often presents with metastatic disease[51-53]. Further surgical management and chemotherapy are commonly required[53].

CIAM *VS* COLLISION TUMOR *VS* MINEN

Composite tumor, such as CIAM, is considered pathogenetically distinct from collision tumor. MiNEN is a broader category than CIAM.

Collision tumor

Lewin[54] first proposed to separate composite tumor and collision tumor when neoplastic endocrine cells and nonendocrine epithelial cells are admixed. In a composite tumor, glandular and neuroendocrine components are intermingled, and both components may share common origin. Whereas in a collision tumor, the two elements "collide" but are pathogenetically independent of each other. One of the two elements may represent a metastasis from another primary site[14,54].

Recently, Schizas *et al*[55] carried out a literature review on collision tumors of the digestive system. In this review, the authors defined collision tumors as those consisting of two or more independent neoplasms without intermingling (thus

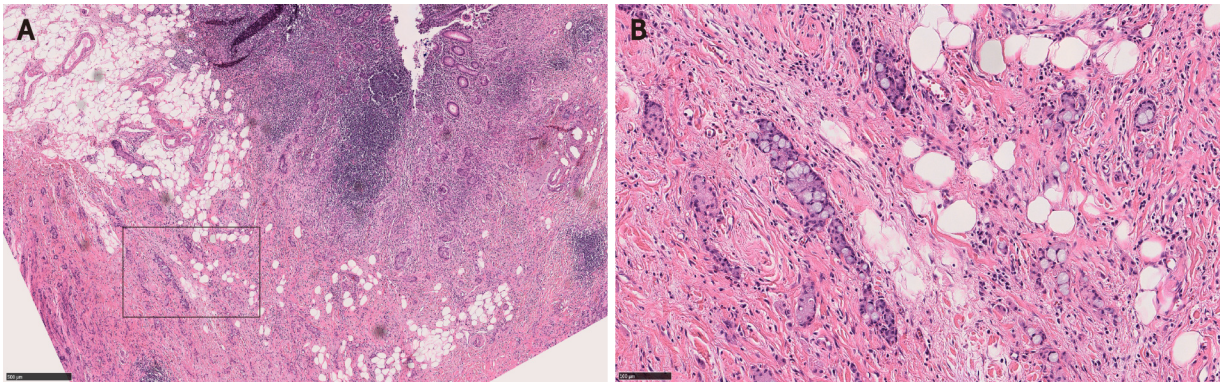

Figure 7 Appendiceal goblet cell adenocarcinoma. A: The tumor nests infiltrate and undermine the appendiceal mucosa (Hematoxylin and eosin, 50 ×); B: Bland cytology may mimic well-differentiated neuroendocrine tumor such as seen in the microcarcinoid component of composite intestinal adenoma-microcarcinoid (Hematoxylin and eosin, 200 ×).

without transition zone). In colon, adenocarcinoma was the main component of collision tumors, found in 78.6% of the cases, followed by carcinoid, seen in 35.7%[55]. Collision tumors are often high grade with early metastasis and a shorter survival[56-58].

Traditionally, collision tumors have been believed to represent "double primaries" though a few studies challenged this concept[56,58,59]. For example, Minaya-Bravo *et al*[58] reported a case of colonic collision tumor consisting of adenocarcinoma and large cell neuroendocrine carcinoma without identifiable transition zone. Three years later, the tumor metastasized to the retroperitoneum. Interestingly, both components metastasized, suggesting that both components of this collision tumor may have originated from the same clone[58]. Similarly, Pecorella *et al*[56] reported a cecal collision tumor consisting of adenocarcinoma and high grade well-differentiated neuroendocrine tumor (reported Ki67 proliferation index was 36%). There was focal positivity for CEA in the neuroendocrine tumor component without clear transition zone between the two components. The authors concluded that some mixed tumors cannot be precisely classified.

MiNEN

MiNEN is a recently introduced umbrella terminology referring to a neoplasm demonstrating a mixture of neuroendocrine and non-neuroendocrine components[4,12,14]. The terms "low grade" MiNEN and MANET have been proposed to describe mixed tumors with adenomatous components and well-differentiated neuroendocrine tumors (to include WHO grades 1 to 3)[4,12]. However, neither low grade MiNEN nor MANET has been officially recognized as a subtype of MiNEN in the current WHO [14]. In fact, in the gastrointestinal tract and hepatopancreatobiliary organs, WHO limits the use of the MiNEN term only to the mixed tumors with malignant non-neuroendocrine components[14] (Figure 8).

Even if low grade MiNEN (MANET) were to be recognized by WHO, there are differences between CIAM and low grade MiNEN. In MiNEN, each component should represent at least 30% of the total volume of the neoplasm. Therefore, some CIAMs with minor MC components would not meet the 30% cutoff criterion for low grade MiNEN. As many studies on CIAM did not specify the amount of MC components relative to the tumor volume, it is difficult to assess how many of the reported CIAM cases had MC components that occupied over 30% of the total tumor volume[2,5,7]. In our study, all 6 CIAM cases had minor MC components constituting much less than 30% of the tumor volume[1]. In addition, most of the MC components in CIAM are low grade with a negligible ki67 proliferation index, whereas low grade MiNEN can have grade 2 and 3 levels of proliferation in the neuroendocrine components[4]. Typical MiNEN with malignant non-neuroendocrine component mixed with neuroendocrine carcinoma is an aggressive neoplasm with a median overall survival of 13.2 mo. The ki67 proliferation index of the neuroendocrine component may drive the prognosis of these tumors[60].

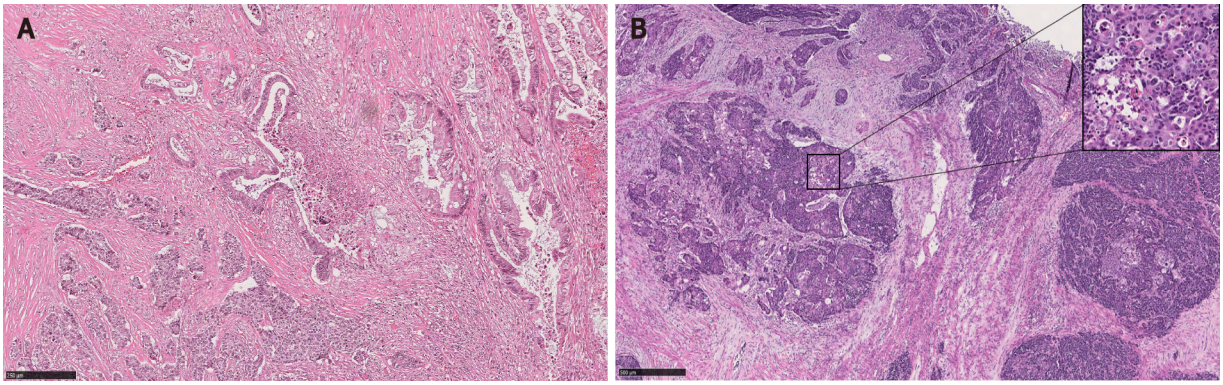

Figure 8 Mixed neuroendocrine-non-neuroendocrine neoplasm. A: Mixed colonic adenocarcinoma (upper right) and large cell neuroendocrine carcinoma (lower left); B: Mixed colonic squamous cell carcinoma and large cell neuroendocrine carcinoma (Inset: high magnification view shows squamous differentiation). Hematoxylin and eosin, 100 ×.

PROGNOSIS

CIAM is an indolent disease with a favorable outcome. One study found that after mean follow-up of 6 (range 0.5 to 27) years, none of the patients had recurrence of CIAM or metastasis after endoscopic or surgical treatment[4,15]. In our study, after mean follow-up of 53 mo, all patients were free of CIAM. In addition, all the lymph nodes retrieved during the surgical resection were devoid of adenocarcinoma or neuroendocrine tumor. Our two patients with MC components extending into the submucosa were followed for 14 and 15 mo, respectively. There was no evidence of recurrence or metastasis of neuroendocrine tumor at the end of the follow-up[1]. In La Rosa *et al*[4]'s study, one CIAM case had MC in the submucosa. The patient was followed for 12 years without evidence of disease[4]. No tumor-related death has been reported in the literature.

The size of MC component appears to have no bearing on the outcome[3]. This is likely due to the fact that the MC component tends to be small, and is usually confined in the mucosa. Likewise, the lesional cells constituting MC are bland with low proliferative activity.

TREATMENT

Given its indolent course, complete removal of both adenoma and MC by polypectomy is considered curative[4]. Additional radical surgeries should be reserved for cases with adverse histologic features such as deep submucosal extension or increased proliferative activity of the MC component[3].

CONCLUSION

CIAM is a rare intestinal lesion consisting of a conventional adenoma and a well differentiated MC component at its base. CIAM is considered to represent a true composite tumor wherein both adenoma and MC appear to share a common origin and develop *via* the Wnt/β-catenin pathway. MC in CIAM poses diagnostic challenges with its morphologic resemblance to other benign and malignant lesions. CIAM is an indolent lesion with a favorable outcome. Complete removal of both adenoma and MC by polypectomy is considered curative. Raising awareness of this rare entity will lead to correct diagnosis and appropriate management.

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MINIREVIEWS

Endoscopic ultrasound-guided biliary drainage-current status and future perspectives

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Abstract

Endoscopic retrograde cholangiopancreatography (ERCP) with stenting is the treatment modality of choice for patients with benign and malignant bile duct obstruction. ERCP could fail in cases of duodenal obstruction, duodenal diverticulum, ampullary neoplastic infiltration or surgically altered anatomy. In these cases percutaneous biliary drainage (PTBD) is traditionally used as a rescue procedure but is related to high morbidity and mortality and lower quality of life. Endoscopic ultrasound-guided biliary drainage (EUS-BD) is a relatively new interventional procedure that arose due to the development of curvilinear echoendoscope and the various endoscopic devices. A large amount of data is already collected that proves its efficacy, safety and ability to replace PTBD in cases of ERCP failure. It is also possible that EUS-BD could be chosen as a first-line treatment option in some clinical scenarios in the near future. Several EUS-BD techniques are developed EUS-guided transmural stenting, antegrade stenting and rendezvous technique and can be personalized depending on the individual anatomy. EUS-BD is normally performed in the same session from the same endoscopist in case of ERCP failure. The lack of training, absence of enough dedicated devices and lack of standardization still makes EUS-BD a difficult and not very popular procedure, which is related to life-threatening adverse events. Developing training models, dedicated devices and guidelines hopefully will make EUS-BD easier, safer and well accepted in the future. This paper focuses on the technical aspects of the different EUS-BD procedures, available literature data, advantages, negative aspects and the future perspectives of these modalities.

Key Words: Endoscopic ultrasound-guided biliary drainage; Malignant bile duct obstruction; Endoscopic ultrasound-guided hepaticogastrostomy; Endoscopic ultrasound-

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Core Tip: Endoscopic retrograde cholangiopancreatography is the current standard of care for bile duct obstruction but is not always possible. The traditional rescue modality is percutaneous transhepatic biliary drainage which has many disadvantages. Endosonography-guided biliary drainage is a new promising interventional technique, showing many advantages over percutaneous biliary drainage and is able to fully replace it when the expertise is available. Developing new devices, training models and guidelines is expected to make this procedure easier, safe and widely accepted in the near future.

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INTRODUCTION

Endoscopic retrograde cholangiopancreatography (ERCP) is a first-line treatment option for patients with biliary obstruction. The success rate is between 90% and 97% and the adverse event rate is less than 10%[1,2]. Some clinical situations: surgically altered anatomy, inaccessible papilla, unsuccessful cannulation require alternative approaches. Percutaneous transhepatic biliary drainage (PTC-D) is a widely accepted alternative after failed ERCP. Despite a high technical success rate (over 95%), the reported mortality remains high. The possible adverse events (AE) are bleeding, infection, drain dislodgement, tract seeding, bile leak, external fistula with a cumulative rate of 30%[2,3]. Contraindications for PTC-D performance are ascites, liver metastasis and obesity. PTB-D is related to the quality of life deterioration[4]. The palliative derivation surgery is related to high morbidity and mortality (35%-50% and 10%-15%)[5] and remains the last choice option for selected cases.

With the implementation of curvilinear-array echoendoscope, various interventional procedures have been made possible, including endoscopic ultrasound-guided biliary drainage (EUS-BD). The first successful EUS-BD was described by Giovannini *et al*[6] in 2001, which indicates the beginning of a new era for mini-invasive biliary drainage.

Currently, three EUS-based techniques are available- EUS-guided rendezvous technique (RV), EUS-guided antegrade stenting (AS), EUS-guided transmural stenting, EUS-guided hepaticogastrostomy (HGS), EUS-guided choledochoduodenostomy (CDS), and EUS-guided hepaticoduodenostomy. These procedures offer same-session internal drainage in cases of ERCP failure. EUS-BD includes complex and risky procedures which are performed in highly specialized centers by a very skilled endoscopist. The widely accepted indications include ERCP failure, duodenal obstruction due to tumor infiltration, duodenal diverticulum, bile duct tortuosity and previous duodenal stent placement or presence of altered anatomy.

EUS-BD TECHNIQUES

EUS-HGS

The technique was first introduced in 2003. In current times, this is a single-step procedure and consists of a transhepatic puncture of the biliary system and the creation of a stable fistula between the gastrointestinal lumen and the bile ducts.

This approach is preferred when the papilla cannot be reached endoscopically (duodenal obstruction or surgically altered anatomy). The most common indications for HGS are palliative therapy of hilar obstruction or distal obstruction when the papilla is not accessible. In rare cases, HGS is used for the creation of a temporary tract to the biliary tree in order to manage benign stricture or lithiasis. Sufficient intrahepatic bile duct dilation is needed for the HGS performance. The major contraindications are tumor infiltration of the gastric wall at the site of puncture, massive ascites, and coagulopathy[7].

This technique is not standardized. The tip of the echoendoscope is positioned in the stomach body at the lesser curvature. The dilated left hepatic duct can be seen (Segment III). Segment II is not a preferred approach to avoid transesophageal puncture and risk of mediastinitis. The puncture is performed using 19G needle and after bile aspiration contrast medium is injected (Figure 1). The procedure is performed under combined endosonographic and fluoroscopic guidance. A hydrophilic guidewire (0.025-inch or 0.035-inch) is inserted through the needle and manipulated in the bile ducts (Figure 2). Large caliber needles reduce the risk of shearing off the guidewire coating. A special needle was developed-19G EchoTip Access Needle (Cook Ireland Ltd., Limerick, Ireland) to avoid shearing off the guidewire coating and leaving a part in the liver. The needle is smooth with a sharp stylet, used to puncture the gastric wall and the liver. After removing the stylet, the guidewire manipulation is more easily compared with the standard FNA needle and reduces the risk of wire stripping. The most important step is the creation of a stable fistula and the proper technique is the prerequisite to avoid major complications like bile peritonitis, bleeding and perforation. The needle is exchanged over the guidewire with a 6 French cystotome and electrocautery-enhanced tract dilation is performed. Biliary dilation catheters or balloons could also be used (Figure 3). The procedure is finished by placing a stent (Figure 4). Especially dedicated HGS stents [Giobor stent TAEWOONG, proximal covered (NC) stent, HANARO] are commonly used for this technique. These are specially designed partially covered metallic stents with a proximal uncovered part to prevent blockage of segmental bile duct branches and a distal covered part to reduce the risk of bile leakage. Fully covered stents can be used in benign obstruction, but are related to increased risk of focal cholangitis, liver abscess, and migration. Plastic stents are not a reasonable option due to unacceptable high risk of bile peritonitis. An alternative to Giobor stents is the so-called "stent in stent technique" with transgastric placement of two metallic stents- a first one uncovered 8 or 10 cm to prevent bile duct blockage and a second 6 cm fully covered to secure the transmural tract[8,9].

EUS-AS

The procedure was first described by Nguyen-Tang *et al*[10] in 2010 and offers a possibility of physiological bile flow in cases of an inaccessible papilla or failed bile duct cannulation during ERCP. The authors report about 5 cases with malignant bile duct obstruction and endoscopically inaccessible biliary orifice. At the time of failed ERCP they performed transhepatic or transbulbar bile duct puncture and self-expandable metal stent (SEMS) deployment in an antegrade fashion without any AE and concluded that EUS-AS is an efficient technique for palliation of bile duct obstruction when standard ERCP has failed[10].

The initial steps of the intervention are the same as HGS-bile duct puncture, guidewire manipulation and tract dilatation. The procedure consists of transgastric left intrahepatic bile duct puncture with 19-gauge needle under EUS visualization. Color Doppler imaging is used to exclude intervening blood vessels and to prevent intra-and postprocedural bleeding. After bile aspiration contrast medium is injected to obtain cholangiogram. The guidewire is inserted through the needle and manipulated and advanced through the stricture and transpapillary in the duodenum or through a biliary anastomosis in the small intestine. After needle tract dilatation using ERCP catheter and mechanical dilators, a stent is placed at the stricture site and most commonly through the papilla of Vater in an antegrade fashion (Figure 5).

There is an increased risk of bile leakage at the puncture site and in cases of stent dysfunction reintervention could be extremely difficult or impossible. For that reason, some authors combine antegrade stenting with HGS. Placing a transenteric metallic stent simultaneously with the antegrade SEMS placement at the stricture site reduces the risk of leakage and bile peritonitis and makes reinterventions through the transhepatic tract possible[11].

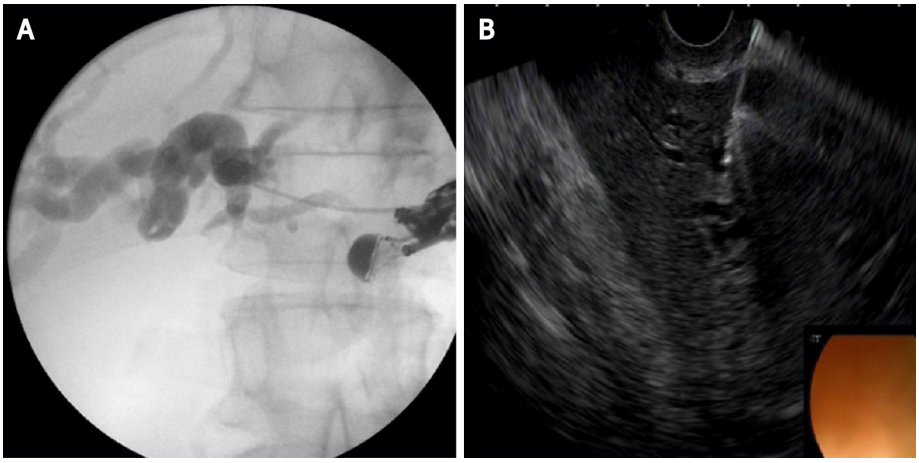

Figure 1 Left hepatic duct puncture and contrast injection. A: Cholangiogram; B: endoscopic ultrasound image.

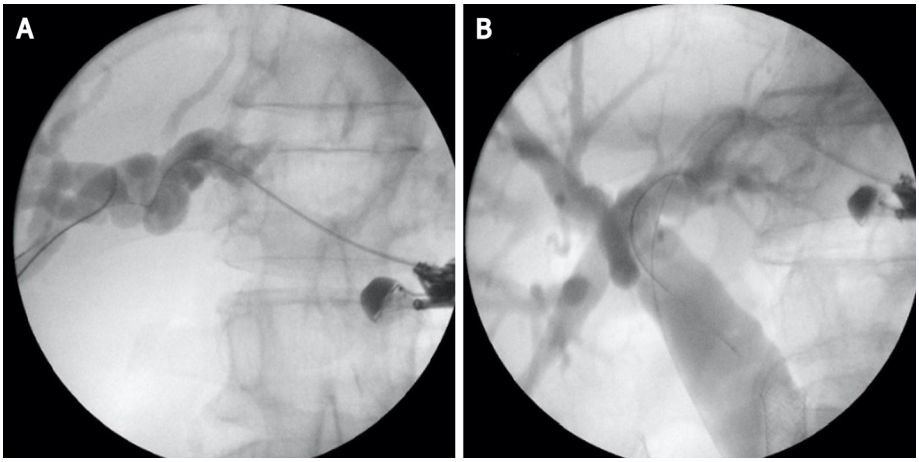

Figure 2 Hydrophilic guidewire insertion. A: In left hepatic duct; B: To the distal common bile duct.

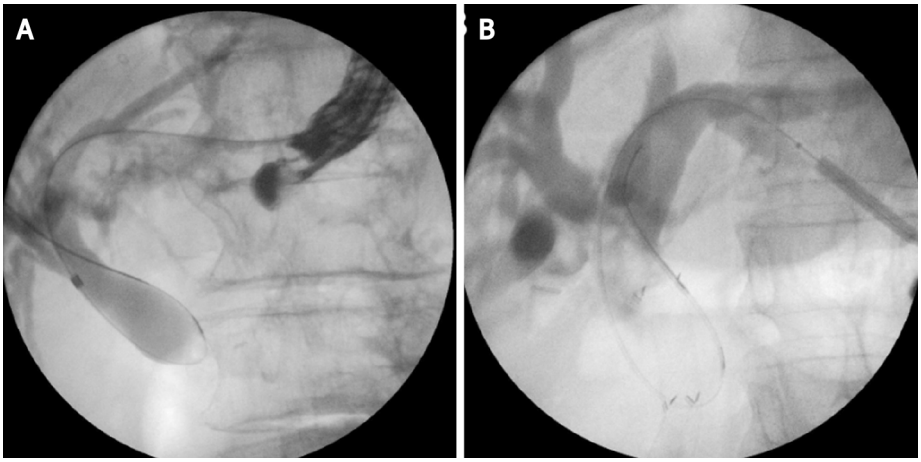

Figure 3 Tract dilatation. A: Biliary dilation catheter; B: 4 mm balloon dilatator.

EUS-CDS

The procedure is usually performed in cases of malignant distal bile duct obstruction when standard cannulation has failed or when endoscopic access to the papilla is not possible. The technique was first described by Giovannini *et al*[6] in 2001.

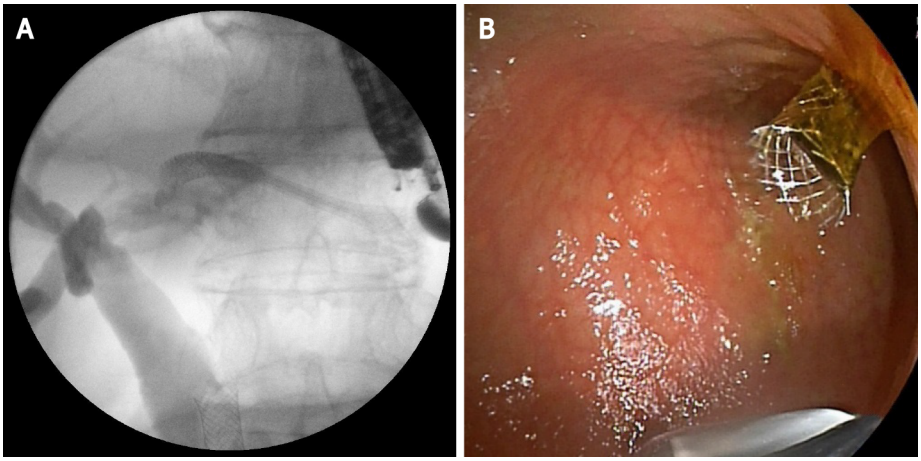

Figure 4 Stent placement-self-expandable metal stent. A: Cholangiogram; B: Endoscopic image.

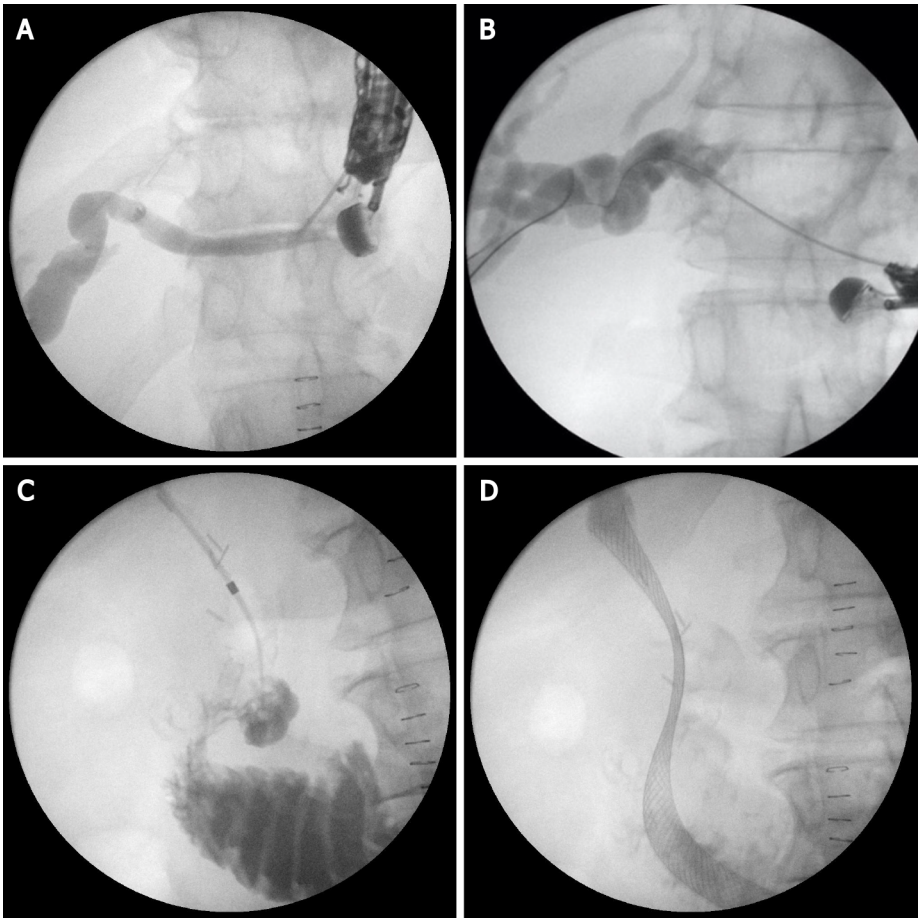

Figure 5 Endoscopic ultrasound-guided antegrade stenting. A: Left hepatic duct puncture with 19G needle; B: Guide-wire insertion; C: Tract dilatation and advancing the biliary catheter tip transpapillary in the duodenum; D: Self-expandable metal stent placement.

The tip of the echoendoscope is positioned in the duodenal bulb (or in the antrum) where the common bile duct (CBD) is very close to the duodenal or gastric wall. Before puncture, fluoroscopy is used to align the direction of the needle tip towards the liver hilum. The CBD is punctured with a 19-gauge needle. After the bile aspiration guidewire is inserted and manipulated in the direction of the intrahepatic bile ducts, the needle is exchanged over the wire with a 6 French cystotome, biliary catheter or a small (4 mm) dilation balloon to dilate the tract. Most commonly a fully covered SEMS is placed (Figure 6). Using plastic stent or a recently developed lumen-apposing metal stent (LAMS) is also possible[9,12].

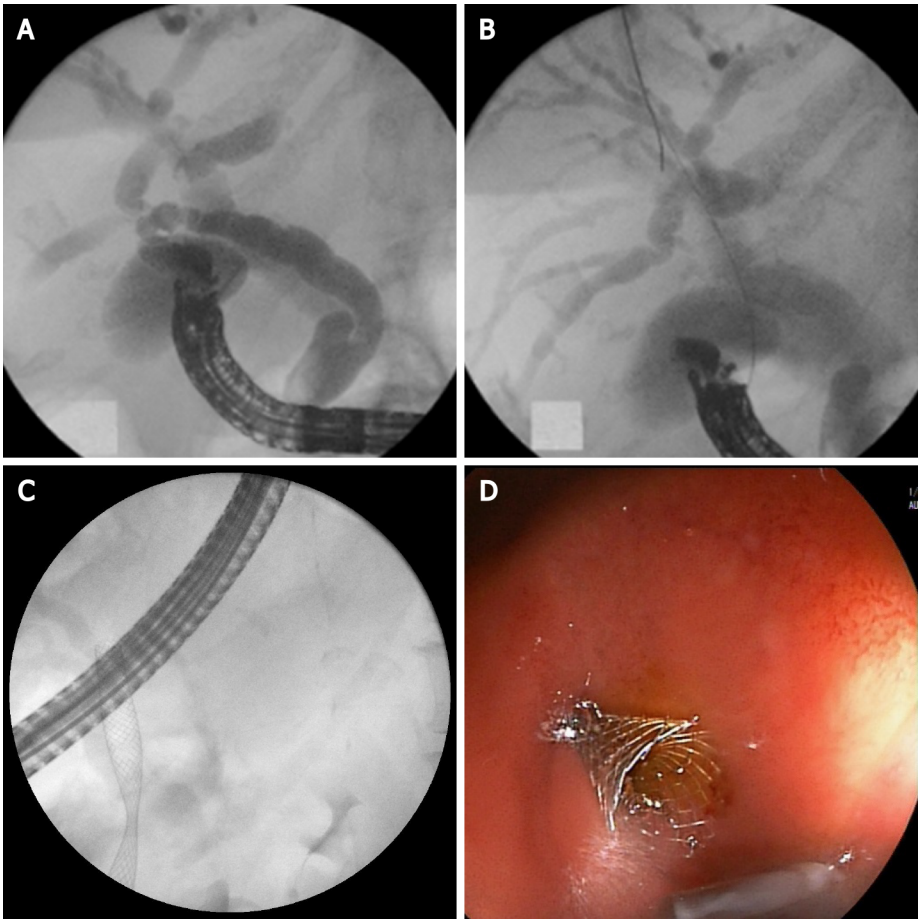

Figure 6 Endoscopic ultrasound-guided choledochoduodenostomy. A: Puncture of the common bile duct with 19G needle and contrast injection; B: Hydrophilic guidewire inserted through the needle into bile ducts; C: Fluoroscopic image of self-expandable metal stent (SEMS); D: Endoscopic image of SEMS.

EUS-RV

EUS-RV was first reported in 2004. The technique is considered when the papilla of Vater is endoscopically accessible but selective bile duct cannulation with ERCP has failed[13].

The procedure consists of intra- or extrahepatic bile duct puncture under EUS guidance with a 19-gauge needle. Contrast is injected through the needle and after obtaining a cholangiogram, a guidewire is inserted and manipulated to negotiate the stricture and to pass across the papilla in the duodenum in an antegrade manner. To maintain a stable position, several loops of the guidewire in the duodenum should be made. Then, the linear echoendoscope is exchanged by duodenoscope. Retrograde cannulation is performed alongside the guidewire or over the guidewire by grasping it with a rath tooth forceps or a snare and pulling it in the duodenoscope working channel. The procedure seems to be the safest of all EUS-guided bile duct approaches. The most common reasons for failure is the inability to manipulate the guidewire across the stricture and the papilla or to reach the bile duct orifice endoscopically (Figure 7). The need for the exchange of two endoscopes and the fact that the procedure is not feasible in cases of altered anatomy are limiting factors for this intervention[12,14].

EFFICACY AND SAFETY OF EUS-BD

A large amount of data that has been collected demonstrates the fast improvement in the technical and clinical success of EUS-BD[15-18]. A recently published systematic review, including 42 studies with 1192 patients, reports about a 94.7% technical success and 91.7% clinical success with a 23.3% adverse even rate. These data indicate that EUS-BD is an acceptable alternative in cases when ERCP has failed or is not possible. The morbidity is high but most of the reported AE are mild, self-limited and respond to conservative therapy. The most commonly reported AE are bleeding (4%),

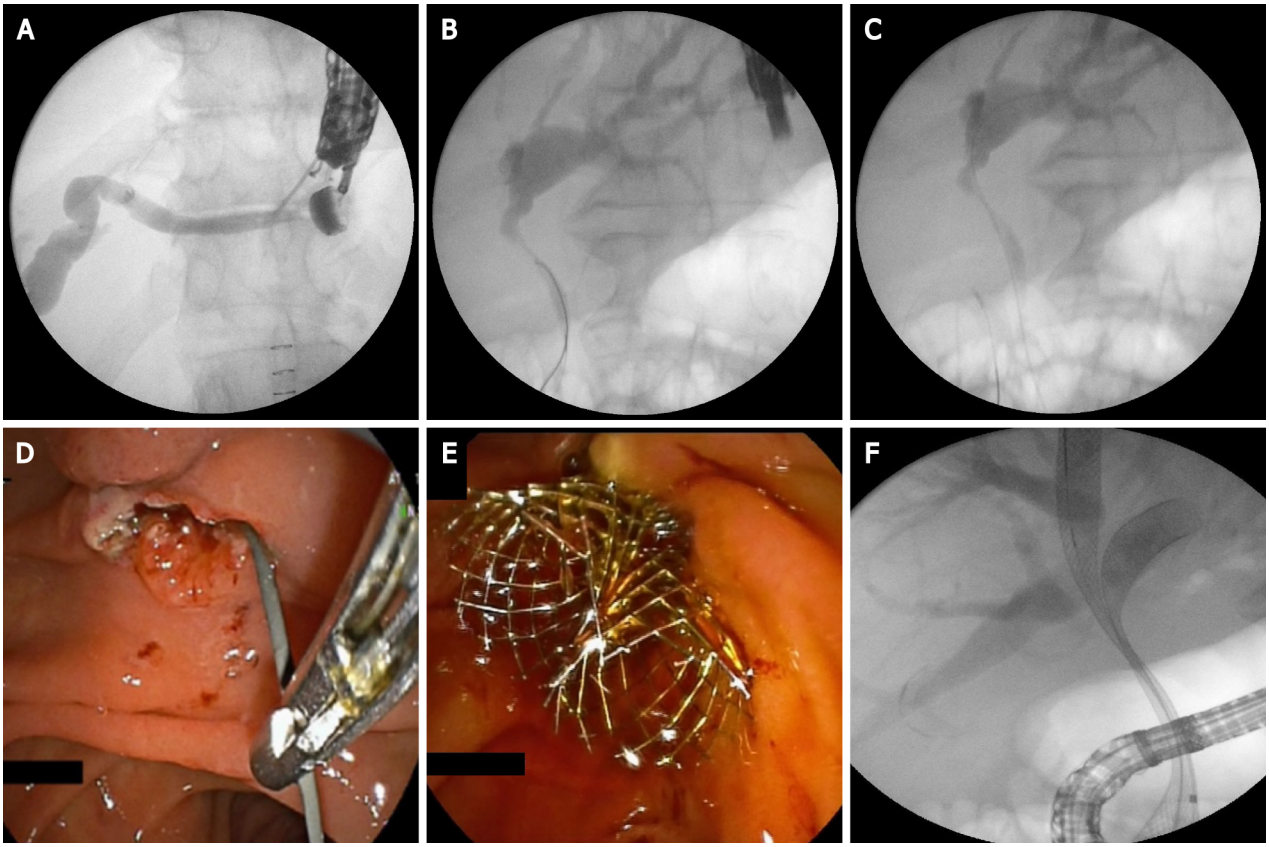

Figure 7 Endoscopic ultrasound-guided rendezvous technique. A: Puncture the left hepatic duct with 19G needle; B: Guide-wire insertion in bile ducts; C: Guide-wire insertion transpapillary in the duodenum; D: Grasping the guide-wire with a rath tooth forceps; E: Endoscopic image of two self-expandable metal stent (SEMS); F: Fluoroscopic image of two SEMS.

bile leakage (4%), pneumoperitoneum (3%), stent migration (2.7%), cholangitis (2.4%), peritonitis (1.3%), abdominal pain (1.5%)[19].

The important point here is that these results are reported from high-volume centers and the procedures were performed by highly experienced endoscopists. "Real-world" data could be much worse and the AE rate-unacceptably high. A national survey in Spain, including 106 patients who have EUS-BD performed, reports 67.2% technical success and a 63.2% clinical success. Improving the safety and reducing the complexity of EUS- BD are the main issues regarding this procedure[20].

ALGORITHM FOR EUS-BD

Algorithms for the EUS-BD approach, based on the nature of obstruction and anatomy of the patient were developed. The patients with a dilated intrahepatic bile duct on cross-sectional imaging should be approached intrahepatically and antegrade stenting should be attempted. When antegrade stenting fails or is not possible, HGS is a suitable option. When the intrahepatic approach fails, conversion to an extrahepatic approach is advisable. In cases without intrahepatic bile duct dilatation, the extrahepatic approach is the method of choice. After transbulbar or transantral puncture of CBD, rendezvous technique is advised. In case of failure, CDS should be performed[21].

According to the published data, there is no significant difference between the EUS-BD techniques in terms of technical, clinical success and AE. Khashab *et al*[22] compared the outcomes of HGS and CDS in a multicenter comparative trial. The technical and clinical success was similar in both groups[22].

CAN EUS-BD REPLACE ERCP AS A PRIMARY TREATMENT MODALITY?

EUS-BD is still used mostly when ERCP is not successful or not feasible. A

retrospective multicenter analysis comparing ERCP with EUS-BD, however, indicated that both techniques have similar efficacy[23]. The growing expertise and the advances in specially dedicated equipment have led to better clinical results with success rates over 90% and comparable AE rates[24,25].

Many clinical situations (altered anatomy, periampullary tumors, presence of duodenal stent covering the ampulla) suggest difficult biliary cannulation. Extended procedural time and numerous cannulation attempts are related to increased AE, consisting mainly in post-ERCP pancreatitis. On the other hand, tumor ingrowth/overgrowth is the major reason indicating the need for re-intervention. Both disadvantages could be overcome by resorting to a EUS-BD procedure[26,27].

Several prospective randomized trials and meta-analyses, published over the last 2 years, have compared the two techniques as a first-choice option for biliary drainage (Table 1).

In a single-center randomized trial Bang *et al*[28] compared EUS-CDS (n = 33) and ERCP (n = 34) as primary treatment for malignant distal biliary obstruction. There was no significant difference in the rates of technical success (90.9% *vs* 94.1%), clinical success and rate of reinterventions. AE rate was reported in 21.2% in the first and 14.7% in the second group (P = 0.49). The authors highlight the potency of EUS to ensure diagnostics (FNA, FNB), and palliative therapy (biliary drainage, celiac plexus neurolysis) in a single endoscopic session. Additionally in this study, the CDS performance did not affect the surgical technique in the operable cases[28].

In another prospective randomized controlled study Park *et al*[29] compared the EUS-BD and ERCP as a primary treatment modality for malignant extrahepatic bile duct obstruction. The authors (n = 30) suggest that EUS-BD has equivalent efficacy to ERCP. No severe AE were observed in both groups. In the ERCP group, four cases were reported with tumor ingrowth, and in the EUS group, two cases were reported with food impaction and another two with stent migration. In cases of stent migration in the EUS-BD group reintervention was not needed because the iatrogenic choledocho-duodenal fistula, created during the procedure provided sufficient bile drainage[29].

In a multicenter randomized trial including 125 patients, Paik *et al*[30] aim to compare EUS-BD (either CDS or HGS) with ERCP-BD for palliative drainage of distal malignant stenosis. The study confirms the similar efficacy and safety of the two techniques. EUS-BD was found to have lower AEs, including post-procedural pancreatitis, also lower re-intervention rate[30].

A meta-analysis (10 studies and 756 patients) from 2019[24] comparing EUS-BD with ERCP as a primary treatment modality of malignant distal bile duct obstruction reports equivalent clinical and technical success in both groups (over 90%), with similar rates of AE (15.5% for EUS-BD and 18.6% for ERCP). The EUS drainage demonstrated longer stent patency and lower rates of reinterventions, but without statistical significance. The most common AE in the EUS-BD group was bile peritonitis, while in the ERCP group, pancreatitis[24].

Another systematic review and meta-analysis by Jin *et al*[26] published in the same year announce similar results in terms of technical and clinical success, AE, reinterventions, procedure duration, stent patency and overall survival for both techniques. EUS-BD was associated with lower rates of stent dysfunction and tumor in/overgrowth[26].

A meta-analysis comparing EUS-BD with ERCP-drainage for primary management of malignant biliary obstruction regardless of stricture site from 2020 by Kakked *et al*[31] demonstrated identical technical and clinical success and AE rates. Patients after ERCP required significantly more re-interventions[31].

A meta-analysis, published in 2019[32] and involving 222 patients, reports comparable procedure time, technical and clinical success and complication rate. In conclusion, the authors report a significantly lower rate of stent dysfunction in the EUS-BD group and distinguish EUS as a reasonable option of the first choice for patients with malignant obstruction[32].

A final meta-analysis, published by Lou *et al*[33] includes 428 patients, (EUS-BD n = 215, ERCP n = 213). No significant difference was reported concerning procedure duration, technical and clinical success. EUS-BD, however, was associated with a lower rate of re-intervention and fewer procedure-related AE regarding pancreatitis and cholangitis[33].

In summary, given the comparable results in terms of AE and treatment outcomes, EUS is likely to become a feasible alternative to ERCP for primary biliary decompression.

Table 1 Summary of outcomes in recently published data on endoscopic ultrasound-guided biliary drainage-endoscopic retrograde cholangiopancreatography comparative analysis

Ref.	Type of evidence	Patients, *n* (%)	Technical success, EUS-BD–ERCP, *n* (%)	Clinical success, EUS-BD-ERCP, *n* (%)	AE, EUS-BD-ERCP, *n* (%)
Dhir *et al*[23], 2015	Multicenter retrospective analysis	208	94.23-93.26 (98/104-97/104)	N/A	8.65-8.65 (N/A)
Kawakubo *et al*[27], 2016	Retrospective study	82	N/A	96.2-98.2 (25/26-55/56)	26.9-35.7 (7/26-20/56)
Park *et al*[29], 2018	Prospective randomized controlled study	30	92.9-100.0 (13/14-14/14)	92.9-100.0 (13/14-14/14)	0.0-0.0 (0/14-0/14)
Paik *et al*[30], 2018	Multicenter randomized trial	125	93.8-90.2 (60/64-55/61)	84.4-85.2 (54/64-52/61)	10.9-39.3 (7/64-24/61)
Bang *et al*[28], 2018	Prospective randomized trial	125	90.9-94.1 (30/33-32/34)	97.0-100.0(32/33-34 /34)	21.2-14.7 (7/33-5/34)
Logiudice *et al*[34], 2019	Meta-analysis	222	91.96-91.81 (N/A)	84.81-85.53 (N/A)	N/A (4/79–25/76)

ERCP: Endoscopic retrograde cholangiopancreatography; EUS-BD: Endoscopic ultrasound-guided biliary drainage-endoscopic.

EUS-BD *VS* PTBD

Over the last decade, enough data have been collected to allow comparative analyses between EUS-BD and percutaneous biliary drainage (PTBD). Several advantages of EUS-BD over PTBD have been proved over time: It could provide drainage of intra- and extrahepatic ducts, according to the obstruction level; it is less invasive and eliminates the need for an external catheter. The latter spare the possibility for catheter-related complications like bleeding, infection, dislocation and bile leak.

The first meta-analysis comparing EUS-BD and PTBD in terms of efficacy and safety is published by Sharaiha *et al*[34] in 2017. Nine studies with 483 patients were included. No difference in technical success and length of hospital stay was found, but EUS-BD was found to have better clinical success, fewer post-procedure AE, lower rate of re-interventions and was more cost-effective[35].

In conclusion, published data suggest that EUS-BD is better compared with PTBD, reducing the risk of AE, hospital stay, the need for re-interventions and offers a better quality of life for the patients[36]. In cases of ERCP failure, whenever an experienced endoscopy team is available EUS-BD should be performed instead of PTBD.

FUTURE OUTLOOK

At the moment, EUS-BD is primarily used as a rescue procedure following a failed ERCP. According to the published data, EUS-BD demonstrates some clinical advantages over ERCP but further randomized studies will determine the real place of EUS as therapy in cases of malignant biliary obstruction. We suggest a simple scheme summarizing the current role of EUS in endoscopic biliary drainage therapy (Figure 8).

There are many questions in consideration before the adoption of EUS as a standard first-line therapeutic option. Despite the promising results, published in the literature, these procedures remain difficult and are not routine outside a few expert centers. The reasons are lack of training, lack of procedure standardization, and few available dedicated devices. Although the similar rate of AE for both procedures, according to some authors, EUS complications are more severe and difficult to be managed. Most of the published data comes from experienced endoscopists in high volume expert centers and it remains unclear if these results can be achieved in smaller centers[36]. On the other hand, EUS-BD is rarely indicated and expertise acquisition is difficult.

The low case volume limits the training opportunities and the existing training models are not able to simulate all the difficulties encountered when performing these procedures. Developing training models is a key step to understand, learn and perform more safely EUS-BD. Dhir *et al*[37] created and evaluated a hybrid model consisting of pig esophagus and stomach and synthetic duodenum and biliary system and concluded that it replicates real situations encountered during EUS-RV and EUS-BD and training and mentoring using this model improves the chances of success

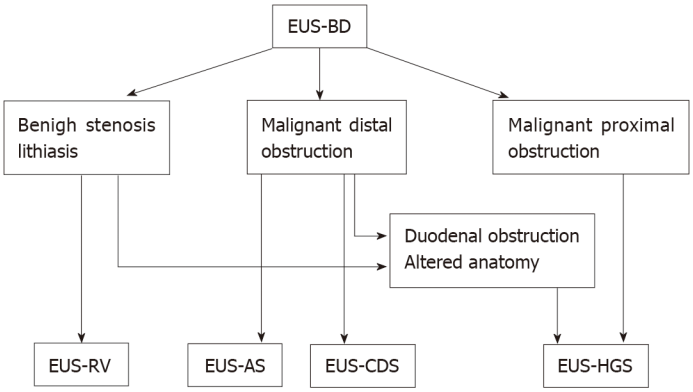

Figure 8 Current place of endoscopic ultrasound-guided biliary drainage in endoscopic biliary drainage therapy. EUS-BD: Endoscopic ultrasound-guided biliary drainage; EUS-RV: EUS-guided rendezvous technique; EUS-AS: EUS-guided antegrade stenting; EUS-CDS: EUS-guided choledochoduodenostomy/choledochoantrostomy; EUS-HGS: EUS-guided hepaticogastrostomy.

performing these procedures[37].

Taking into consideration the above-mentioned limitations, important steps were made to improve safety, reduce complexity, and standardize these procedures. The creation of the dedicated devices, training models, and guidelines presume a promising future of EUS-BD.

The development of dedicated devices is an important step toward making EUS-BD easier, reducing procedure time, and improving safety. The introduction of cautery-enhanced LAMS and their implementation for EUS-CDS is a step forward to make the procedure less complex and to reduce the number of AE. Significant progress has been made by the development of dedicated stents for EUS-HGS (Giobor-TaeWoong; Proximally covered SEMS-Hanarostent). This has led to a substantial reduction of severe AE like cholangitis, stent migration and bile peritonitis. Cautery-enhanced HGS- stents and "one step delivery" stents without the need for tract dilation are on the way and hopefully will make EUS-HGS a more popular, easy and safe intervention. There is a real perspective of full replacement of PTBD and surgery in malignant bile duct disease and ERCP failure cases. Gaining experience and widely spread expertise for the technique could lead to further expansion of indications and new treatment opportunities.

In an attempt to standardize EUS-BD the Asian EUS group published the first guideline on the optimal management in interventional EUS procedures. Fifteen statements address the indications, technical aspects, pre-and post-procedural management, management of complications, competency and training of EUS-BD[38].

CONCLUSION

EUS-BD is a new, promising mini-invasive biliary drainage modality, offering many advantages over traditional interventional methods and surgery. The accepted indications are ERCP failure, duodenal obstruction or biliary diseases in patients with surgically altered anatomy. EUS-BD includes several techniques which could be adapted to the unique patient anatomy and condition such as EUS-guided rendezvous technique, antegrade stenting or transmural drainage. A large amount of data suggests that EUS-BD should be preferred over PTBD if required expertise is available.

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MINIREVIEWS

When should we perform colonoscopy to increase the adenoma detection rate?

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Abstract

The rate of adenoma detection is the most reliable quality indicator of colonoscopy. Studies have reported that colonoscopy performed in morning has a higher adenoma detection rate (ADR) than that performed in the afternoon. These studies have explained that several physician-related factors such as undergoing an emergency procedure the night before colonoscopy, accumulated workload, and increased fatigue level in the afternoon might have led to such finding. However, several opposing articles have indicated that the time of day and ADR is not quite related. Complex confounding factors can impact study results. Colonoscopy withdrawal time and bowel preparation quality are key factors. However, queue list numbers, participation of academic fellows, nurses' assistance, and the number of colonoscopies allocated *per* hour are also notable factors. Recently, an attempt has been made to homogenize the ADR in the morning and afternoon through artificial intelligence-assisted colonoscopy. This review article introduces the history of this long-debated topic, discusses points to consider in real-world practice, and suggests new ideas for planning future research. By understanding this issue, the rate of adenoma detection during colonoscopy is expected to be improved further.

Key Words: Colonoscopy; Colorectal cancer; Time of endoscopy; Afternoon colonoscopy; Adenoma detection rate

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Core Tip: Adenoma detection rate is the most reliable indicator of colonoscopy quality. Studies suggest that colonoscopy performed in the morning is associated with a higher detection rate of adenoma than the procedure performed in the afternoon. However, it is important to endeavor not only to improve patients' bowel preparation quality in the

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afternoon, but also to create an environment conducive to adenoma detection by physicians during afternoon sessions.

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INTRODUCTION

According to the statistics from the World Health Organization (WHO)[1], colorectal cancer is the third most common cancer around the world, with approximately 1.93 million newly diagnosed cases in the year 2020. It is the second most commonly diagnosed cancer in women and the third most common cancer in men, accounting for 9.4% (2nd) of the total number of cancer deaths. In the United States, the mortality due to colorectal cancer has substantially declined over the past few decades mainly due to a decrease in the incidence of colorectal cancer thanks to a sensitive detection[2] and the removal of adenomas by colonoscopy[3].

Since more than 95% of colon cancers originate from colorectal adenomas, the rate of adenoma detection [adenoma detection rate (ADR)] during colonoscopy is concerned as the most reliable benchmark quality assessment indicator for determining adequate screening efficacy[3,4]. Some studies have reported that patients examined by endoscopists with ADR of less than 20% have over ten times greater risk of interval colorectal cancer[5,6].

Factors associated with ADRs include nonmodifiable factors (such as age, gender, race, body mass index, and comorbidities) and modifiable factors such as scope withdrawal time (WT) and bowel preparation[7-9]. However, most of these factors are either technical or patient-related factors. On the other hand, studies regarding endoscopist-related factors are scarce. Since the first report by Sanaka *et al*[10] showing that there might be a difference in ADR between morning and afternoon colonoscopies in 2006, several studies have shown that physician's fatigue in the afternoon is related to ADR. However, conflicting results have also been reported. Therefore, we are still uncertain whether colonoscopies performed in the morning show better ADR than those performed in the afternoon.

This review article will introduce the history of this long-debated topic with the latest study results and discuss points to consider when planning future research.

THE BEGINNING OF THE DEBATE

Previous studies have shown that fatigue of medical professionals, including anesthesiologists[11], surgeons[12] and resident trainees[13] has a negative impact on patient safety outcomes. This phenomenon is not only observed for medical personnel, but also observed for non-medical employees such as pilots[14] and truck drivers[15].

In the early 2000s, several retrospective studies have reported that fatigue caused by doctors' sleep deprivation can affect laparoscopic performance[13], and that patients who are hospitalized at weekend have higher mortality than weekday patients in some disease entities[16]. These were the first reports showing that a patient's treatment outcome could vary by the day of the week. In 2004, a study suggested that a decrease in the detection rate of polyps of more than 9 mm was due to the practice pattern with a rapid increase in the number of screening colonoscopy after July based on the National Endoscopic Database[17]. As a result, it has been hypothesized that if the number of colonoscopy procedures by the time increases, the polyp detection rate (PDR) may be inversely affected. This result has been thought to be related to the fatigue of endoscopists.

The first article suggesting that an endoscopist's fatigue during the day might affect colonoscopic cecal intubation rate (CIT) was published in 2006[10]. The authors investigated colonoscopic incompletion rates through a retrospective chart review of total 2087 colonoscopies (1084 in the morning and 999 in the afternoon). As a result, a significantly higher failure rate in the afternoon (6.5% *vs* 4.1%) was found. Even after

correcting for poor bowel cleansing quality in the afternoon, the afternoon failure rate was still significantly higher (5.0% *vs* 3.2%). The authors explained that the time of day could possibly be an independent predictor of the completion rate of colonoscopy. Considering such result, the time factor could also lead to a decrease in the afternoon WT, which was expected to reduce ADR consequently. In a retrospective study[18] of 3619 colonoscopies, ADR was found to be significantly higher in morning colonoscopies than in afternoon colonoscopies (29.3% *vs* 25.3%). In addition, there was a trend toward declining ADR for each subsequent hour of the day.

A prospective study of Veteran's administration teaching hospital[19] has shown comparable results. Data were analyzed both as a dichotomous time period ("early-morning case" *vs* "later case") and as a continuous variable (start time). In univariate analysis, early-morning cases yielded 27% more polyps *per* patient than later cases. Numbers of hyperplastic and adenomatous polyps decreased hour-by-hour as the day progressed. These early studies were pioneer studies for many subsequent community-based studies (Table 1 and Figure 1).

TIME OF DAY MAY NOT AFFECT ADR

However, several articles have indicated that the time of the day and ADR are not quite actually related. According to retrospective studies of single center hospitals that used a 3-h colonoscopy shift schedule[20] or an assigned time of 45 min *per* colonoscopy[21], PDR was the highest during the mid-day (shift 2)[20], showing no decrease in PDR as the day progressed[21]. In these studies, patients with poor bowel preparation were relatively less included using exclusion criteria and split-dose preparation methods. In addition, these studies could not reflect various amounts of workload among endoscopists for each institution.

In a retrospective study[22] based on a tertiary medical center where only attending physicians (excluding fellows) participated, PDR showed a decreasing trend for both half and all-day shifts (OR: 0.67, 95%CI: 0.44-1.00). However, due to related small numbers of confirmed adenomas, it could not demonstrate a significant difference in ADR. This result implicates that even in tertiary medical centers where endoscopists suffer high workload, the time of day alone may not have a strong influence on ADR as previously reported.

ENDOSCOPIST FATIGUE AND ADR

Despite these negative results, studies focusing on physician's fatigue and ADR were steadily published in 2014 and 2015. One study has compared ADR between a control group and cases of on-call duty or emergency procedure the night before screening colonoscopy[23]. Interestingly, overnight on-call duty was irrelevant to ADR. However, undergoing an emergency procedure the night before colonoscopy resulted in a significant decrease (24%) in ADR compared to the control group, indicating the influence of sleep deprivation on procedural outcomes. In a prospective, multi-center study[24] on screening colonoscopies when endoscopist fatigue was measured using a Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) questionnaire with a cutoff score of 25, ADR was found to be lower for fatigued endoscopists than for the non-fatigued group. FACIT-F was 3.6 time higher for the ADR in a multivariate regression analysis.

LATEST RESEARCH

A prospective observational study[25] performed in 2016 analyzed the influence of endoscopist-related characteristics on quality indicators for colonoscopy. In that study, factors associated with ADR were found to be age and life-long number of colonoscopies. Only exclusive dedication to endoscopy practice was found to be independently related to adenoma detection of proximal colon. Besides, none of other endoscopist characteristics, including the number of hours/week or annual volume of colonoscopies, was associated with a higher ADR. This was also supported by a following large community-based study[26] including more than 76000 colonoscopies with the aim to objectively reflect procedure related fatigue, considering both the number of colonoscopy procedures and the complexity of the procedure using

Table 1 Study characteristics (including evaluated adenoma detection rate result)

Ref.	Country	Study design	Investigated blocks	Physician (Fellow inclusion: O, X)	Bowel preparation	No. of a.m./p.m. procedure	ADR (%)
Sanaka *et al*[18], 2009	United States	Retrospective	Full day	Certified endoscopist (O)	Single PEG 4 L or oral fleet	1748/1871	AM (29.3); PM (25.3)
Chan *et al*[19], 2009	United States	Prospective	Full day	Certified endoscopist (O)	Single PEG 4 L or oral fleet	432/15	AM (49.2); PM (45.1)
Freedman *et al* [21], 2011	United States	Retrospective	Full day	Certified endoscopist (X)	Split dose PEG 4 L	756/730	AM (41); PM (44)
Long *et al*[22], 2011	United States	Retrospective	Full day	Certified endoscopist (X)	Single PEG 4 L	2219/1202	24.9
Lurix *et al*[23], 2012	United States	Retrospective	Half day. Full day	Certified endoscopist (O)	Single or Split PEG 4 L	2148/937	AM (30); PM (33)
Paeck *et al*[39], 2013	South Korea	Retrospective	Half day. Full day	Certified endoscopist (O)	Single PEG 4 L	420/881	AM (42.3); PM (34.7)
Subramanian *et al* [40], 2015	United Kingdom	Retrospective	Half day. Full day	Certified endoscopist (O)	Single PEG. Sodium picosulphate	1091/994 (evening:489)	27.6
Singh *et al*[41], 2016	United States	Retrospective	Full day	Certified endoscopist (O)	Split dose PEG 4 L	1574/731	AM (23.1); PM (18.3)
Teng *et al*[42], 2016	Singapore	Prospective	Full day	Certified endoscopist (X)	Single PEG (morning); Split-dose PEG (afternoon)	270/263	AM (29); PM (21)
Lei *et al*[27], 2020	China	Retrospective	Full day	Certified endoscopist (O)	Split-dose PEG	261/223	AM (36); PM (35)

Detection of adenoma was assisted by computer-aided detection (CADe). ADR: Adenoma detection rate.

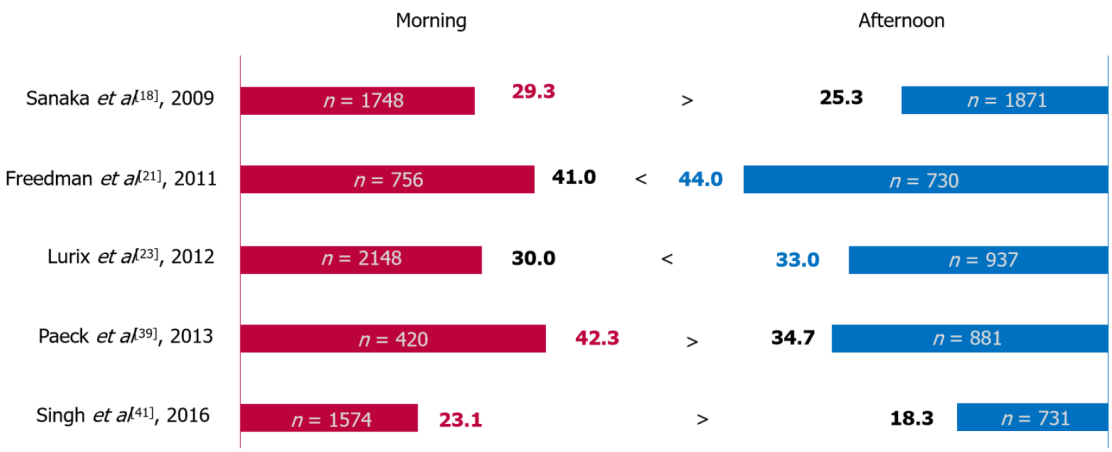

Figure 1 Comparison of morning and afternoon adenoma detection rates of studies with more than 1000 patients.

consensus weights and relative value units. As a result, there was no association between ADR and endoscopist fatigue. Increasing levels of fatigue did not impact ADR, even after adjusting for confounding factors at patient-level and provider-level in multivariable regression analyses.

Meanwhile, the latest study has determined whether there is a difference in ADR between morning and afternoon colonoscopies assisted by artificial intelligence[27]. It was a prospective, single-center study with 484 colonoscopies through computer-aided detection (CAD) for polyps. There seemed to be no significant difference in ADR between morning and afternoon colonoscopies. Indeed, deep learning algorithm with real-time computer-aided polyp detection was proven to produce a significant increase in the detection of smaller adenomas compared to conventional colonoscopy (RR: 1.69; 95%CI: 1.48-1.84), according to a recent systemic review and meta-analysis[28]. It is expected that AI technology will be an effective tool minimizing the influence of 'endoscopist-related' factors in ADR.

Since 2006, numerous works have been done on whether colonoscopies performed in the afternoon are below the standard quality. It is not as easy as expected to conclude because various confounding variables such as patient, physician, assistant nurse, and the type of hospital are all factors that can affect the detection of adenomas during colonoscopy.

COMPLEX CONFOUNDERS

Increasing colonoscopy WT is thought to be able to improve ADR. A minimum WT of over 6 min during a normal colonoscopy is widely recommended[29]. A prospective observational study has been performed to determine how endoscopist fatigue can affect performance quality according to continuous and embedded volumes of colonoscopies[30]. It was found that WT and ADR remained stable while median CIT was lengthened as the repetitive procedure progressed. According to a prospective study (BECOP-3) that analyzed endoscopist factors related to ADR, WT within 6 to 11 min was not related to a reduced ADR[31]. However, ADR showed a significant reduction regardless of sufficient WT when a physician performed an emergency overnight procedure the day before the index colonoscopy[32]. If a physician sacrifices the WT to make up for a longer insertion time, less adenomas is expected to be found.

Along with WT, another substantial factor for ADR is bowel preparation quality. As it is crucial for adenoma detection, afternoon colonoscopies are known to be associated with both inadequate bowel preparation and lower ADR. There is no difference in the detection of adenomas by the time of day in studies when bowel preparation quality in the afternoon is maintained relatively well using a split-dose method[21] or statistically corrected for bowel cleanliness[33]. Another study has stated that bowel preparation is an inevitable confounder in assessing the quality of colonoscopy[34]. Therefore, various ways need to be investigated to improve the preparation quality of afternoon colonoscopies.

Other possible confounding factors include hospital system-related issues such as the participation proportion of academic fellows in endoscopy[34], queue list numbers that differ quite a lot for each endoscopic clinic[35], overnight duty systems for endoscopists or nurses[32], and the number of colonoscopies allocated every hour[20] (Table 2). If an endoscopist is in state of sleep deprivation or if an awaited patient comes in right after a previous laborious colonoscopy, it would be reasonable to question the procedural quality. However, if a highly skilled physician who performs more than 200 colonoscopies a year and if WT can be secured to be over 6 min, ADR can remain stable throughout the day[31]. Factors that might interfere with concentration on endoscopic procedures such as attending educational conferences, replying to frequent consultations, and educating medical students should be emphasized[25, 36]. "Social influencing" using notice or posters, personal auditing reports, and physical or electronic reminders are emerging as part of efforts to prevent deterioration of polyp and ADRs due to fatigue in the afternoon in busy academic teaching institutions[37] .

Finally, how many hours of the day the endoscopist devotes to colonoscopies is another issue that should be pointed out. Some physicians may only work in the morning or afternoon (half-day block), while others may perform colonoscopies the entire day (full-day block). This can significantly affect study results. However, it has been poorly controlled across studies. For example, only half-day blocks were included in some studies, whereas full-day and half-day blocks of work were all taken into account in other studies. It seems inappropriate to compare these studies on the same line[33].

WHERE DO WE STAND? AND WHAT'S NEXT?

Meta-analyses on whether a morning colonoscopy is superior to an afternoon colonoscopy have shown cautious but consistent results. According to a study that analyzed a total of 16 eligible publications (14 retrospective studies and two prospective studies), ADRs for morning and afternoon colonoscopies were similar. However, the PDR of the afternoon was significantly less than that of the morning. Since it is generally considered that PDR does not significantly affect the quality of colonoscopy, there should be no change in the quality of colonoscopies throughout the day. Interestingly, the authors also concluded that fellow participation did not impact ADR difference between morning and afternoon colonoscopies. Barakat *et al*[38]

Table 2 Factors related with higher adenoma detection rate

Category	Factors
Patient-related	Good Bowel preparation
	Age (Older age), gender (male)
	Obesity (Higher body mass index)
Endoscopist-related	Withdrawal time (> 6 min)
	Assist from nurses/additional observer
	Queue list numbers (Small)
	Overnight duty (Less or none)
	Number of colonoscopies allocated *per* hour (Less)
	Half-day or Full-day schedule (Half-day)
	Attending CMEs, conferences, frequent consultations (Less)
Device-related	Higher definition processors, endoscopes

analyzed the effect of the time of day on ADR through multiple subgroup analyses in 2020, showing that the net effect of the time of day did not impact ADR in general. In addition, there was no difference in ADR between morning and afternoon not only for physicians with a half-day block schedule, but also for endoscopists who continuously performed full-day colonoscopies by the same operator.

These meta-analyses have strengths, including a large number of studies with a large sample size with a diverse international population. However, due to relatively high heterogeneity existed in data used for the analysis (allotted time for a colonoscopy, WT, indications for colonoscopy), homogenization of the study design is required. In addition, it must be acknowledged that the unevenness of data among included studies in terms of different fellow participation and bowel preparation quality might affect the interpretation of results. Besides, as these meta-analyses did not estimate operator fatigue, results reflecting a physician's various stamina levels and the complexity of previous procedures might come out differently.

Every colonoscopy is performed under different circumstances. There would be the first procedure of the day, some might be performed after a number of arduous duties. Performing 'full-day' colonoscopies may not necessarily lead to a less careful procedure. The physician who performs colonoscopy until the afternoon may receive additional financial compensation accordingly, which will increase the operator's motivation. Therefore, it is presumable that 'financial compensation policy' of each institution should be also considered as one of the various factors affecting ADR in the afternoon. On the other hand, from experience, the procedural result is not good from time to time when the following colonoscopy is forced to be started immediately after a difficult therapeutic endoscopy due to long waiting patients. We hope that future well-designed studies will be able to evaluate effects of previous endoscopies on ADR. Besides, it will be interesting to see if ADR in the morning and afternoon can be differently affected by the experience of endoscopists (novice/experienced), weekday or weekend, and gender of patients through subgroup analysis.

NO EFFECT OF TIME OF THE DAY ON ADR

Several studies indicated the lack of correlation between the time of the day and the ADR. Single-center retrospective studies at hospitals based on 3-h colonoscopy shift schedule or an assigned time of 45 min *per* colonoscopy revealed that PDR was the highest during the mid-day (shift 2), without decreasing as the day progressed. In these studies, relatively few patients with poor bowel preparation were included based on exclusion criteria and split-dose preparation methods. In addition, these studies failed to reflect various levels of workload among endoscopists at each institution.In a retrospective study based on a tertiary medical center involving only attending physicians (excluding fellows) as the participants, the PDR showed a decreasing trend in both half and full-day shifts (OR: 0.67, 95%CI: 0.44-1.00). However, due to the small number of confirmed adenomas, the study failed to demonstrate a

significant difference in ADR, suggesting that even in tertiary medical centers with endoscopists ensuring increased workload, the time of day alone may not have a strong influence on ADR as previously reported.

CONCLUSION

In conclusion, data up to date did not demonstrate a significant difference in the quality of colonoscopies by the time of the day in either a full day setting or in a half-day block setting. Despite negative results, we believe it is still too early to conclude on this issue. Future systematic randomized clinical trials that can control for confounding factors mentioned above and analyze an endoscopist's fatigue level more objectively might change conclusions on this subject. For now, considering that the PDR (or maybe ADR) in the afternoon may get deteriorated in the full-day block schedule, it is important to make efforts not only to improve patients' bowel preparation quality in the afternoon, but also to create an environment that a physician can focus solely on detecting adenomas during afternoon colonoscopy sessions.

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MINIREVIEWS

Primary prophylaxis of variceal bleeding in patients with cirrhosis: A comparison of different strategies

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Abstract

Patients with cirrhosis and esophageal varices bleed at a yearly rate of 5%-15%, and, when variceal hemorrhage develops, mortality reaches 20%. Patients are deemed at high risk of bleeding when they present with medium or large-sized varices, when they have red signs on varices of any size and when they are classified as Child-Pugh C and have varices of any size. In order to avoid variceal bleeding and death, individuals with cirrhosis at high risk of bleeding must undergo primary prophylaxis, for which currently recommended strategies are the use of traditional non-selective beta-blockers (NSBBs) (*i.e.*, propranolol or nadolol), carvedilol (a NSBB with additional alpha-adrenergic blocking effect) or endoscopic variceal ligation (EVL). The superiority of one of these alternatives over the others is controversial. While EVL might be superior to pharmacological therapy regarding the prevention of the first bleeding episode, either traditional NSBBs or carvedilol seem to play a more prominent role in mortality reduction, probably due to their capacity of preventing other complications of cirrhosis through the decrease in portal hypertension. A sequential strategy, in which patients unresponsive to pharmacological therapy would be submitted to endoscopic treatment, or the combination of pharmacological and endoscopic strategies might be beneficial and deserve further investigation.

Key Words: Cirrhosis; Esophageal varices; Primary prophylaxis; Non-selective beta-

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Core Tip: Variceal hemorrhage still is an important cause of death among patients with cirrhosis, and primary prophylaxis against variceal bleeding is of the utmost importance. Traditional non-selective beta-blockers, carvedilol or endoscopic variceal ligation are currently recommended for primary prophylaxis, and the superiority of one alternative over the others is controversial. This review will provide a comparison of the strengths and weaknesses of the different strategies for primary prophylaxis against variceal bleeding, so that practitioners make an informed decision when choosing among them.

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INTRODUCTION

In patients with compensated cirrhosis, esophageal varices develop in an annual rate of 7%-8%, characterizing state 2 in the natural history of the disease. Once they develop, they will bleed in 5%-15% of patients *per* year, marking their transition to decompensated cirrhosis (state 3 in the natural history of cirrhosis). When patients bleed, the mortality rate reaches 20%[1,2].

In order to avoid bleeding and death, individuals with cirrhosis should be screened for esophageal varices, and primary prophylaxis against their rupture is recommended to patients at higher risks[3-6]. The Baveno VI consensus recommends that patients with cirrhosis and medium-large varices should be submitted to prophylaxis with either traditional non-selective beta-blockers (NSBBs) (*i.e.*, propranolol or nadolol), carvedilol (a beta-blocker with an alpha-adrenergic blocking effect) or endoscopic variceal ligation (EVL). Patients with small varices should also be submitted to prophylaxis with NSBBs as long as they are classified as Child-Pugh C or have varices with red signs[3]. The most important medical associations in the field of hepatology support these recommendations[4,5]. Nevertheless, there are divergences in medical literature regarding the superiority of one prophylactic alternative over the others[7-9].

This article aims at reviewing the main strategies for primary prophylaxis against variceal hemorrhage, as well as comparing their strengths and weaknesses (Table 1). Knowing the characteristics of each prophylactic strategy will enable physicians to make better decisions when choosing among them in the management of particular patients.

TRADITIONAL NSBBs

NSBBs are considered the main pharmacological intervention in the treatment of portal hypertension since Lebrec *et al*[10] demonstrated that propranolol administration effectively reduced the hepatic venous pressure gradient (HVPG) in patients recovering from an acute episode of gastrointestinal bleeding due to ruptured esophageal varices. This reduction was associated with a significant decrease in portal blood flow, which is usually increased in patients with cirrhosis due to significant splanchnic arterial vasodilation. Later studies confirmed that NSBBs-induced portal blood flow reduction is caused by the activity of these drugs on beta-1 cardiac receptors, determining a negative chronotropic response and a reduced cardiac output, and, most importantly, by their effects on beta-2 receptors of the splanchnic vascular bed, resulting in splanchnic vasoconstriction[11,12].

Table 1 Strengths and weaknesses of the different strategies for primary prophylaxis of variceal bleeding in cirrhosis

	NSBBs	Carvedilol	EVL
Prevention of mortality	+	+?	+?
Prevention of bleeding	+	+	++
Prevention of other complications of cirrhosis	+	+	-
Reduction in HVPG	+	++	-
Adverse effects	--	--	-
Serious adverse effects	-	-	--

The plus sign (+) indicates strength. The minus sign (-) indicates weakness. The question mark (?) indicates uncertainty. NSBBs: Traditional non-selective beta-blockers; EVL: Endoscopic variceal ligation; HVPG: Hepatic venous pressure gradient.

When NSBBs are used in primary prophylaxis of variceal bleeding, the hemodynamic goal is to achieve an HVPG reduction ≥ 20% of the baseline levels or a decrease in absolute levels to under 12 mmHg. Below those thresholds, patients would be protected from variceal bleeding[13]. Even a reduction ≥ 10% is likely to be clinically relevant for primary prophylaxis[3]. Nevertheless, only 33%-50% of patients undergoing NSBB prophylaxis achieve the proposed hemodynamic goals[8].

Different randomized controlled trials (RCTs) have evaluated the role of NSBBs in primary prophylaxis against variceal bleeding. A meta-analysis evaluating 6 of these studies and including 811 patients with cirrhosis and medium or large varices demonstrated that primary prophylaxis with NSBBs was more effective than placebo, with 2-year bleeding rates of 30% in the control group and 14% in the NSBB group[14].

In clinical practice, the most commonly used NSBBs are propranolol and nadolol, and treatment with these drugs should begin with low doses that are gradually increased to the maximum tolerated dose or to a heart rate target around 55-60 beats *per* minute. Propranolol can be started at 20-40 mg twice a day, and maximal daily dose should be 320 mg/d in individuals without ascites or 160 mg/d in those with ascites[4] (80 mg/d for patients with severe or refractory ascites according to the European Association for the Study of the Liver[5]). Nadolol can be started at 20-40 mg once a day, and maximal daily dose should be 160 mg/d in patients without ascites or 80 mg/d in those with ascites[4].

Some concern has been shown regarding the use of NSBBs by patients with end-stage cirrhosis. According to the window hypothesis, the therapeutic window for the use of NSBBs would close at end-stage cirrhosis, particularly with the development of refractory ascites, because these drugs would not only be less effective in that stage, but also might lead to a higher risk of hepatorenal syndrome and mortality due to a negative impact on the cardiac compensatory reserve[15]. This hypothesis was based on an observational study of 151 individuals with cirrhosis and refractory ascites, in which those using propranolol had a shorter survival[16]. Later on, other observational studies associated the use of NSBBs to a higher risk of hepatorenal syndrome and a lower transplant-free survival among patients with spontaneous bacterial peritonitis[17] and to a higher risk of acute kidney injury among those with severe alcoholic hepatitis[18]. Nevertheless, the methodological limitations of these observational studies should be noticed, and a meta-analysis of 11 studies (3145 patients) failed to demonstrate evidence of a negative impact of NSBBs on the mortality of individuals with ascites (including a subgroup analysis focused on patients with refractory ascites)[19].

Therefore, considering existing evidences, the current recommendations are that NSBBs should be reduced or discontinued (or should not be initiated) in patients with systolic blood pressure < 90 mmHg, with acute kidney injury or with serum sodium < 130 mEq/L[3-5]. In the settings of acute decompensation of cirrhosis with spontaneous bacterial peritonitis, sepsis or bleeding, NSBBs should be discontinued. If NSBBs cannot be reinitiated after 3-6 d, EVL should be considered[5].

As previously mentioned, international guidelines recommend the use of either NSBBs or EVL as first-line options with similar effectiveness for primary prophylaxis of variceal bleeding[3]. Yet, some issues should be considered when choosing between these options in clinical practice. Firstly, NSBBs work by reducing portal hypertension through a decrease in splanchnic blood flow. Theoretically, this could benefit patients in relation to the prevention of other complications of portal hypertension, such as

ascites, hepatic encephalopathy or infections[20]. Indeed, a recent RCT on the role of NSBBs in patients with clinically significant portal hypertension (individuals who did not have an indication for primary prophylaxis against variceal bleeding) has demonstrated that those receiving propranolol or carvedilol had a lower risk of developing the primary endpoint (cirrhosis decompensation or death, hazard ratio of 0.51, P = 0.041). Interestingly, the benefit was predominantly related to the lower incidence of ascites among individuals receiving the intervention (hazard ratio of 0.42, P = 0.03)[21]. Of course, this is not an expected effect of EVL, which works mechanically on the obliteration of varices.

Another important aspect that might influence the choice of the method of prophylaxis is the occurrence of adverse events. Usually, studies suggest that there are more side effects with NSBBs (around 15% of patients require dose reduction due to fatigue or hypotension), although they are more severe with EVL (pain, esophageal ulcers, strictures, and bleeding). In addition, NSBBs are cheap and easy to manage, while EVL requires more complex resources and permanent endoscopic surveillance to monitor the recurrence of varices[4].

Finally, although strong evidence is lacking in medical literature, prophylaxis against the rupture of small varices is recommended for individuals classified as Child-Pugh C or for those who have red wale marks on the surface of the varices[22]. These red signs reflect increased tension on the vessel wall and imminent risk of rupture. Currently, the recommendation for these patients is that primary prophylaxis should be performed with NSBBs, since the use of EVL for these varices can be technically complex[3-5].

CARVEDILOL

Carvedilol is a NSBB with an additional activity on alpha-1 cardiac receptors. Therefore, aside from reducing cardiac output (beta-1 blocking effect) and from leading to splanchnic vasoconstriction (beta-2 blocking effect), it promotes sinusoidal vasodilation (alpha-1 blocking effect). For this reason, most authors believe that carvedilol promotes greater reductions in HVPG than NSBBs, leading to better hemodynamic response rates during primary prophylaxis against variceal bleeding [23]. However, the superiority of carvedilol over NSBBs regarding portal hypertension improvement is still not consensual[24].

Four RCTs evaluated the role of carvedilol in the primary prophylaxis against variceal bleeding. Two of them demonstrated that this drug was superior to EVL in preventing first variceal bleeding[25,26]. On the other hand, the other 2 RCTs failed to identify a benefit of carvedilol when compared to EVL[27] or to either EVL or propranolol[28]. The largest RCT on this issue is currently in progress and will hopefully put an end to this controversy[29].

While that trial is not published, another recent study contributed with data on the comparison between NSBBs and carvedilol. The study evaluated patients with a past history of ascites who were undergoing both primary or secondary prophylaxis against variceal bleeding with propranolol. Subjects were randomized either to switch to carvedilol or to remain under propranolol. When compared to individuals remaining on propranolol, patients switching to carvedilol had significant decreases in plasma renin activity, plasma aldosterone and serum noradrenaline, as well as significant increases in systemic vascular resistance and glomerular filtration rate. Moreover, patients on carvedilol had fewer decompensating events at 2 years than their counterparts (10.3% *vs* 37.5%, P = 0.002), as well as lower liver-related mortality (64.1% *vs* 86%, P = 0.01). It must be highlighted, though, that an intention-to-treat approach was not used in this study[30].

In clinical practice, carvedilol should be started at a dose of 6.25 mg/d and increased to 12.5 mg/d after three days, as long as systolic blood pressure does not fall below 90 mmHg[4]. The adverse effects profile of carvedilol does not seem to be different from that of NSBBs, but doses should not be increased over 12.5 mg/d, except in patients with persistent systemic arterial hypertension[4,23]. Heart rate should not be used as a target while titrating the dose of carvedilol. Non-invasive methods of verifying the response to carvedilol have been studied as an alternative to HVPG. In a recent prospective cohort study, the difference between baseline and post-treatment spleen stiffness measured by acoustic radiation force impulse elastography was able to predict hemodynamic response to carvedilol during primary prophylaxis with areas under the receiver operating characteristic curve over 0.8. This might become a useful tool for verifying response to carvedilol after further validation[31].

EVL

EVL was first described in 1986[32]. Ten years later, the first RCT on the efficacy of EVL for primary prophylaxis against variceal bleeding was published. In that trial, in which 62 individuals with cirrhosis and 6 with non-cirrhotic portal hypertension were included, EVL was associated with a significantly lower incidence of first variceal bleeding when compared to no treatment (8.5% *vs* 39.4%, $P < 0.01$). There was also a trend towards lower bleeding-related mortality favoring EVL (2.9% *vs* 15.2%, $P = 0.08$) [33]. In the following years, EVL also was compared with NSBBs, with evidence suggesting that the endoscopic treatment was associated with a significant lower probability of variceal bleeding, which did not translate into lower mortality[34].

EVL has replaced injection sclerotherapy as the endoscopic therapy of choice not only for the prevention of the first variceal hemorrhage, but also for the treatment of acute variceal bleeding and for secondary prophylaxis. This was due to lower rates of mortality[35], recurrent hemorrhage and adverse events[35,36] with EVL when compared to sclerotherapy. Because of mounting evidence showing an increase in mortality in subjects submitted to sclerotherapy for the prevention of variceal hemorrhage[35-38], most experts and international associations no longer recommend sclerotherapy for primary prophylaxis[3-5,39]. Moreover, there does not seem to be a role for combined EVL and sclerotherapy in order to improve variceal eradication[40]. EVL has also been compared to tissue adhesive injection for primary prophylaxis with varying results, but there is no evidence-based recommendation advocating the latter over the former, not even in Child-Pugh C patients[32]. Thus, up to this moment, EVL should be considered the best endoscopic therapy to prevent the first bleeding from medium to large esophageal varices and it is considered as a first line option for primary prophylaxis, along with NSBBs and carvedilol[3-5,39].

According to the American Association for the Study of Liver Diseases (AASLD), EVL should be performed every 2-8 wk until esophageal varices eradication is achieved. Then, first follow-up esophagogastroduodenoscopy (EGD) would be repeated in 3-6 mo and every 6-12 mo thereafter. If esophageal varices reappear during follow-up, EVL should be reinitiated[4]. We believe, however, that a shorter interval of time between each EVL session (2-4 wk) could be advisable in order to avoid bleeding from occurring while varices are not eradicated, and that first follow-up EGD should be ideally performed at 3 mo[39].

Small esophageal varices and gastroesophageal varices type 1 (GOV1) are less likely to bleed unless in the presence of red signs or advanced Child-Pugh C cirrhosis. In this scenario, EVL is not considered to be the best option[3-5,39] since it may not be technically feasible and might be more prone to induce complications[32]. Moreover, despite anecdotal reports, EVL is not considered the procedure of choice for gastric or ectopic varices, because those vessels tend to have large diameters and to lay deep in the submucosa, making them not amenable to fully entrapment under suction to perform banding. Tissue adhesive injection is instead the procedure of choice for gastric or ectopic varices[32].

OTHER STRATEGIES FOR PRIMARY PROPHYLAXIS AGAINST VARICEAL BLEEDING

As previously mentioned, NSBBs, carvedilol or EVL are first line options for primary prophylaxis against esophageal varices hemorrhage. These options are recommended in monotherapy, and the choice should take into account the status of cirrhosis (compensated or decompensated), individual preferences, local resources and expertise, contraindications, potential complications of each strategy and their costs[3-5]. Nevertheless, combining therapies in order to achieve a greater reduction in the risk of the first episode of bleeding has been examined in the literature. An RCT comparing the combination of propranolol and EVL *vs* EVL alone for primary prophylaxis failed to demonstrate differences in the incidence of bleeding or death between groups. On the other hand, combination therapy was associated with a higher number of side effects[41]. Another RCT compared primary prophylaxis with carvedilol, EVL or the combination of both in 270 individuals with cirrhosis classified as Child-Pugh B or C. In that study, the probability of the first bleeding was lower with combination therapy when compared to either carvedilol or EVL alone (8.9%, 37.8% and 22.2% respectively)[42].

Considering that pharmacological therapy has beneficial effects on other complications of portal hypertension aside from preventing variceal bleeding, the combination of pharmacological agents has also been studied in order to promote greater reductions in portal pressure. The combination of NSBBs and nitrates, for instance, has resulted in conflicting evidences. In a long-term study, 146 patients assigned to receive nadolol monotherapy or nadolol along with isosorbide mononitrate were followed up for a median of 55 mo. Cumulative risk of bleeding was 29% and 12% respectively, and authors concluded that nadolol plus isosorbide mononitrate was significantly more effective than nadolol alone in the long-term use[43]. In contrast, another RCT could not demonstrate the benefits of combination therapy. A total of 349 subjects were randomized to receive either propranolol plus placebo or propranolol plus isosorbide mononitrate, and no significant differences in 1- and 2-year actuarial probabilities of variceal bleeding were observed between the groups (monotherapy 8.3% and 10.6% respectively; combination therapy 5% and 12.5% respectively)[44].

It was also hypothesized that adding statins to carvedilol could improve its effects on portal hypertension. The rationale for this lies on the fact that statins could decrease intrahepatic vascular resistance due to a reduction in stellate cells contractility, an increase in the levels of nitric oxide and thrombomodulin and a reduction in the levels of endothelin-1. Nevertheless, in the only RCT on the addition of simvastatin to carvedilol for primary prophylaxis against variceal bleeding, there was no significant benefit of the combined prophylaxis regarding either hemodynamic or clinical outcomes[45].

Other strategies for primary prophylaxis against variceal bleeding have been studied, particularly focused on specific clinical settings. Gastric varices, for instance, are less common in patients with cirrhosis and seem to bleed less frequently, but bleeding episodes are usually more severe and difficult to control when compared to those originating in esophageal varices. No single method has yet been established and there are no robust recommendations for the prophylaxis against the first bleeding from gastric varices. Despite the lack of strong evidences, GOV1 should be approached as esophageal varices. Aside from NSBBs, which are the suggested prophylaxis for gastroesophageal varices type 2 (GOV2) and isolated gastric varices type 1 (IGV1), endoscopic variceal obliteration with cyanoacrylate and balloon occluded retrograde transvenous obliteration (BRTO) have been evaluated[3-5].

Data from a single RCT suggested that endoscopic variceal obliteration with cyanoacrylate might be more effective than NSBBs in preventing the first bleeding episode from GOV2 or IGV1, despite increasing portal pressure during the follow-up. However, the risk of thromboembolic events and increasing the size of esophageal varices represents a serious concern[46]. More data are required for stablishing recommendations in this regard[3].

BRTO is a radiological technique for obliteration of gastric varices both for prophylaxis and for treatment of bleeding. It is a much more popular modality in Asian countries than in Western ones. It requires the patency of a large gastro-renal shunt, which is accessed to delivery sclerosant or obliterative agents and coils. Preliminary data suggest that it is safe and effective for the prevention of bleeding in the subset of patients with high-risk gastric varices in connection with large shunts [47]. Transjugular intrahepatic portosystemic shunt (TIPS) is another radiological technique, which is more widely used than BRTO in the treatment of portal hypertension. However, studies specifically evaluating the efficacy of TIPS in the setting of primary prophylaxis are lacking, and there is a concern regarding the increased risk of hepatic encephalopathy induced by this technique. Currently, neither BRTO nor TIPS are recommended by AASLD for primary prophylaxis against variceal bleeding[4].

COMPARATIVE ANALYSIS

Several meta-analyses have compared NSBBs, carvedilol and EVL[7-9,48,49]. Li *et al* [48] performed a meta-analysis of 12 RCTs on this issue. Authors only included RCTs that were peer-reviewed and fully-published, and there was no evidence of significant differences between pharmacological therapy and EVL regarding the prevention of gastrointestinal bleeding, all-cause mortality or bleeding-related deaths.

In the following year, the Cochrane group published a meta-analysis, including 19 RCTs, which compared NSBBs, including propranolol (17 trials), nadolol (1 trial) and carvedilol (1 trial), to EVL. In the main analysis, the authors found a lower rate of bleeding favoring EVL, with no effect on mortality. Nevertheless, in subgroup

analyses excluding trials of lower quality, the benefit of EVL could not be confirmed [7].

In the former meta-analyses, NSBBs and carvedilol were considered together as beta-blockers. This is why another systematic review by the Cochrane group aimed at comparing NSBBs and carvedilol for both primary or secondary prophylaxis against variceal bleeding. Eleven RCTs were included in the systematic review, and 10 in the meta-analysis. Carvedilol led to a significantly greater decrease in HVPG when compared to NSBBs, but there was no evidence of a significant benefit of carvedilol regarding the achievement of a satisfactory hemodynamic response. Moreover, there was no evidence of significant difference between NSBBs and carvedilol regarding mortality, upper gastrointestinal bleeding and serious adverse events[8].

More recently, one further meta-analysis compared carvedilol to EVL. Seven RCTs met the inclusion criteria, 4 of which were focused on primary prophylaxis, while the other 3 assessed secondary prophylaxis. Considering studies on primary prophylaxis, there was no evidence of difference between carvedilol and EVL regarding the incidence of the first bleeding episode, bleeding-related mortality or all-cause mortality. The risk of side effects, though, was significantly higher with carvedilol [risk ratio (RR): 4.18, 95% confidence interval (CI): 2.19-7.95]. On the other hand, EVL seemed to be associated with more severe complications than carvedilol[49].

The most relevant and comprehensive comparative study on this matter, however, is a network meta-analysis, which included 32 RCTs and evaluated NSBBs, carvedilol, isosorbide mononitrate, EVL and their combinations in the primary prophylaxis of variceal bleeding among individuals with cirrhosis. Regarding mortality (the primary outcome), NSBBs in monotherapy [odds ratio (OR): 0.70, 95%CI: 0.49-1.00] or in combination with EVL (OR: 0.49, 95%CI: 0.23-1.02) or with isosorbide mononitrate (OR: 0.44, 95%CI: 0.21-0.93) were significantly better than placebo or no intervention, but none of the evaluated therapies was significantly superior to another active treatment. Concerning the prevention of first variceal bleeding, EVL was significantly superior to NSBBs (OR: 0.51, 95%CI: 0.34-0.76), any active treatment was significantly better than isosorbide mononitrate alone, and any active treatment was significantly superior to placebo, except for isosorbide mononitrate alone or in combination with NSBBs[9].

It is important to highlight that the benefits of NSBBs regarding mortality might probably result not only from the prevention of variceal bleeding, but also from the prevention of other life-threatening complications of cirrhosis and maybe particularly those related to ascites[21]. Such advantages are especially noticed in those subjects achieving hemodynamic response to NSBBs[50]. Since EVL does not act on the pathophysiology of portal hypertension, but directly on its consequence (esophageal varices), it is not reasonable to expect that it could prevent other complications of cirrhosis. In this context, the combination of NSBBs and EVL might be a quite interesting alternative, since it would add the systemic effects of these drugs to the local effects of the endoscopic therapy. Nevertheless, it must be stressed that there is no recommendation for this association at the moment.

Evidences are still scarce regarding the best approach for patients with intolerance or no hemodynamic response to NSBBs. Carvedilol seems to be more potent and better tolerated than other NSBBs and might be considered as an alternative for individuals both intolerant or unresponsive to these drugs. In these circumstances or in patients also intolerant or unresponsive to carvedilol, EVL could be a good option[51]. In this context, Reiberger *et al*[52] proposed an interesting strategy, using NSBBs, carvedilol or EVL sequentially according to the hemodynamic response to the previous treatment. The authors evaluated a cohort of 104 individuals with cirrhosis who were initially treated with propranolol. Ten patients were intolerant to propranolol, while 37 achieved a satisfactory hemodynamic response. The 57 patients who were propranolol non-responders and 10 individuals who were intolerant to the drug received carvedilol, to which 38 were hemodynamic responders. Finally, the 29 patients unresponsive to either propranolol or carvedilol were submitted to EVL. In this study, carvedilol was superior to propranolol in decreasing HVPG (-19% *vs* -12% respectively, $P < 0.001$). Moreover, there was no additional benefit when the dose of carvedilol was increased over 12.5 mg/d. First variceal bleeding occurred in 11% of patients under propranolol, in 8% of those receiving carvedilol and in 24% of the individuals submitted to EVL ($P = 0.0429$). Transplant-free survival was higher with propranolol or carvedilol than with EVL ($P = 0.0455$). Hemodynamic responders to either of these drugs also developed less ascites than individuals requiring EVL ($P = 0.031$). Despite worse outcomes among patients undergoing EVL, it must be highlighted that only individuals unresponsive to propranolol and carvedilol were treated with EVL, so that it is likely that this was a more severely ill population[52].

CONCLUSION

Primary prophylaxis against variceal bleeding is of the utmost importance for patients with cirrhosis and high-risk varices. Currently recommended strategies include NSBBs, carvedilol or EVL. While EVL might be superior to pharmacological therapy regarding the prevention of the first bleeding episode, pharmacological therapy seems to prevent different complications of liver disease and probably play a more prominent role concerning mortality reduction. The sequential use of these alternatives or their combination should be further studied so that patients might benefit from the best aspects of each strategy.

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MINIREVIEWS

Large polyps: Pearls for the referring and receiving endoscopist

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Abstract

Polyps are precursors to colorectal cancer, the third most common cancer in the United States. Large polyps, *i.e.*,, those with a size ≥ 20 mm, are more likely to harbor cancer. Colonic polyps can be removed through various techniques, with the goal to completely resect and prevent colorectal cancer; however, the management of large polyps can be relatively complex and challenging. Such polyps are generally more difficult to remove en bloc with conventional methods, and depending on level of expertise, may consequently be resected piecemeal, leading to an increased rate of incomplete removal and thus polyp recurrence. To effectively manage large polyps, endoscopists should be able to: (1) Evaluate the polyp for characteristics which predict high difficulty of resection or incomplete removal; (2) Determine the optimal resection technique (*e.g.*, snare polypectomy, endoscopic mucosal resection, endoscopic submucosal dissection, *etc.*); and (3) Recognize when to refer to colleagues with greater expertise. This review covers important considerations in this regard for referring and receiving endoscopists and methods to best manage large colonic polyps.

Key Words: Adenoma; Endoscopic mucosal resection; Endoscopic tattoo; Colorectal cancer; Polypectomy

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Core Tip: Large polyps, often defined as ≥ 20 mm in size, are generally more challenging to resect than smaller polyps with regard to both difficulty of complete removal and risk of adverse events. To effectively manage large polyps, endoscopists should be able to evaluate them for characteristics which may increase the difficulty of endoscopic resection, determine the optimal resection technique, and recognize when to refer to colleagues for more advanced approaches. Herein, we review important considerations and methods to best manage large colonic polyps.

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INTRODUCTION

Colonic polyps have a risk of developing into colorectal cancer (CRC), the third most common cause of cancer-related deaths in the United States[1]. Prior studies have demonstrated that the removal of adenomatous polyps during a colonoscopy is associated with a significant reduction in CRC-related death[2,3]. However, achieving complete resection of a polyp can be challenging, especially with larger polyps. Previous studies have reported that 70%-90% of CRCs are preventable with routine screening colonoscopy and polypectomy[3]; however, 7%-9% are reported to occur despite being up-to-date with colonoscopy[4]. This subset of CRCs is thought to be likely due to either missed polyps or incompletely removed polyps.

The risk of incomplete polyp removal has been reported to increase with increasing polyp size[5]. "Large polyps" are generally defined as being ≥ 20 mm in size (though other cut offs may also be used) and carry a greater likelihood of underlying advanced dysplasia and carcinoma[6]. Indeed, the term "advanced adenoma"[7] has been introduced to stress the clinical and histopathological significance of polyps ≥ 10 mm in size. With advances in polyp removal techniques, management of large polyps has shifted away from surgery and towards endoscopic resection, using novel methods like endoscopic submucosal dissection (ESD) and endoscopic mucosal resection (EMR). In this review, we expound key considerations and techniques to best manage large colonic polyps from the perspective of both the referring and the receiving endoscopist.

INITIAL EVALUATION OF A COLONIC POLYP

Inspection goals and components

When a polyp is detected, a decision must be made whether endoscopic resection is possible[8,9], and if so, what the best method of resection may be (Figure 1). Certain features, including large size, can pose a technical challenge for complete resection and may indicate a need for advanced endoscopic techniques, as discussed in forthcoming sections, or surgical resection[10]. In addition to polyp size, features including morphology, location, and associated local features are all important determinants in gauging endoscopic resectability[10]. For instance, pedunculated polyps tend to be, on average, easier to grasp (along the peduncle or "stalk") and resect as opposed to sessile polyps[11,12]. Polyp location also influences resectability, as right-sided lesions tend to be more difficult to resect due to the presence of colonic folds which can impede visualization and maneuverability, increasing the risk of incomplete removal, among other factors[13]. Surface characteristics, discussed in the next section, can also predict submucosal invasion, which may prevent safe resection. Invasive cancers are associated with polyps that fail to lift with submucosal injection, a non-granular surface, depressed subtype, firmness, and redness[14-16]. However, non-lifting does not always predict invasion, as a failure to lift can also be seen in previously biopsied or partially resected polyps with associated tissue fibrosis. Finally, associated local

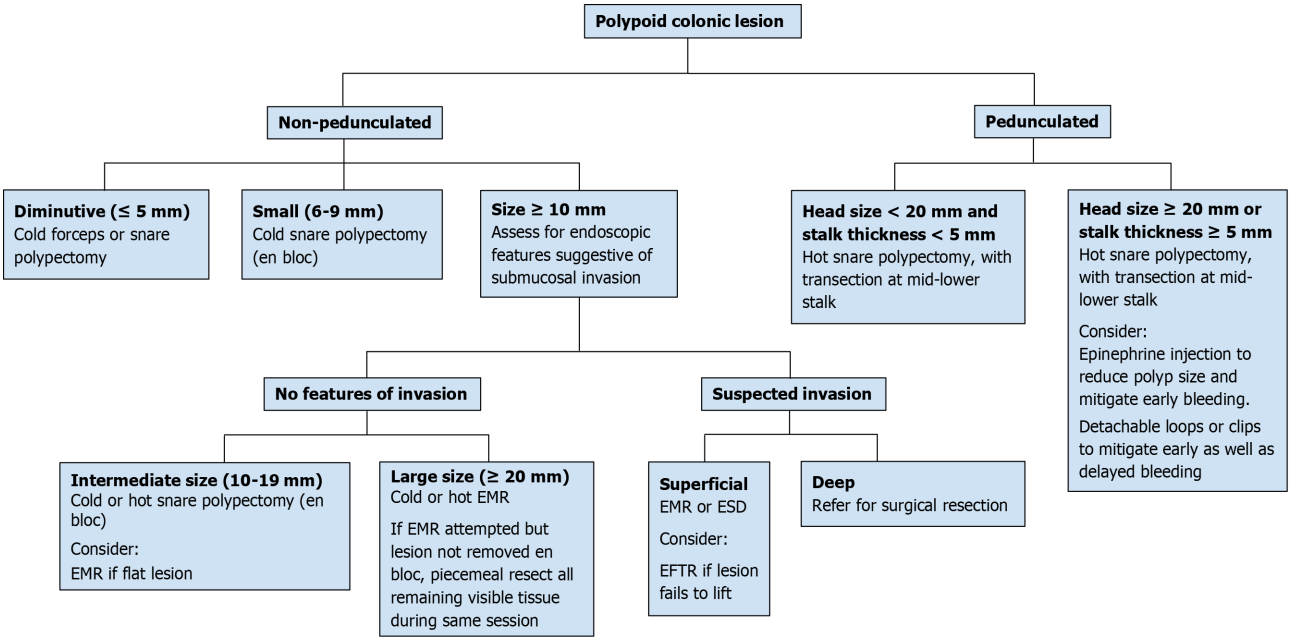

Figure 1 Polyp management algorithm based on morphology, size, and suspicion of submucosal invasion.

features can impact endoscopic resection; for instance, severe refractory colitis can impede large polyp resection and potentially result in the need for a colectomy[17]. Endoscopic ultrasound (EUS) can be used to evaluate rectal polyps (in particular T stage) and determine feasibility of endoscopic resection when the endoscopic appearance is concerning for possible deep invasion[18,19]. When EUS is not available or feasible (*e.g.,* polyps proximal to the rectosigmoid), cross-sectional imaging such as magnetic resonance or computed tomography can be considered.

Size, morphology, site, access (SMSA) is a scoring system used to predict the difficulty encountered during polyp resection[20]. The scoring is as follows: size (1-9 points), morphology (1-3 points), site (1-2 points), and access (1-3 points). Based on the total score, polyps are classified as Level 1 (4-5), Level 2 (6-9), Level 3 (10-12), or Level 4 (> 12). This system provides an objective assessment of the complexity of a polyp with higher scores suggesting increased complexity. Endoscopists should be aware of complex (and usually large) polyps scored under this system and consider the level of expertise needed to deal with these difficult polyps, referring the patient in necessary cases. Endoscopically unresectable polyps are generally referred to surgery, and are often managed with segmental colectomy, though studies have reported success using hybrid laparoendoscopic approaches *i.e.,,* combined endoscopic laparoscopic surgery (CELS), to avoid colon resection[21,22].

Polyp classifications systems

In addition to the features mentioned thus far, critically important here is determining whether a polyp is benign or premalignant, and within the latter, the degree of dysplasia that may be harbored within. There are several validated systems that can help to characterize and classify polyps in this regard, including the Paris classification [23], the narrow-band imaging international colorectal endoscopic (NICE) classification[24], and the Kudo pit pattern classification[25]. The Paris classification classifies polyps as pedunculated (1p), sessile (1s), flat (IIa, IIb, IIc), or ulcerated (III) [24]. It also classifies surface morphology as granular or non-granular for non-pedunculated polyps (1s and II). However, recent studies have questioned the validity of the Paris classification because of interobserver variability, recommending the system not be used for routine practice[26,27]. The NICE classification classifies polyps as hyperplastic or sessile serrated polyps (SSP) (type 1), conventional adenomas (type 2), or deep submucosal invasive cancer (type 3) based on color, associated vessels, and surface patterns[24]. The Kudo classification classifies polyps based on mucosal surface analysis. Also called the pit-pattern system, it requires magnification during colonoscopy to evaluate the pit pattern of polyps. This classification system classifies pit patterns as round (Type I), papillary/stellar (Type II), tubular or small round (Type III-S), large tubular or round (Type III-L), gyrus/branch-like (Type IV), non-structured/amorphous (Type V-I), and decrease of amorphous pits (Type V-N). Type I

and II polyps are considered benign while types III-V are considered to show neoplastic and malignant changes[28]. Despite the existence of the above classification systems, it is important to note that there is significant variability and agreement as to what the optimal method of classifying polyps should be.

Artificial intelligence and polyp detection

The emergence of artificial intelligence (AI) applications has direct implications in colonoscopy practices. The use of computer-aided detection (CADe) software has been demonstrated to decrease the polyp miss rate[29], especially for non-polypoid lesions in the right colon. AI has also been used to characterize polyps, also known as colonoscopy practice-polyp characterization (CADx). This can improve the accuracy of polyp diagnosis and reduce unnecessary resection of non-dysplastic polyps[29]. Although data on the outcomes of AI for polyp detection are evolving rapidly, the few completed studies have demonstrated a significant increase in the detection of adenomas and polyps[30,31]. However, the detection of more polyps does not necessarily improve outcomes; one study found that non-advanced adenomas were detected to a greater extent using AI-colonoscopies while identification of advanced adenomas was not substantially improved[32]. More research is needed to determine the value of AI systems in polyp detection and characterization.

CONSIDERATIONS FOR THE REFERRING ENDOSCOPIST

Provider experience

Studies have shown that incomplete polyp removal in daily clinical practice, especially in the case of large polyps, can contribute to future interval cancers[33]. Consequently, appropriate technique and complete resection of large colonic polyps is essential in preventing CRC (Figure 1). Incomplete removal renders future endoscopic resection more challenging; therefore, an endoscopist should aim for complete resection on the first attempt. For polyps ≥ 20 mm in size, the United States Multi-Society Task Force (USMSTF) recommends that an endoscopist be experienced in advanced polyp resection techniques to ensure complete resection[9]. Although polyps that are endoscopically resectable are occasionally sent for surgery, studies show that only about 5-10% of patients subsequently require surgery if they undergo endoscopic resection first[34]. Knowing your expertise and comfort level is particularly important on a variety of levels in the case of polyps that may be challenging to resect; for instance, it is relevant to ensuring the best outcome for the patient, peace of mind for the performing provider, and to avoid potential medical professional liability. Referring to a more experienced provider for a complete resection is thus generally recommended over attempting to complete a polypectomy but failing to achieve complete resection, especially if thermal energy is applied in the process and/or when the *a priori* probability of incomplete removal seems high. In addition, biopsies of the polyp should be performed with caution so as to avoid scarring and complicating future endoscopic resection. If a biopsy is needed, the biopsy should be performed cold and avoid flat areas of the lesion[35].

Tattoo placement

If a polyp is deemed unresectable by a provider, it is often advised to tattoo so it can be easily recognized by the receiving provider. Currently, India Ink, a compound known commercially as "Spot Ex," is most commonly used for endoscopic tattooing [36]. With respect to tattoo location and number of tattoos, best practice depends in large part on whether the polyp is planned for referral to a surgeon or to an advanced endoscopist, as shown in Figure 2[37,38]. Generally speaking, a tattoo should be placed a) immediately distal to the polyp and circumferentially in multiple quadrants to facilitate intraoperative visualization when planning to refer for surgical resection or b) in one quadrant 3-5 cm distal to the polyp, with care to not inject into or under the polyp, when planning to refer for advanced endoscopic resection. Tattoo placement may not be necessary if the polyp is in the cecum or distal rectum, as these locations are typically easily identifiable on future examinations, but this may vary based on individual (*e.g.*, anatomical) and institutional (*e.g.*, surgeon or advanced endoscopist preference) factors[9]. Irrespective of such factors, photodocumentation and clear description regarding tattoo placement are critical[39,40].

With respect to tattoo injection technique, a few options exist. The "bleb" method is one which is considered reliable for the placement of tattoos[41], wherein, 0.5 to 1.0 mL of saline is placed into the submucosa, followed by a needle inserted into the saline

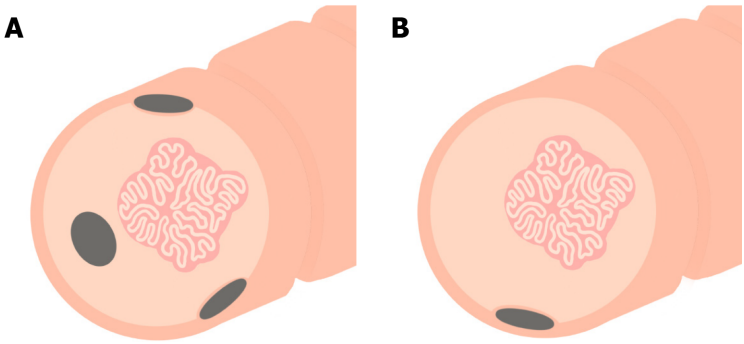

Figure 2 Guidelines for placing an endoscopic tattoo prior to resection. As an overarching principle, the location of the tattoo relative to a polyp should be guided by anatomical factors and institutional practices in addition to being well-described and photodocumented in the procedure report. A: When tattooing with the intent of referral for surgical resection, the tattoo should generally be placed immediately distal to the polyp and circumferentially in multiple quadrants to facilitate intraoperative visualization; B: When tattooing with the intent of referral for advanced endoscopic resection, tattoo should not be injected into or under the polyp, and care should be taken to not inject an excess volume of ink, as this may spread submucosally toward the polyp and subsequently complicate resection; a single tattoo, 3-5 cm distal to the polyp (or one haustral fold distal), is generally appropriate.

bleb to inject the tattoo agent. The bleb method ensures that the tattoo only enters the submucosal space and not into extracolonic tissue. A second method involves directly injecting the tattoo into the submucosa and lifting the needle toward the center of the lumen, although this technique requires greater expertise[36]. Of note, analogous to polypectomy snares, different length and caliber injection needles are available, the appropriate choice of which may, depending on polyp location and other considerations, best facilitate tattoo placement[42-44]; for instance, a shorter, smaller caliber needle may be opted for when tattooing a right colonic polyp in a coagulopathic patient (as opposed to a standard/larger length and caliber needle for a rectal polyp).

Adverse events with tattoo placement

Adverse events (AEs) associated with endoscopic tattooing, albeit rare, have been reported. For example, tattooing can cause submucosal fibrosis (Figure 3) and consequent muscle injury during future endoscopic resection if the tattoo ink spreads underneath the polyp, *e.g.*, if injection is performed too close to or into the polyp or if an excess volume of ink is injected (which can later dissipate laterally to involve the submucosa below the polyp)[40]. Thus, when a polyp is planned for referral for endoscopic resection, the closer the tattoo is to the polyp, the less tattoo volume should be used. Reports of inflammatory responses, localized necrosis from an inflammatory pseudotumor, and rectus muscle abscess have also been described[45-47]. These potential AEs should be taken into account when placing an endoscopic tattoo and accordingly established techniques should be followed.

THE PERFORMING ENDOSCOPIST: RESECTION TECHNIQUES AND CONSIDERATIONS

The endoscopic resection technique that is used largely depends on the morphology of the polyp, in particular its size and whether it is pedunculated or not, as discussed below[9].

Pedunculated polyps

Large polyps can be pedunculated or non-pedunculated. For pedunculated polyps ≥ 10 mm in size, hot snare polypectomy (HSP), in which electrocoagulation is used for resection, is suggested[9]. For larger pedunculated polyps, epinephrine injection into the head or stalk can also be considered to reduce the polyp size and make resection easier[48]. Other strategies include using a detachable loop or placing clips at the polyp stalk before resection. Cold snare polypectomy (CSP) may also be used for resection and has been reported to have a lower rate of post-polypectomy bleeding [49]; however, the rate of complete resection may be higher with HSP compared with CSP when resecting large pedunculated polyps[50].

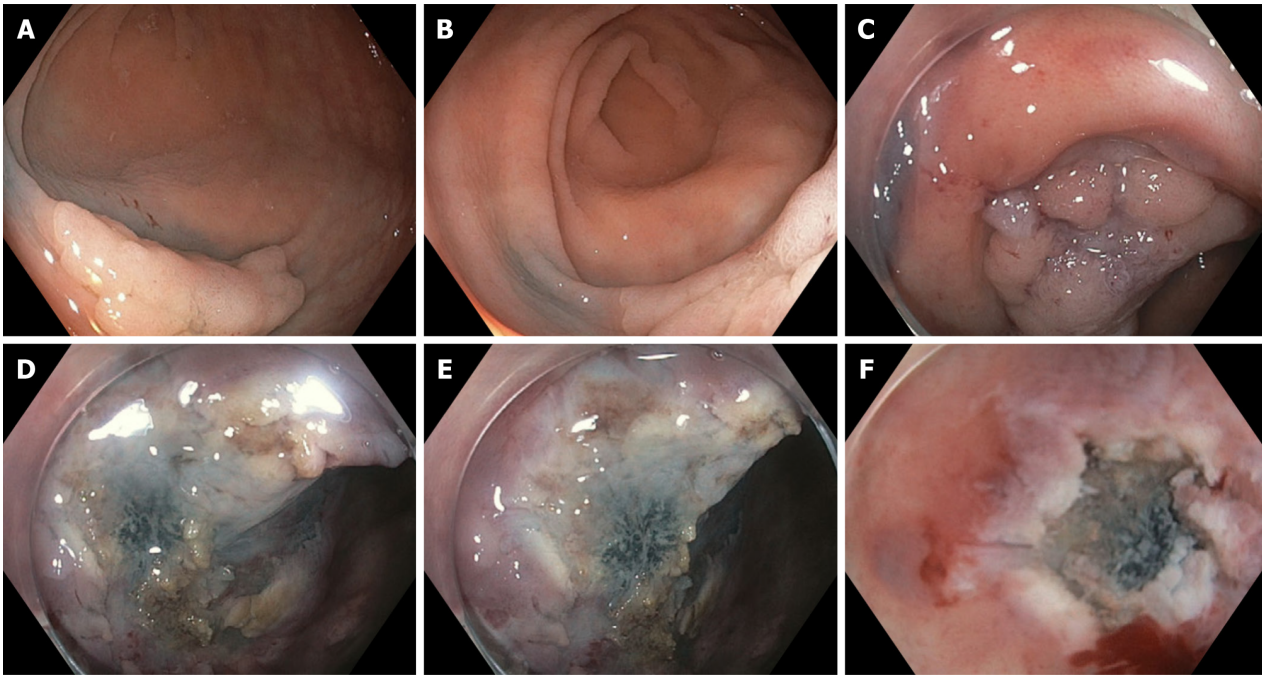

Figure 3 Endoscopic mucosal resection complicated by prior endoscopic tattooing. A and B: Presence of previously placed tattoo ink proximal and lateral to a large (25 mm) sessile polyp, suggestive of injection being made too close to (or under) the polyp and/or an excess volume of ink injected; C: Suboptimal lifting after 10 cc of saline and 13 cc of submucosal injectable composition as a result of submucosal fibrosis from the prior tattoo, complicating en bloc endoscopic mucosal resection; D, E and F: Tattoo ink and associated tissue fibrosis can be seen infiltrating the submucosa directly under the polyp.

Non-pedunculated polyps

Endoscopic mucosal resection: The majority of non-pedunculated (*i.e.*, sessile) polyps can be removed by endoscopic mucosal resection (EMR). In this technique, fluid is injected submucosally to lift the polyp and facilitate resection. Many variations of this technique have been developed, such as hot snare EMR, cold snare EMR, and underwater EMR.

In the hot snare EMR (HS-EMR) technique, the underlying submucosa is first injected with a contrast dye, such as methylene blue, to achieve lifting of the polyp, which allows optimal placement of a snare to grab the polyp away from the mucosa, followed by resection with application of electrocautery. Polyps < 20 mm in size can be removed entirely (en bloc resection), while larger polyps can be removed in segments (piecemeal resection). Because HS-EMR utilizes electrocautery, it can minimize intraprocedural bleeding of cut tissue due to its coagulation effect and also destroy the polyp margins, thus leading to a lower recurrence rate[9]. However, the use of electrocautery is also associated with a higher risk of post-procedural bleeding and perforation, compared to the cold snare technique[51].

Cold snare EMR (CS-EMR) allows for large polyp resection without use of electrocautery. In this variation of EMR, the submucosa may be injected to raise the polyp, similar to HS-EMR, after which the snare is then opened slightly larger than the area of the polyp (resecting some normal tissue margin) to remove it en bloc or piecemeal. As previously mentioned, this technique is associated with lower rates of post-procedural bleeding and perforation compared to HS-EMR. Studies of CS-EMR have shown low rates of polyp recurrence and AEs with excellent resection rates[52-54]. Although HS-EMR is currently the standard of care in endoscopic resections, CS-EMR represents an equally effective and safe resection method for large polyps.

Given that complete en bloc resection rates decrease in polyps ≥ 10 mm using traditional EMR techniques (which in turn increases the rate of recurrence), underwater EMR (UEMR) has been proposed as an alternative effective strategy to resect large polyps[18,19]. This method avoids the use of submucosal injection by aspirating gas and instilling water into the colonic lumen, which raises the mucosal pathology (polyp) away from the underlying submucosa, allowing safer and complete resection of the polyp. Especially useful in the case of large polyps, UEMR has shown significantly increased rates of R0 resections for polyps 10-20 mm in size without increasing the rate of AEs[55]. This variant of EMR represents a viable alternative to traditional resection techniques for large polyps that are difficult to remove

completely.

Endoscopic submucosal dissection: Endoscopic submucosal dissection (ESD) allows for the complete removal of polyps too large for EMR (≥ 20 mm in size) and/or that are strongly suspicious for cancer. ESD is also utilized in cases with suspected submucosal invasion, local early carcinoma, or laterally spreading polyps/tumors[56]. Studies have demonstrated that ESD may have better outcomes for larger polyps, as EMR often requires piecemeal removal which has an increased rate of recurrence (about 20%)[57].

In the ESD technique, the area underneath the polyp is first injected to lift the polyp, followed by creation of an incision into the mucosa using an ESD knife. The submucosal edges are trimmed to allow access to the submucosal plane where the dissection is performed (Figure 4), resulting in an en bloc resection of large polyps/tumors. While ESD has excellent rates of en bloc resection, it has higher rates of AEs compared to EMR, including perforation, bleeding, and hospitalization related to the procedure[58]. Low-voltage coagulation ("soft" ESD) can be performed after resecting the polyp to reduce the risk of post-resection bleeding[59].

Endoscopic full-thickness resection: Endoscopic full-thickness resection (EFTR) is a novel approach which enables all layers of the colon wall to be removed[60,61]. This technique is often used for polyps < 30 mm in size which either fail to lift after submucosal injection or that are difficult to resect with conventional EMR techniques. Multiple studies have shown the efficacy and safety of EFTR[59], in both animal models and human patients, with excellent resection rates for non-lifting adenomas and low rates of AEs (about 14%)[62]. The technique uses a full-thickness resection device (FTRD®), which has been shown to enable complete resection of polyps beneath the mucosa[63]. At this time, EFTR is not widely practiced as few endoscopists are trained in this technique.

Post-resection elements

Endoscopic clipping: Bleeding, the most common AE after EMR, is more likely to occur in patients undergoing resection of large polyps, polyps ≥ 10 mm with a thick stalk, right-sided polyps, and in patients on anticoagulation/antiplatelet agents or with comorbid conditions that increase the risk of bleeding[64,65]. Clipping can be used to effectively stop or prevent bleeding through mechanical pressure. In one study, endoscopic clipping significantly reduced the risk of bleeding after resection of large polyps (≥ 20 mm), with 7.6% of subjects without clipping having bleeding compared to 4.3% with clipping[66]. In addition, clip placement is often utilized to close post-polypectomy mucosal defects[67].

Surveillance: After complete resection of large polyps, close surveillance is recommended to detect disease recurrence and/or metachronous colorectal polyps. Surveillance is important for early detection of asymptomatic and resectable recurrences, which increases patients' chances for curative therapy[68]. The USMSTF recommends that colonoscopy should be performed within 1 year after resection to look for metachronous polyps. If this examination is normal, a subsequent examination should be performed after 3 years, and then 5 years (if the second examination is also normal). However, shorter examination intervals may also be used if additional polyps are found[68]. Shorter examinations are also favored in the case of piecemeal resection of a large polyp because of the significantly increased risk of residual polyp tissue and recurrence. Thus, a period of 2-6 mo is typically the recommended interval for surveillance colonoscopy in such cases[69].

CONCLUSION

As endoscopic resection techniques have evolved, there has been a shift in the management of large colonic polyps from being referred for colon surgery to endoscopic resection. Effective resection of these large polyps can be complex, but success has been documented using methods like EMR and ESD. Endoscopists should be comfortable at recognizing large colonic polyps through classification systems such as the NICE or Paris classification, and these polyps should be resected by endoscopists experienced with advanced resection techniques. Standardized practices coupled with clear communication can help ensure optimal outcomes.

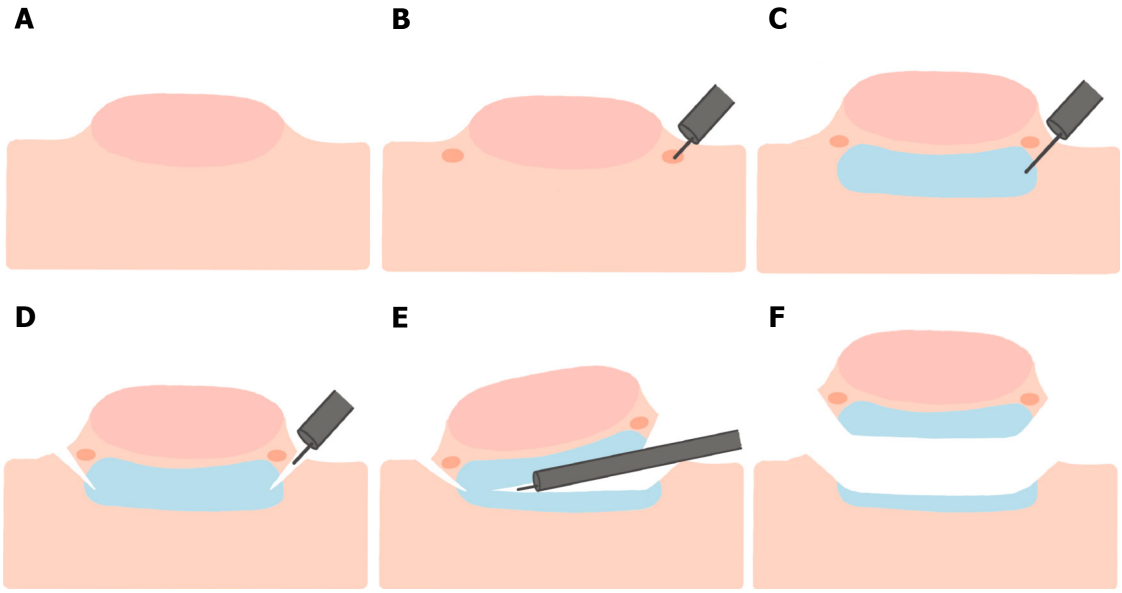

Figure 4 Key steps in performing endoscopic submucosal dissection. A: A large polyp is encountered and deemed to be endoscopically resectable; B: Markings are made around the polyp to delineate the borders; C: The polyp is raised with a submucosal injection solution; D: Incision is made into the submucosa using an endoscopic submucosal dissection (ESD) knife; E: The ESD knife is subsequently used to dissect the polyp in conjunction with serial additional injections; F: The polyp is removed en bloc.

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ORIGINAL ARTICLE

Retrospective Study

Role of endoscopic ultrasound guided fine needle aspiration/biopsy in the evaluation of intra-abdominal lymphadenopathy due to tuberculosis

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Author contributions: Priya SK helped in subject recruitment and data entry of the study; Rao B H and Nair P were involved with data analysis, interpretation and drafted the manuscript; George A and Sathyapalan DT gave initial insight related to the pathology and management of TB; Koshy AK and Venu RP revised the article critically for important intellectual content.

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Abstract

BACKGROUND

Intra-abdominal lymphadenopathy due to tuberculosis (TB) poses a diagnostic challenge due to difficulty in tissue acquisition. Although endoscopic ultrasound guided fine needle aspiration/biopsy (EUS-FNA/B) has shown promise in the evaluation of mediastinal lymph nodes, its role in the evaluation of intra-abdominal lymphadenopathy is not clear.

AIM

To assess the role of EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy due to TB.

METHODS

This was a retrospective study where patients with intra-abdominal lymphadenopathy who underwent evaluation with EUS-FNA/B were included. TB was diagnosed if the patient had any one of the following: (1) Positive acid fast bacilli (AFB) stain/TB GeneXpert/TB-polymerase chain reaction/AFB culture of tissue sample; and (2) Positive Mantoux test and response to anti-tubercular therapy. EUS-FNA reports, clinical reports and imaging characteristics of patients were recorded for a detailed analysis of patients with TB.

RESULTS

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Data sharing statement: No additional data are available.

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Specialty type: Gastroenterology and hepatology

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Peer-review report's scientific quality classification
Grade A (Excellent): 0
Grade B (Very good): B
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Grade E (Poor): 0

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A total of 149 patients underwent an EUS-FNA/B from lymph nodes (mean age 51 ± 17 years, M:F = 1.2). Benign inflammatory reactive changes were seen in 45 patients (30.2%), while 54 patients (36.2%) showed granulomatous inflammation with/without caseation. Among these, 51 patients (94.4%) were confirmed to have TB as *per* pre-defined criteria. Patients with TB were more likely to have hypoechoic and matted nodes [40 patients (67.7%)]. EUS-FNA/B was found to have a sensitivity and specificity of 86% and 93% respectively, with a diagnostic accuracy of 88% in the evaluation of intra-abdominal lymphadenopathy due to TB.

CONCLUSION
EUS-FNA/B has a high diagnostic yield with a good sensitivity and specificity in the evaluation of intra-abdominal lymphadenopathy due to TB. However, the validity of these findings in populations with low prevalence of TB needs further evaluation.

Key Words: Endoscopic ultrasound; Lymph nodes; Tuberculosis; Mesenteric; Intra-abdominal

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Core Tip: Intra-abdominal lymphadenopathy due to tuberculosis (TB) poses a significant diagnostic challenge primarily due to difficulty in tissue acquisition. Endoscopic ultrasound guided fine needle aspiration/biopsy (EUS-FNA/B) has shown promise in the evaluation of TB presenting with mediastinal lymph nodes; however, its role in intra-abdominal lymphadenopathy due to TB remains unclear. In this study, a large cohort of patients who underwent EUS-FNA/B were studied. EUS-FNA/B was found to have a sensitivity and specificity of 86% and 93%, respectively, with a high diagnostic accuracy of 88% in the evaluation of intra-abdominal lymphadenitis due to TB. This study provides valuable data on the pivotal role of EUS-FNA/B in the evaluation of this difficult sub-group of patients. However, the validity of these findings in populations with low prevalence of TB needs further evaluation.

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INTRODUCTION

Intra-abdominal lymphadenopathy due to tuberculosis (TB) is a common clinical entity in regions endemic for the disease. The presence of concomitant lung parenchymal findings can aid in the diagnosis of these patients[1]. However, isolated mesenteric lymphadenopathy usually poses a significant diagnostic challenge[1-3]. Multiple factors including clinical scenario, number, size and imaging characteristics have been described that can help in the differential diagnosis of patients with intra-abdominal lymphadenopathy[4]. Moreover, a positive Mantoux test and/or adenopathy with peripheral rim enhancement with a low density center is supportive for TB at best with fungal infections, atypical mycobacteria and sarcoidosis also presenting with a similar clinical picture[5,6]. The causes of mesenteric lymphadenopathy other than TB include sarcoidosis, lymphoma, metastatic deposits from other malignancies and other rare infectious causes[7].

Tissue acquisition is usually essential for establishing the diagnosis in patients with intra-abdominal lymphadenopathy. Earlier, tissue acquisition was accomplished by computed tomography guided/laparoscopy assisted biopsy. Currently, these modalities have largely been replaced by endoscopic ultrasound guided fine needle aspiration/ biopsy (EUS-FNA/B) over the last decade owing to superior reliability and safety profile and is now the modality of choice in the evaluation of intra-

abdominal and mediastinal lymphadenopathy. EUS has been reported to be capable of imaging and enabling tissue sampling from nodes as small as 5 mm[8]. It has also been proven to be safe for tissue acquisition from lymph nodes with a reported complication rate of less than 0.5%[9].

EUS-FNA/B has been shown to be invaluable in the diagnosis of malignancy (primary/metastatic) during evaluation of intra-abdominal lymphadenopathy. There is also a growing body of evidence that highlights the role of EUS-FNA/B in the manage-ment of mediastinal lymphadenopathy[4-6,10]. However, there is no clarity on the efficacy of EUS-FNA in the evaluation of intra-abdominal lymphadenopathy due to TB. In this study, we analyzed the patients who underwent EUS-FNA for intra-abdominal lymphadenopathy, at a high-volume tertiary care center and assessed the diagnostic yield of EUS-FNA for TB in these patients.

MATERIALS AND METHODS

This was a single center retrospective study conducted in a large tertiary care hospital where patients with intra-abdominal lymphadenopathy referred for EUS-FNA/B between January 1, 2015 and December 31, 2019 were included. Institutional ethics committee clearance for data acquisition and analysis were obtained. All relevant data such as patient demographics (age, gender, comorbidities), procedure details (type of needle, number of passes, size of nodes, echogenicity) and post-procedure complications were noted. On retrospective analysis, TB was diagnosed if the patient had any one of the following: (1) Positive acid fast bacilli (AFB) staining of the tissue sample/positive TB GeneXpert of the tissue sample/positive TB-polymerase chain reaction (PCR) of the tissue sample; (2) Granulomas with caseation; (3) Positive AFB culture; and (4) Positive Mantoux test and an adequate response to anti-tubercular therapy (ATT). EUS-FNA reports, demographics and imaging characteristics of patients with TB were studied in detail to determine the diagnostic yield of the procedure.

EUS procedure

All EUS-FNA procedures were performed by an experienced endosonographer. Institutional protocol was followed wherein procedures were performed under moderate or deep sedation which was provided by a dedicated anaesthetist. All patients received prophylactic antibiotics prior to the procedure as *per* protocol. Initial diagnostic endosonographic evaluation was carried out using a linear array echoendoscope (Olympus GFUCT180, Tokyo, Japan) and upon identification of the lymph nodes, relevant imaging characteristics were noted. Only EUS-FNA/B results of abdominal lymph nodes were analyzed in the study. All procedures were performed with Rapid On-Site Evaluation (ROSE) by a dedicated cytopathologist. Depending upon the site of the nodes, gastric or duodenal approaches were considered. A 22 gauge needle was used for all procedures. A FNA needle (22G Cook EchoTip®, 22G Olympus EZ-shot 3) was used in most cases; while a fine needle biopsy needle (22G Boston Scientific Acquire™) was used in only 10 patients. The needle was passed *via* the instrument channel and the node was targeted under sonographic guidance. The sharp tip of the needle punctured the node after unlocking the needle apparatus and multiple passes were made into the target node. Suctioning was reserved for cases where the initial few passes were inadequate as assessed by the on-site cytopathologist. The needle was passed multiple times into the node typically for 20-30 s each pass while continuously adjusting the position of the needle in a "fanning" pattern to maximize tissue volume. The needle was then removed from the endoscope, and the tissue was prepared for pathological examination.

Pathological examination

All the FNA material was placed onto glass slides and smears were made. Smears for ROSE were fixed in 80% isopropyl alcohol which was then rapidly stained with 1% Toluidine blue. The on-site cytopathologist evaluated the adequacy of tissue in each pass and also gave a preliminary opinion on pathological changes on the slide. The number of passes were determined on the basis of this information until a maximum of 5 passes were made. When staining was complete, all EUS-FNA specimens were evaluated for cytological diagnosis and cellular preservation by a pathologist. These slides were subsequently stained with Papanicolaou stain in the cytology laboratory for further evaluation. Visible core tissue was placed in formalin-alcohol mixture (formalin and 80% isopropyl alcohol in 1:1 ratio) and subsequently paraffin embedded to produce cell blocks. Sections from the cell blocks were stained with hematoxylin

and eosin. The slides were meticulously observed to arrive at a final diagnosis.

On pathological examination, reactive nodes will exhibit a polymorphous lymphoid population including mature lymphocytes, germinal center cells and tingible body macrophages. Granulomatous inflammation was diagnosed when there were collections of epithelioid histiocytes forming an epithelioid cell granuloma with or without necrosis(Figure 1). In such cases, further sampling was performed with microbiological tests such as AFB staining, GeneXpert and TB culture. Diagnosis of lymphoma was applicable when the lymphoid cells were monomorphic populations of atypical lymphoid cells. Secondary malignant deposits in the node were identified when tumor cells were admixed with a reactive lymphoid population.

Diagnosis and follow-up

Patients with features of lymphoma or metastatic malignancy were treated with an appropriate chemotherapy regimen as *per* hospital protocol by the oncologist. Patients with TB as defined above, received ATT for 6 mo. Patients with sarcoidosis were treated with steroids. All patients were followed up 15 d after the procedure to discuss biopsy findings and treatment plan. All patients were followed up clinically every month for symptomatic improvement or drug side effects.

Statistical analysis

Statistical analysis was carried out using IBM SPSS software version 20.0. The pathology reports were correlated with clinical diagnosis in order to determine the diagnostic validity of EUS-FNA in the evaluation of intra-abdominal lymph nodes resulting from TB. A descriptive analysis of all patients with TB was carried out. Comparisons of means for continuous variables were carried out using the independent 2-sample *t* test and Mann Whitney U tests for parametric and non-parametric variables, respectively. Categorical variables were analyzed using Chi square test/Fisher's Exact test. A $P < 0.05$ was considered statistically significant.

RESULTS

EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy

A total of 149 patients underwent EUS-FNA/B of lymph nodes. The mean age of these patients was 51 ± 17 years with a male to female ratio of 1.2. The most common clinical presentation was fever of unknown origin [78 patients (52.3%)], whereas, 48 patients (32.2%) underwent EUS-FNA of lymph nodes for staging of malignancy and the remaining 23 patients (15.5%) were incidentally detected to have abdominal lymphadenopathy. A total of 91 patients (61.1%) had only abdominal lymphadenopathy and the remaining 58 patients (38.9%) had both mediastinal as well as abdominal lymphadenopathy. Most of the patients (n = 139) underwent EUS-FNA using a 22G aspiration needle (22G Cook EchoTip®, 22G Olympus EZ-shot 3), while only 10 patients (6.7%) underwent the procedure using a 22G biopsy needle (22G Boston Scientific Acquire™). No differences in patient characteristics and procedures results were observed between the two needle types. All patients had adequate cellularity to make a diagnosis, from the samples taken from abdominal lymph nodes, as assessed by the on-site cytopathologist, in this study. The cytology results showed only reactive changes in 45 patients (30.2%), while 54 patients (36.2%) showed granulomatous inflammation with or without caseation. Malignant cells were seen in a total of 50 patients (33.6%), of which, features suggestive of lymphoma were seen in 11 patients (22%) and metastatic deposits were seen in 39 patients (78%) (Table 1). Among the 54 patients with granulomatous inflammation on EUS-FNA cytology, 51 patients (94.4%) were confirmed to have TB on the basis of confirmatory tests or response to ATT on follow-up; and 3 patients (5.55%) had elevated angiotensin I-converting enzyme levels along with systemic symptoms of sarcoidosis which was managed accordingly. On follow-up of patients with reactive changes on EUS-FNA cytology (n = 45), 30 patients (66.67%) showed non-specific inflammation which was managed conservatively, 8 patients (17.78%) had TB and were treated accordingly, 1 patient (2.22%) was diagnosed with sarcoidosis, while 3 patients (6.66%) showed malignant cells as *per* the surgical histopathology report; 3 patients (6.66%) were lost to follow-up.

EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy due to TB

A total of 59 patients were diagnosed with TB during follow-up and were treated with

Table 1 Baseline characteristics of patients who underwent endoscopic ultrasound fine needle aspiration/biopsy for abdominal lymphadenopathy

Baseline characteristics	Overall (*n* = 149)
Age (mean ± SD) in yr	51 ± 17
Gender, *n* (%)	
Male	84 (56.38)
Female	65 (43.62)
Clinical presentation, *n* (%)	
Fever of unknown origin	78 (52.3)
Staging of malignancy	48 (32.2)
Incidental	23 (15.5)
Cytology, *n* (%)	
Granulomatous inflammation	54 (36.2)
Reactive changes	45 (30.2)
Malignant cells	50 (33.6)
Final clinical diagnosis, *n* (%)	
Tuberculosis	59 (39.59)
Primary lymphoid malignancy (lymphoma)	11 (7.38)
Secondary malignant deposits	39 (26.17)
Sarcoidosis	3 (2.01)
Benign inflammatory lymphadenopathy	37 (24.8)

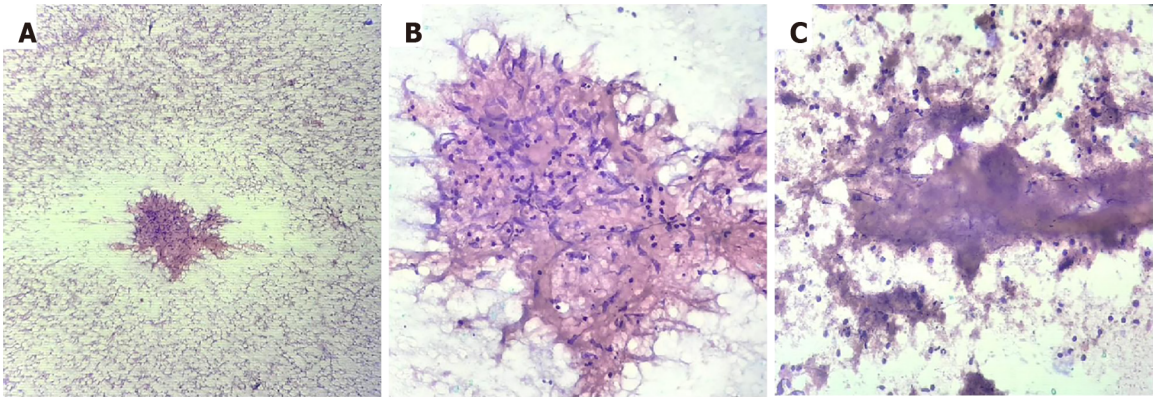

Figure 1 Histopathology findings on the fine needle aspiration sample of a patient with tuberculosis. A: An epithelioid cell granuloma with scattered lymphocytes and red blood cells in the background (100 ×); B: Collection of epithelioid histiocytes forming a granuloma (400 ×); C: Necrotic material and inflammatory cells (400 ×).

standard anti-tubercular drugs. The baseline characteristics of these patients are shown in Table 2. Isolated abdominal lymphadenopathy was seen in 31 patients (52.5%), while 28 patients (47.4%) had both mediastinal and abdominal lymphadenopathy. All the patients presented with fever of unknown origin and a majority of them also had systemic symptoms such as weight loss and night sweats [40 patients (67.7%)].

Patients with TB were more likely to have hypoechoic nodes [37 patients (62.7%)], while 22 patients (37.3%) had heteroechoic nodes on endosonographic examination (Figure 2). A majority of these patients also had matted nodes forming a conglomerate lymphnodal mass [40 patients (67.7%)]. All patients underwent EUS-FNA using an aspiration needle except for 2 patients (3.4%) in whom a biopsy needle was used. TB GeneXpert of the biopsy sample was performed in a total of 34 patients (57.6%), of which only 14 patients (41.1%) had a positive result and the remaining 20 patients

Table 2 Characteristics of patients diagnosed with tuberculosis (*n* = 59)

Baseline characteristics	Overall (*n* = 59)
Age (mean ± SD) in yr	45 ± 18
Gender, *n* (%)	
Male	31 (52.5)
Female	28 (47.4)
Echogenicity, *n* (%)	
Hypoechoic node	37 (62.7)
Heteroechoic node	22 (37.3)
Matting of lymph nodes, *n* (%)	
Yes	40 (67.7)
No	19 (32.2)
Cytology, *n* (%)	
Granulomatous inflammation with or without caseation	51 (86.4)
Reactive changes only	8 (13.5)
TB GeneXpert, *n* (%), *n* = 34	
Positive	14 (41.1)
Negative	20 (58.9)
TB culture, *n* (%), *n* = 38	
Growth	12 (31.6)
No growth	26 (68.4)
Fine needle aspiration (22 Gauge needle) (%)	
Sensitivity	86
Specificity	93
Accuracy	88

TB: Tuberculosis.

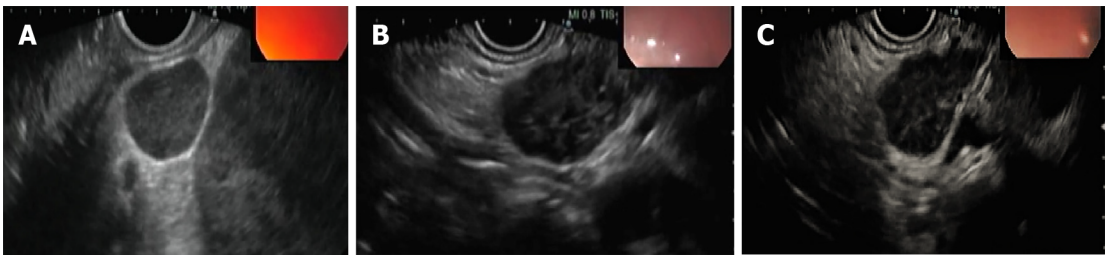

Figure 2 Endoscopic ultrasound. A: Hypoechoic node due to tuberculosis (TB) as seen on endoscopic ultrasound (EUS); B: Heteroechoic node due to TB as seen on EUS; C: Typical findings of TB lymphadenitis on EUS and fine needle aspiration cytology.

(58.9%) had a false negative result. Samples from a total of 38 patients were sent for TB culture. Of these, only 12 samples (31.6%) grew *Mycobacterium tuberculosis*, while the remaining 26 samples (68.4%) did not show any growth of organisms.

Among the patients with confirmed TB, EUS-FNA/B showed granulomatous inflammation with or without caseation in 51 patients (86.4%), while the remaining patients showed non-specific reactive changes [8 patients (13.5%)]. EUS-FNA/B was found to have a sensitivity and specificity of 86% and 93%, respectively, with a diagnostic accuracy of 88% in the evaluation of mesenteric lymphadenitis due to TB.

DISCUSSION

Extrapulmonary TB accounts for 15%-20% of all cases of TB[11,12]. TB presenting with isolated lymphadenopathy is common in endemic areas and poses a significant diagnostic challenge[13]. In the absence of characteristic symptoms or pathognomic radiographic features, isolation of the bacilli and/or identification of caseous granulomas from biopsy samples remains the gold standard. Therefore, accurate and reliable tissue acquisition from these nodes remains the cornerstone in the diagnostic evaluation of these patients. However, intra-abdominal lymphadenopathy poses unique challenges and this is where EUS-FNA/B can potentially prove invaluable in establishing a correct diagnosis. Historically, FNA cytology in conjunction with the presence of AFB, caseating necrosis and granulomas can usually provide the diagnosis in most patients. However, the sensitivity of these findings are less than ideal[14-16]. In one study, 272 patients with a proven diagnosis of tubercular lymphadenopathy had AFB positivity only in 30% of direct and concentrated smears. Moreover, TB cultures were positive only in 49% with only a marginal improvement when combined with cytologic necrosis (63%)[14]. In another study which included 390 patients with tubercular lymphadenopathy, only 24% were positive for AFB on the smear and cultures yielded a positive result in 35%[17]. These findings highlight the poor sensitivity of tests that rely on identification of the bacilli in FNA samples.

EUS-FNA/B has seen tremendous progress in the last decade with improved image resolution, increased experience with therapeutic interventions and unique biopsy needles that can increase the quantum of tissue obtained and thereby potentially address existing pitfalls of FNA cytology in establishing a diagnosis of TB. EUS-FNA has also already been evaluated for mediastinal lymphadenopathy with an overall accuracy of 93%, sensitivity of 71% and specificity of 100% for the diagnosis of TB in the Indian population[7]. However, the role of EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy due to TB remains an area that merits further evaluation. The results of the present study provide valuable evidence of the validity of EUS-FNA/B in the evaluation of TB presenting with intra-abdominal lymphadenopathy. Granulomas were seen in a total of 54 samples (36.2%) and the finding of granulomatous inflammation in the biopsy specimens correlated well with the diagnosis of TB in this study, with only 3 patients diagnosed with sarcoidosis. Only a minority of patients [8 patients (13.5%)] with TB (based on follow-up data and response to treatment) did not show granulomas on the FNA/B sample. Overall, EUS-FNA/B was found to be a safe and reliable modality in the evaluation of intra-abdominal lymphadenopathy due to TB with a diagnostic accuracy of 88% and a reasonable sensitivity and specificity for TB. Based on the findings of this study, an approach for the evaluation of intra-abdominal lymphadenopathy is proposed in Figure 3.

In general, the quantum of tissue samples obtained from lymph nodes after EUS-FNA have been found to be sufficient in most indications[4]. Ancillary techniques such as applying suction and slow withdrawal have been evaluated in the setting of pancreatic lesions. However, the utility of these techniques in the setting of lymph nodes needs further clarity. In our experience, we have found no added benefit with these ancillary techniques. A thorough endosonographic evaluation prior to FNA with emphasis on choosing an ideal node that is adequately enlarged and with sharp borders, with/without matting is essential to ensure a high yield. Particular attention should be paid to the morphology of the lymph node wherein hypoechoic areas which might indicate necrosis should be avoided. Sampling of peripheral tissue within the node has yielded better tissue samples in our experience. However, this requires further validation in larger studies.

There are a few limitations in the present study. This study was performed in an area endemic for TB. Therefore, the pre-test probability of TB would be high and as such, the findings of this study would be applicable only in similar demographic groups. In addition, a definitive diagnosis of TB requires a positive culture/GeneXpert and/or PCR for tubercular bacilli. A proportion of our study population could not undergo these tests due to financial considerations and poor patient compliance. Empirical ATT is a practice followed in most regions endemic for TB, but carries with it a high risk of treatment failure and can even pose a risk for the emergence of resistant organisms. Tissue acquisition in these cases can provide valuable information and dictate therapy. Moreover, a high pre-test probability of TB, a positive Mantoux test and granulomas on the FNA sample has been shown to be a reasonable approach to start a patient on ATT[18]. Moreover, all the patients who were treated with ATT using this approach showed good response to treatment on follow-up.

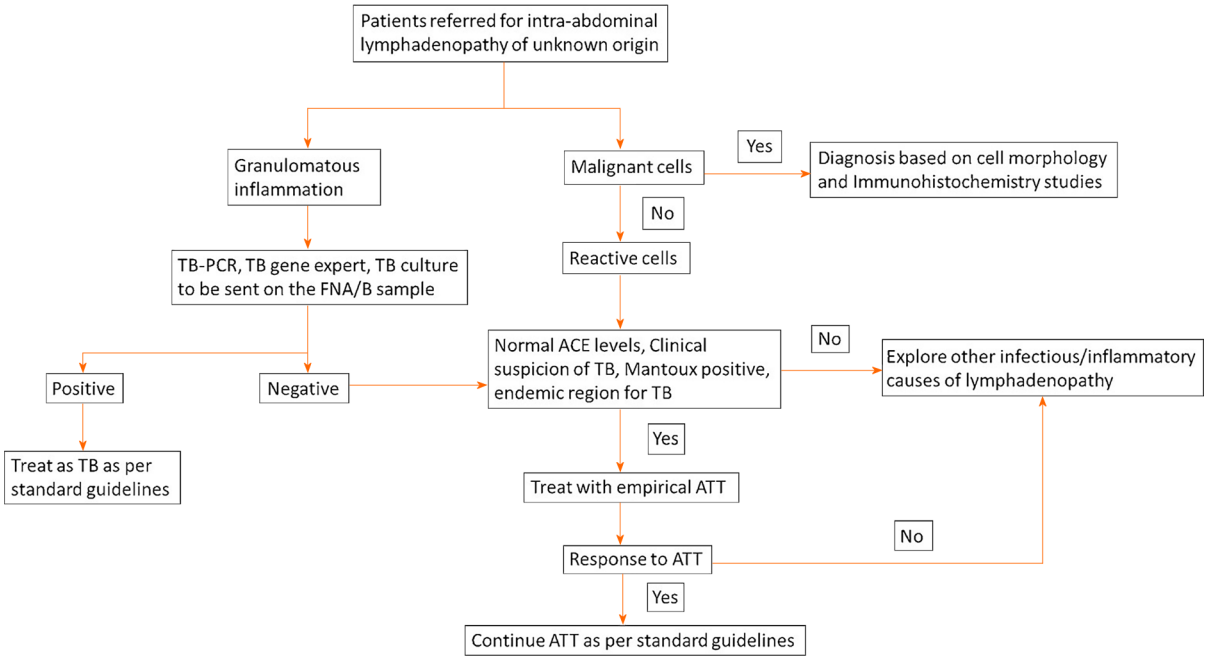

Figure 3 Proposed approach to intra-abdominal lymphadenopathy in a region endemic for tuberculosis. TB: Tuberculosis; PCR: Polymerase chain reaction; ATT: Anti-tubercular therapy; FNA/B: Fine needle aspiration/biopsy; ACE: Angiotensin I-converting enzyme.

CONCLUSION

In conclusion, EUS-FNA/B has a high diagnostic yield with a good sensitivity and specificity in the evaluation of intra-abdominal lymphadenopathy in patients with a clinical suspicion of TB. The procedure is safe, performed with moderate sedation and can potentially prevent further invasive testing in this subgroup of patients. However, the utility of this procedure in populations with a low prevalence of TB needs more clarity. In addition, a protocol-based approach with additional tests such as TB culture, AFB stain, TB-PCR or GeneXpert in specific subgroups of patients at risk for TB needs to be developed and evaluated in future studies.

ARTICLE HIGHLIGHTS

Research background

Intra-abdominal lymphadenopathy due to tuberculosis (TB) poses a diagnostic challenge due to difficulty in tissue acquisition.

Research motivation

Endoscopic ultrasound guided fine needle aspiration/biopsy (EUS-FNA/B) has shown excellent results in patients with mediastinal lymphadenopathy. However, its role in the evaluation of abdominal lymphadenopathy due to TB needs further clarity.

Research objectives

The utility of EUS-FNA/B in the evaluation of intra-abdominal lymphadenopathy was assessed by evaluating the diagnostic yield in patients with confirmed TB.

Research methods

This was a single center retrospective study conducted in a large tertiary care hospital where patients with intra-abdominal lymphadenopathy referred for EUS-FNA/B were studied. The diagnosis of TB was confirmed and EUS-FNA/B results including cytology, pathological diagnosis, ancillary test findings (TB culture, GeneXpert) and demographics in these patients were carefully analyzed.

Research results

This study showed that EUS-FNA/B has a high diagnostic yield with good sensitivity

(86%), specificity (93%) and diagnostic accuracy (88%) in the evaluation of intra-abdominal lymphadenopathy in patients with a clinical suspicion of TB. Morphological findings on EUS evaluation of intra-abdominal lymphadenopathy include hypoechoic/heteroechoic nodes, with sharp borders, with/without matting.

Research conclusions

EUS-FNA/B is a viable, reliable and safe procedure, which can be performed with moderate sedation and can potentially prevent further invasive testing in this subgroup of patients.

Research perspectives

This study provides vital information that can guide the approach and management of patients with intra-abdominal lymphadenopathy. A management algorithm that highlights key points during the management of these patients is provided. However, the utility of this procedure in populations with a low prevalence of TB needs more clarity. In addition, a protocol-based approach with additional tests such as TB culture, acid fast bacilli stain, TB-polymerase chain reaction or GeneXpert in specific subgroups of patients at risk for TB needs to be developed and evaluated in future studies.

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ORIGINAL ARTICLE

Observational Study

Efficacy and tolerability of high and low-volume bowel preparation compared: A real-life single-blinded large-population study

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Abstract

BACKGROUND

Low-volume preparations for colonoscopy have shown similar efficacy compared to high-volume ones in randomized controlled trials (RCT). However, most RCTs do not provide data about clinical outcomes including lesions detection rate. Moreover, real-life comparisons are lacking.

Institutional review board statement: The study was approved by the local Ethics Committee of San Raffaele Hospital (Approval No. 90/INT/2014).

Informed consent statement: A specific written informed consent was taken from all the study participants.

Conflict-of-interest statement: The authors declare that there is no conflict of interest.

Data sharing statement: Dataset of this study is available from the corresponding author at luca.pastorelli@unimi.it, upon reasonable request. Informed consent for data sharing was not obtained but the presented data are anonymized and risk of identification is low.

STROBE statement: The authors have read the STROBE Statement—checklist of items, and the manuscript was prepared and revised according to the STROBE Statement—checklist of items.

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AIM

To compare efficacy (both in terms of adequate bowel preparation and detection of colorectal lesions) and tolerability of a high-volume (HV: 4 L polyethylene glycol, PEG) and a low-volume (LV: 2 L PEG plus bisacodyl) bowel preparation in a real-life setting.

METHODS

Consecutive outpatients referred for colonoscopy were prospectively enrolled between 1 December 2014 and 31 December 2016. Patients could choose either LV or HV preparation, with a day-before schedule for morning colonoscopies and a split-dose for afternoon procedures. Adequate bowel preparation according to Boston Bowel Preparation Scale (BBPS), clinical outcomes including polyp detection rate (PDR), adenoma detection rate (ADR), advanced adenoma detection rate (AADR), sessile/serrated lesion detection rate (SDR) and cancer detection rate and self-reported tolerability of HV and LV were blindly assessed.

RESULTS

Total 2040 patients were enrolled and 1815 (mean age 60.6 years, 50.2% men) finally included. LV was chosen by 52% of patients (50.8% of men, 54.9% of women). Split-dose schedule was more common with HV (44.7% *vs* 38.2%, P = 0.005). High-definition scopes were used in 33.4% of patients, without difference in the two groups (P = 0.605). HV and LV preparations showed similar adequate bowel preparation rates (89.2% *vs* 86.6%, P = 0.098), also considering the two different schedules (HV split-dose 93.8% *vs* LV split-dose 93.6%, P = 1; HV day-before 85.5% *vs* LV day-before 82.3%, P = 0.182). Mean global BBPS score was higher for HV preparations (7.1 ± 1.7 *vs* 6.8 ± 1.6, P < 0.001). After adjustment for sex, age and indications for colonoscopy, HV preparation resulted higher in PDR [Odds ratio (OR) 1.32, 95%CI: 1.07-1.63, P = 0.011] and ADR (OR 1.29, 95%CI 1.02–1.63, P = 0.038) and comparable to LV in AADR (OR 1.51, 95%CI 0.97-2.35, P = 0.069), SDR and cancer detection rate. The use of standard-definition colonoscopes was associated to lower PDR (adjusted OR 1.59, 95%CI: 1.22-2.08, P < 0.001), ADR (adjusted OR 1.71, 95%CI: 1.26–2.30, P < 0.001) and AADR (adjusted OR 1.97, 95%CI: 1.09-3.56, P = 0.025) in patients receiving LV preparation. Mean Visual Analogue Scale tolerability scored equally (7, P = 0.627) but a ≥ 75% dose intake was more frequent with LV (94.6% *vs* 92.1%, P = 0.003).

CONCLUSION

In a real-life setting, PEG-based low-volume preparation with bisacodyl showed similar efficacy and tolerability compared to standard HV preparation. However, with higher PDR and ADR, HV should still be considered as the reference standard for clinical trials and the preferred option in screening colonoscopy, especially when colonoscopy is performed with standard resolution imaging.

Key Words: Bowel preparation volume; Polyethylene glycol; Bisacodyl; Colonoscopy; Colonic adenomas; Tolerability

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Core Tip: Quality of bowel preparation is one of the main factors influencing outcomes of colonoscopy. This prospective real-life study compared bowel cleansing (according to the Boston Bowel Preparation Scale), clinically relevant colonoscopy outcomes (lesions detection rate) and tolerability of a standard high-volume bowel preparation and a low-volume preparation (2 L polyethylene glycol + bisacodyl). Even if the two study groups did not show differences in terms of adequate bowel preparation, the use of the high-volume preparation was associated with higher polyp and adenoma detection rates. There were no differences in terms of advanced adenomas, sessile/serrated lesions and cancer detections. Performance of low-volume preparation seems influenced by image resolution of colonoscopes, with fewer lesions detected compared to high-volume when using standard-definition colonoscopes. The two preparations were comparable in terms of patients' self-reported tolerability, but

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complete adherence to preparation was more common with the low-volume product.

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INTRODUCTION

The clinical performance of colonoscopy is markedly influenced by the quality of bowel preparation. In fact, inadequate bowel preparation has proved to have a detrimental effect on different clinically significant outcomes, such as complete colonoscopy rate[1-3], polyp (PDR) and adenoma detection rates (ADR)[4-6]. Moreover, inadequate preparation may require to repeat the procedure, with the subsequent increase in waiting times, risks and costs[7,8]. Large volumes (4 L) of polyethylene glycol (PEG) have been classically prescribed to achieve adequate cathartic effect. Over the past years, several low-volume preparations have been developed to increase the patients' acceptability, compliance and willingness to repeat the procedure. Randomized controlled trials (RCTs) and some meta-analysis have shown that low-volume preparations have similar efficacy in terms of adequate bowel preparation rate compared to high-volume preparations[9-15], however two meta-analysis[16,17] reported a superiority of high-volume PEG over low-volume PEG. Moreover, the direct comparison of clinical outcomes such as ADR is available only in a minority of trials[11,12], and real-life data suggest higher detection rates with high-volume preparations[18].

Therefore, we have performed a real-life study to (1) compare efficacy of HV and LV preparations by means of adequate bowel preparation rate and detection of colonic lesions; and (2) to compare self-reported tolerability of different regimens.

MATERIALS AND METHODS

Study design and subjects

We prospectively enrolled the consecutive patients referred for colonoscopy to the Digestive Endoscopy Outpatient Service of IRCCS Policlinico San Donato between 1 December 2014 and 31 December 2016. The patients enrolled in the regional colorectal cancer screening program were not included as in our Center they are all advised to use high-volume PEG-based preparation. If a patient underwent multiple colonoscopies during the study period, only the first procedure was taken into account for the study.

The exclusion criteria were: inability to give informed consent, use of cleansing products different from the recommended ones, incomplete patient forms as to the type of preparation used, incomplete colonoscopy because of a pathological stricture.

At the time of booking the examination, all the patients received written detailed instructions about the diet regimen (no fruit, legumes, or vegetables for 3 d before the procedure; light breakfast and lunch the day before colonoscopy, followed by clear liquids only) and about bowel preparation. Instructions contained an introductory paragraph underlying the importance to adhere to the prescriptions provided in order to increase the chance to achieve good diagnostic and therapeutic results and to reduce adverse events of colonoscopy. Patients were free to choose either a high-volume (HV) or a low-volume (LV) preparation. The HV preparation (SELG ESSE; Promefarm, Italy) was a PEG 4000 solution plus simethicone and electrolytes that had to be diluted in 4L still water, while the LV preparation was a combination of a PEG 4000 solution plus simethicone and electrolytes (Lovol-Esse; Alfasigma, Italy) diluted in 2 L still water and the stimulant laxative bisacodyl (Lovoldyl; Alfasigma, Italy). In the written instructions handed to the patients, the two preparations were stated as equally effective and tolerated and complete free choice was left to patients' preferences. The

preparations were listed with the HV preparation first.

For the procedures planned before 12:00 pm, the patients were instructed to take the entire quantity of the PEG solution the evening before colonoscopy, starting from 7 pm; in case of LV preparation, 4 tablets (20 mg) of bisacodyl were also taken at 3:00 pm. For afternoon procedures a split-dose regimen was prescribed: half the dose of PEG was taken in the afternoon before and half the dose at 7:00 a.m. in the morning on the day of the colonoscopy; in case of LV preparation 20 mg bisacodyl was taken at sleep time.

The study was approved by the local Ethics Committee of San Raffaele Hospital and a specific written informed consent was taken from all the study participants. The study was conducted in accordance with the Declaration of Helsinki 1975 and subsequent amendments.

Colonoscopy

All the procedures were performed under mild-to-moderate sedation (midazolam ± pethidine i.v.) by 5 experienced endoscopists (> 1000 colonoscopies overall, > 300/year), well-trained in the use of bowel preparation rating scales and blinded to the content of the patient form and to the preparation taken. The indication for colonoscopy was collected by the endoscopist matching medical prescription and pre-colonoscopy interview, following the standard clinical protocol. The endoscopes used were either standard-definition (SD) or high-definition (HD) scopes by Pentax (Tokyo, Japan).

Data collection

On the morning of colonoscopy, the patients were asked to fill a specific questionnaire covering the kind of bowel preparation used (HV or LV), amount of PEG solution taken (the 75% threshold was chosen to define the PEG intake as "full"), time of the exam, demographics, morphometrics, social circumstances (living alone, instruction level) and clinical data. The questionnaire included a specific section about personal bowel habits (Bristol stool chart, frequency of bowel movements per week). Constipation was defined as Bristol stool chart type 1-2 and less than 3 bowel movements/week, and/or chronic constipation as indication for colonoscopy. The form also contained a section about general satisfaction about the used preparation [evaluated by visual analogue scale (VAS) score, from 0 = 'absolutely unsatisfied' to 10 = 'perfectly satisfied'] and symptoms (nausea, vomit, bloating, abdominal pain) experienced during the preparation.

The quality of bowel preparation was assessed using the Boston bowel preparation scale (BBPS)[19]. Bowel preparation was defined adequate if a global score ≥ 6 with segmental scores ≥ 2 in all colonic segments was achieved. For any patients with previous bowel resection, the preparation was considerate adequate if all the segmental sub-scores were ≥ 2.

The number, size and final histology of lesions resected or biopsied during the procedures were collected. PDR, ADR, advanced adenoma (adenomas ≥ 1 cm or with villous component or harboring high-grade dysplasia) detection rate (AADR), sessile/serrated lesion detection rate (SDR, excluding hyperplastic polyps) and cancer detection rate were calculated.

Statistical analysis

Considering an expected adequate preparation rate of 87.1% with LV preparation and of 92.5% with HV preparation from a previous study[20], power of 90% with an alpha error of 0.05, we estimated that 1384 patients would be sufficient. A possible drop-out rate of 30% was considered for the study, therefore the final required sample size was 1977 patients.

The descriptive statistics were expressed as counts and percentages for categorical variables and mean ± SD or median (interquartile ranges, IQR) for continuous variables, as appropriate. Normality assumption was to be tested in continuous variables by visual inspection of the qq-plot.

The association between bowel preparation and baseline variables was investigated with the χ^2 test for categorical variables; the continuous variables were compared by analysis of variance ANOVA or by the non-parametric Kruskal–Wallis test for non-normally distributed data.

Univariate and multi-variate logistic regression was used to identify if adequate bowel preparation and volume of bowel preparation were independently associated with clinical outcomes (PDR, ADR, AADR, SDR and cancer). Multivariate analysis was performed considering age (as a continuous variable), sex and indications for

colonoscopy [positive fecal blood test (FBT), surveillance, symptoms or inflammatory bowel disease (IBD)]. Separate analysis was also performed considering the type of colonoscopes used (HD or SD imaging). Odds ratios (ORs) with their corresponding 95%CIs were calculated, and *P* values were considered statistically significant if they were less than 0.05.

Statistical analysis was carried out by computer software SAS version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Total 2040 patients were enrolled and 1815 patients (mean age 60.6 years, 50.2% male) were finally included according to exclusion criteria (study flowchart in Supplementary Figure 1). 944 patients (52%) chose a LV preparation, while 871 patients (48%) preferred a HV preparation. 750 patients (41.3%) had their colonoscopy scheduled in the afternoon and thereafter used a split-dose regimen; the use of a split-dose regimen was more common in the HV group (44.7% *vs* 38.2%, *P* = 0.0055).

Indications for colonoscopy were symptoms (altered bowel movements, anemia or bleeding, abdominal pain) in 60.6%, post-polypectomy or post-colorectal cancer surveillance in 24.0%, positive FBT in 8.3% and follow-up of known IBD in 7.1% of the cases. Positive FBT was more common in the HV group and known IBD in the LV group. The patients in the HV preparation group were more frequently male, had higher body mass index and more frequently had a cardiac disease and a low-level education. There were no statistically significant differences in terms of age and other possible risk factors for poor bowel preparation (previous abdominal/pelvic surgery, constipation, living-alone status or non-adherence to low-fiber dieting before colonoscopy). HD colonoscopes were used in 606 patients (33.4%), without difference in the two groups (*P* = 0.605) (Table 1).

Overall, adequate preparation was observed in 1595/1815 (87.9%) patients. Complete colonoscopy was possible in 1793 patients (98.8%). At least one polypoid lesion was found in 520/1815 colonoscopies (PDR 28.7%). Histology revealed at least one adenoma in 381/1815 colonoscopies (ADR 20.1%) and at least one sessile/serrated lesion in 28/1815 colonoscopies (SDR 1.5%). Non adenomatous/non serrated lesions were mostly hyperplastic (*n* = 81) or inflammatory (*n* = 23) polyps, with less common histology encountered in 7 cases.

Adequate bowel preparation was associated with a higher complete colonoscopy rate (99.7% *vs* 92.5%, OR 24.05, 95%CI: 7.82–73.92, *P* < 0.001), higher PDR (29.8% *vs* 20.1%, OR 1.69, 95%CI: 1.20–2.40, *P* = 0.003) and ADR (21.8% *vs* 15.5%, OR 1.52, 95%CI: 1.04–2.23, *P* = 0.033), while no significant differences were found in AADR, cancer detection and SDR (Table 2).

PDR, ADR, AADR and cancer rates were higher in the positive FBT group, followed by the surveillance, symptoms and IBD groups (Supplementary Table 1). The use of HD instruments was related to significantly higher ADR (*P* = 0.040) compared to standard definition instruments, without significant difference in other clinical outcomes (Supplementary Table 2).

Efficacy of bowel preparation

The adequacy of preparation was independent of the use of HV or LV preparations (89.2% *vs* 86.6%, *P* = 0.098). The split-dose schedule was superior to day-before for either HV (93.8% *vs* 85.5%, *P* < 0.001) or LV preparation (93.6% *vs* 82.3%, *P* < 0.001). Also considering the two different schedules, there was no difference among HV and LV preparation (HV split-dose 93.8% *vs* LV split-dose 93.6%, *P* = 1; HV day-before 85.5% *vs* LV day-before 82.3%, *P* = 0.182) (Figure 1). The efficacy of HV and LV preparations was similar in all the colonic segments (Supplementary Figure 2), irrespective of the use of the day-before or a split-dose schedule (Supplementary Figure 3).

The mean global BBPS scores were higher with HV preparations compared to LV (overall: 7.1 ± 1.7 *vs* 6.8 ± 1.6, *P* < 0.001; day-before schedule: 6.9 ± 1.7 *vs* 6.6 ± 1.7, *P* = 0.003; split-dose schedule: 7.5 ± 1.6 *vs* 7.2 ± 1.5, *P* = 0.019).

Clinical endpoints

As compared to LV preparation, HV preparation was associated with higher PDR (32.5% *vs* 25.1%, OR 1.43, 95%CI: 1.17–1.76, *P* < 0.001), higher ADR (24.1% *vs* 18.1%, OR 1.44, 95%CI: 1.14-1.80, *P* = 0.002) and higher AADR (6.4% *vs* 3.7%, OR 1.79, 95%CI: 1.16–2.75, *P* = 0.009) without differences in cancer detection and SDR. After adjustment for age, sex and indication for colonoscopy, the difference remained statistically

Table 1 Demographic and clinical features of the study population, *n* (%)

Characteristics	High volume (*n* = 871)	Low volume (*n* = 944)	*P* value[1]
Age	61.2 ± 14.3	60.1 ± 14.6	0.092
Male sex	463 (53.2)	448 (47.5)	0.015[3]
Split-dose	389 (44.7)	361 (38.2)	0.006[3]
High-definition colonoscope	296 (33.9)	310 (32.8)	0.605
Indication			
Symptoms	538 (61.8)	563 (59.6)	
Surveillance			< 0.001[3]
Post polypectomy	134 (15.4)	154 (16.3)	
Post colonic resection for CRC	73 (8.4)	73 (7.7)	
Positive FBT	94 (10.8)	57 (6.1)	
IBD	32 (3.6)	97 (10.3)	
BMI, mean ± SD[2]	25.5 ± 4.3	25.0 ± 4.0	0.015[3]
Previous abdominal surgery	98 (11.3)	96 (10.2)	0.456
Constipation	66 (7.6)	86 (9.1)	0.239
Comorbidities			
Heart disease	90 (10.3)	65 (6.9)	0.009[3]
Diabetes	72 (8.3)	65 (6.9)	0.266
Stroke/dementia	19 (2.2)	25 (2.6)	0.518
Severe CKD	21 (2.4)	15 (1.6)	0.209
Cirrhosis	12 (1.4)	13 (1.4)	0.999
GERD	192 (22.0)	219 (23.2)	0.557
Waiting time > 1 mo	485 (55.7)	570 (60.4)	0.090[3]
Non-adherence to low fiber diet	91 (10.5)	112 (11.9)	0.329
Lives alone[2]	123 (14.8)	149 (16.3)	0.395
Low instruction[2]	157 (19.6)	122 (14.1)	0.002[3]

[1]*P* value degrees of freedom = 1, except for age (1814), indication (4) and body mass index (BMI) (1726).
[2]BMI available for 1727 patients; information about living alone available for 1747 patients; instruction level available for 1662 patients.
[3]Significant different.
CRC: Colorectal cancer; FBT: Fecal blood test; IBD: Inflammatory bowel disease; BMI: Body mass index; CKD: Chronic kidney disease; GERD: Gastroesophageal reflux disease.

significant for PDR (adjusted OR 1.320, 95%CI: 1.07-1.63, P = 0.011) and for ADR (adjusted OR 1.29, 95%CI: 1.02-1.63, P = 0.038) but not for AADR (adjusted OR 1.51, 95%CI: 0.97–2.35, P = 0.069) (Table 3).

HV and LV preparations were associated to comparable PDR, ADR, AADR, SDR and cancer detection when colonoscopy was performed under HD endoscopic imaging (Table 4). On the contrary, the use of HV preparation was linked to significantly higher PDR, ADR and AADR compared to LV preparation in patients receiving colonoscopy with SD imaging, after adjustment for age, sex and indications for colonoscopy (Table 5).

The use of the split-dose schedule was not linked with significantly better clinical outcomes as compared to day-before for either HV or LV preparations (Table 6).

Tolerability

Overall, HV and LV preparations were equally well tolerated (median VAS score 7, interquartile range 5-9 for both preparations). Total 860 patients (47.4%) reported gastrointestinal symptoms during preparation: nausea (26.5%) and bloating (19.9%) were the most frequently self-reported symptoms. The occurrence of nausea, vomiting

Table 2 Clinical outcomes according to quality of preparation, *n* (%)

Outcome	Adequate preparation (*n* = 1595)	Inadequate preparation (*n* = 220)	OR (95%CI)	*P* value[1]
Complete examination	1590 (99.7)	203 (92.3)	26.63 (9.72-72.96)	< 0.001[2]
PDR	476 (29.8)	44 (20.1)	1.69 (1.20-2.40)	0.003[2]
ADR	347 (21.8)	34 (15.5)	1.52 (1.04-2.23)	0.033[2]
AADR	82 (5.1)	9(4.1)	1.27 (0.63-2.57)	0.505
Cancer	27 (1.7)	7 (3.2)	0.52 (0.23-1.22)	0.133
SDR	26 (1.6)	2 (0.9)	1.81 (0.43-7.66)	0.423

[1]*P* value degrees of freedom = 1.
[2]Significant different.
OR: Odds ratio; PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

Table 3 Clinical outcomes according to volume of bowel preparation, *n* (%)

Outcome	High volume (*n* = 871)	Low volume (*n* = 944)	OR (95%CI)	*P* value[1]	Adjusted[2] OR (95%CI)	*P* value[2]
PDR	283 (32.5)	237 (25.1)	1.43 (1.17–1.76)	< 0.001[3]	1.32 (1.07–1.63)	0.011[3]
ADR	210 (24.1)	171 (18.1)	1.44 (1.14–1.80)	0.002[3]	1.29 (1.02–1.63)	0.038[3]
AADR	56 (6.4)	35 (3.7)	1.79 (1.16–2.75)	0.009[3]	1.51 (0.97–2.35)	0.069
Cancer	19 (2.2)	15 (1.6)	1.38 (0.70–2.74)	0.354		
SDR	16 (1.8)	12 (1.3)	1.45 (0.68–3.09)	0.331		

[1]*P* value degrees of freedom = 1.
[2]Adjustment for age (as a continuous variable), sex and indications for colonoscopy; *P* value degrees of freedom = 7.
[3]Significant different.
OR: Odds ratio; PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

Table 4 Clinical outcomes according to volume of bowel preparation, high-definition colonoscopes, *n* (%)

Outcome	High volume (*n* = 296)	Low volume (*n* = 310)	OR (95% CI)	*P* value[1]
PDR	97 (32.7)	93 (30.0)	1.13 (0.81–1.60)	0.462
ADR	70 (23.6)	74 (23.9)	0.99 (0.68–1.44)	0.948
AADR	21 (7.1)	17 (5.5)	1.31 (0.68–2.54)	0.415
Cancer	5 (1.7)	5 (1.6)	1.05 (0.30–3.66)	0.941
SDR	4 (1.4)	4 (1.3)	1.05 (0.26–4.23)	0.947

[1]*P* value degrees of freedom = 1.
OR: Odds ratio; PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

and abdominal pain was more frequent among the patients in the LV group (Table 7). Self-reported incomplete (*i.e.*, ≤ 75%) intake of the PEG solution was more common in the HV group (7.9% *vs* 5.4%, *P* = 0.003). For the HV preparation the split-dose regimen was related to better tolerability (higher VAS score) as compared to day-before, even if with no differences in terms of reported symptoms. For the LV preparation, the split-dose regimen was related to lower incidence of symptoms (in particular nausea and bloating) (Table 8).

DISCUSSION

The standard high-volume PEG-based preparation is safe and effective, but even in

Table 5 Clinical outcomes according to volume of bowel preparation, standard-definition colonoscopes, *n* (%)

Outcome	High volume (*n* = 575)	Low volume (*n* = 634)	OR (95%CI)	*P* value[1]	Adjusted[2] OR (95%CI)	*P* value[2]
PDR	186 (32.3)	144 (22.7)	1.63 (1.26–2.10)	< 0.001[3]	1.59 (1.22–2.08)	< 0.001[3]
ADR	140 (24.3)	97 (15.3)	1.78 (1.34–2.38)	< 0.001[3]	1.71 (1.26–2.30)	< 0.001[3]
AADR	35 (6.1)	18 (2.8)	2.23 (1.24–3.96)	0.007[3]	1.97 (1.09–3.56)	0.025[3]
Cancer	14 (2.4)	10 (1.6)	1.56 (0.69–3.53)	0.289		
SDR	12 (2.1)	8 (1.3)	1.67 (0.68–4.11)	0.266		

[1]*P* value degrees of freedom = 1.
[2]Adjustment for age (as a continuous variable), sex and indications for colonoscopy; *P* value degrees of freedom = 7.
[3]Significant different.
OR: Odds ratio; PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

Table 6 Clinical outcomes of high and low-volume preparations according to different schedules, *n* (%)

Outcome	High volume day before (*n* = 482)	High volume split-dose (*n* = 389)	*P* value[1]	Low volume day before (*n* = 583)	Low volume split-dose (*n* = 361)	*P* value[1]
PDR	149 (30.9)	134 (34.4)	0.277	145 (24.9)	92 (25.5)	0.833
ADR	108 (22.4)	102 (26.2)	0.191	103 (17.7)	68 (18.8)	0.650
AADR	30 (6.2)	26 (6.7)	0.783	20 (3.4)	15 (4.2)	0.567
Cancer	11 (2.3)	8 (2.1)	0.827	6 (1.0)	9 (2.5)	0.088
SDR	5 (1.0)	11 (2.8)	0.050	8 (1.4)	4 (1.1)	1.000

[1]*P* value degrees of freedom = 1.
PDR: Polyp detection rate; ADR: Adenoma detection rate; AADR: Advanced adenoma detection rate; SDR: Sessile lesion detection rate.

Table 7 Self-reported tolerability of bowel preparations according to volume, *n* (%)

	Total (*n* = 1815)	High volume (*n* = 871)	Low volume (*n* = 944)	*P* value[1]
Global tolerance, VAS score[2], median (interquartile range)	7 (5-9)	7 (5-9)	7 (5-9)	0.627
Incomplete preparation (< 75% of PEG assumed)	116 (6.6)	67 (7.9)	49 (5.4)	0.032[3]
Any symptom during preparation	860 (47.4)	369 (42.4)	491 (52)	< 0.001[3]
Bloating	363 (20)	183 (21)	180 (19.1)	0.301
Nausea	480 (26.5)	187 (21.5)	293 (31)	< 0.001[3]
Vomiting	174 (9.6)	55 (6.3)	119 (12.6)	< 0.001[3]
Abdominal pain	281 (15.5)	104 (11.9)	177 (18.8)	< 0.001[3]

[1]*P* value degrees of freedom = 1.
[2]Visual analogue scale: 0 absolutely non-tolerated, 10 perfectly tolerated. Data available for 1772 patients.
[3]Significant different.
VAS: Visual analogue scale; PEG: Polyethylene glycol.

clinical studies a significant proportion of patients is unable to take all the prescribed dose[21] with detrimental effect on its efficacy. RCTs and some meta-analyses have shown a comparable efficacy of different low-volume preparations compared to high-volume PEG[9,10,13-15,22], and the use of these preparations is now recommended in both the European[23] and North American[24] guidelines. However, robust comparisons in RCTs between HV and LV preparations in terms of clinically relevant outcomes (such as ADR) are missing, in particular for the two most recently introduced LV preparations: 2 L PEG plus citrate and 1L PEG plus ascorbate. The former has been compared to HV preparation in a RCT[14] in terms of adequate bowel

Table 8 Tolerability of high and low-volume preparations according to different schedules, *n* (%)

	High volume one-day (*n* = 482)	High volume split dose (*n* = 389)	*P* value[1]	Low volume one-day (*n* = 583)	Low volume split dose (*n* = 361)	*P* value[1]
Global tolerance, VAS score[2], median (interquartile range)	7 (5-8)	7 (5-9)	0.006[3]	7 (5-9)	7 (5-9)	0.033
Incomplete preparation	37 (7.9)	30 (7.9)	0.994	31 (5.5)	18 (5.2)	0.840
Any symptom during preparation	211 (43.8)	158 (40.6)	0.384	324 (55.6)	167 (46.3)	0.005[3]
Bloating	103 (21.4)	80 (20.6)	0.772	126 (21.6)	54 (14.9)	0.011[3]
Nausea	112 (23.2)	75 (19.3)	0.158	196 (33.6)	97 (26.9)	0.029[3]
Vomiting	33 (6.9)	22 (5.7)	0.473	73 (12.5)	46 (12.7)	0.921
Abdominal pain	54 (11.2)	50 (12.9)	0.455	105 (18.0)	72 (19.9)	0.459

[1]*P* value degrees of freedom = 1.
[2]Visual Analogue Scale: 0 absolutely non-tolerated, 10 perfectly tolerated. Data available for 1772 patients.
[3]Significant different.
VAS: Visual analogue scale.

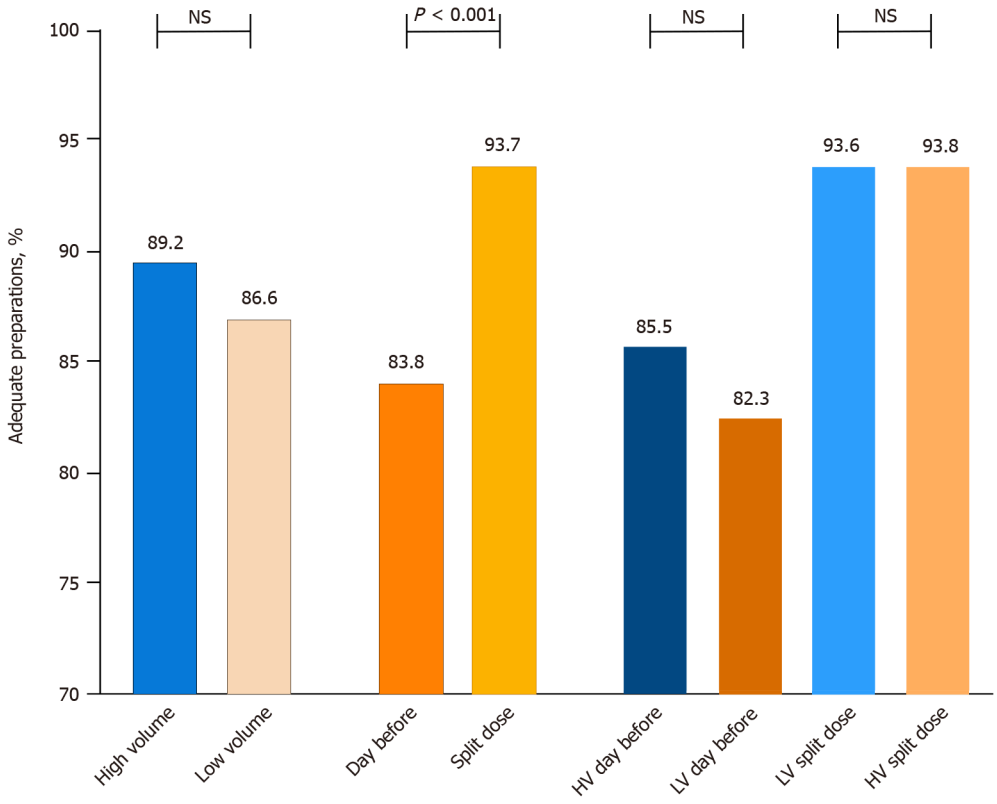

Figure 1 Frequency of adequate preparations (Boston Bowel Preparation Scale ≥ 2 in all bowel segments) according to volume and schedules of preparations. NS: Not significant; HV: High volume; LV: Low volume.

preparation rate and tolerability but not in terms of lesions detection rates, while the latter has been compared in RCTs[25-27] only to other low-volume preparations. Moreover, real-life data are scarce and conflicting: a recent real-life direct comparison of 1 L PEG plus ascorbate and HV preparation[28] has showed higher cleansing success and tolerability in the LV group, but did not analyze lesions detection. Lesions detection rates were not reported also in a recently presented abstract comparing HV and 2 L PEG plus ascorbate and sodium sulfate[29]. In addition, a recent prospective observational study has shown better cleansing results and higher ADR and AADR with 4 L PEG compared to lower volume preparations[18].

In our real-life setting, we confirmed that the low-volume PEG plus bisacodyl preparation is equally effective than HV in all the colonic segments (while some studies have shown worse performances of low-volume preparations in the right colon [30]) and irrespective of the intake schedule, with split-dose regimens largely superior to day-before ones. In particular, it is to note that the split LV preparation was as effective as the split HV preparation, confirming the results achieved in a recent meta-analysis[22], in opposition to previous ones[16,17].

Overall, 87.9% of our patients achieved adequate preparation. This result is in line or superior to the results reported in the literature[31,32], even if slightly inferior to the 90% target proposed by the European Society of Gastrointestinal Endoscopy in 2019 [33]. We confirmed the importance of bowel preparation in terms of relevant outcomes such as complete colonoscopy rate, PDR and ADR, while we did not find differences in terms of AADR, SDR and cancer detection. Advanced adenomas and cancers are usually bigger lesions, easier to find even in a not well-prepared colon[6], while the SDR result can be explained by their low prevalence in our population.

Quite surprisingly, only a slight majority of patients (52%) preferred the LV preparation over the standard HV. This may be partially explained by the order in which the two preparations were listed in the instructions handed to the patients (HV preparation listed first). Even if stated equally effective in the instructions given, it is also possible that the patients perceived more effective a high-volume preparation and leaned towards that choice, especially for "strong" indications such as positive FBT. In fact, we have observed a different distribution of indications for colonoscopy in the two study groups. While FBT-positive patients chose more frequently the HV preparation, the large majority (75.2%) of IBD patients chose LV preparation. Women also used more frequently the LV preparation, while we did not find any age-related difference. Interestingly, 52% of patients with colonoscopy planned in the afternoon chose the HV preparation. This may suggest that the possibility to reduce the volume of PEG was not felt so compelling once given the possibility to split its assumption.

Quite surprisingly, despite similar efficacy in terms of bowel cleansing, the use of the HV preparation was related to higher PDR, ADR and AADR compared to the LV preparation. To remove confounding factors due to the absence of randomization, we adjusted the OR considering three main characteristics related to the prevalence of colorectal lesions such as age, sex and indication. Even after this adjustment, the HV preparation showed better results, with a statistically significant difference for PDR (adjusted OR 1.32, $P = 0.011$) and ADR (adjusted OR 1.29, $P = 0.038$). This result is unlikely to be explained by the more frequent use of split-dose in the HV group, considering that we did not find differences in lesions detection among split and day-before schedules. The type of colonoscopes used seems to have a relevant role in our study. HD colonoscopes, that have shown better diagnostic performances compared to SD ones[34], were used in a similar proportion of patients in the two groups. However, while we did not observe a difference in performance in the two preparations with HD instruments, performance of LV preparation was significantly inferior to HV in terms of lower PDR, ADR and AADR when SD imaging colonoscopy was adopted. This is likely to be linked to the lower mean BBPS score observed in patients using LV preparation. We hypothesize that the persistence of some fluids in the bowel lumen may reduce visibility of lesions, especially when SD scopes are used. Our results suggest that the use of SD definition colonoscopes in patients prepared with LV preparation should be avoided because of an increased risk of missed lesions.

About tolerability, LV preparations[10,14] and in particular 2 L PEG plus bisacodyl [9] were found to be better tolerated as compared to high-volume PEG in previous RCTs. On the contrary, we have observed more self-reported gastrointestinal symptoms such as nausea, vomiting and abdominal pain in the LV group. This result can be explained by the real-life observational design of our study, rather than reflecting an intrinsic lower tolerability of the LV preparation. Nonetheless, these GI symptoms affected neither the patients' adherence nor tolerability. In fact, the LV preparation was judged as tolerable as the HV preparation according to the VAS scale, and it was more frequently taken completely. The use of a split-dose regimen increased the reported tolerability of both the HV (higher VAS score) and the LV (less frequent symptoms) preparations, as previously shown in RCTs and meta-analyses[17, 35].

We recognize that our study has several limitations. The most important limitation is the adoption of day-before schedule for morning procedures; day-before preparations are not recommended by guidelines because of its inferior efficacy when compared to split-dose, as confirmed by our results. Due to the extension of the metropolitan area served by our center, however, we decided to maintain the possibility to choose a day-before regimen. In fact, living far from the endoscopic

centers has been demonstrated to be a significant limitation for adherence to split dose regimen, especially for early morning scheduled colonoscopy[36]. Secondly, the opportunity to leave the choice of the preparation to the patient may be debatable. However, both the preparations used in this study are equally recommended by international guidelines[23,24] and clinical criteria to prefer a specific preparation over another in a specific patient are lacking. Thirdly, as compared to RCTs, the real-life "patients-determined" allocation among different study groups could result in an unbalanced distribution of risk factors. Even if most of the baseline characteristics were comparable in the two study groups, the higher number of male and FBT-positive patients in the HV group could lead to overestimation of performances of HV preparation. However, we performed multivariate analysis considering these factors to provide reliable adjusted odds ratio for lesions detection rates in the two study groups. Fourthly, in our study HD scopes were used only in approximately one-third of cases. We recognize that the use of HD colonoscopes is preferable over SD because of better mucosal visualization. However, SD colonoscopes are still widely used in many centers worldwide. For this reason, we think that our real-life observation that LV preparations could be less effective combined with SD scopes may be of particular interest. Lastly, the single-center observational design implies the risk of sub-optimal reproducibility. However, the large sample size and the prospective nature of this study support our results. On the other hand, additional strengths of our study consist in the blindness of the endoscopists to the type of preparation taken, the use of a well-validated bowel preparation scale and the available histology for all the resected lesions.

CONCLUSION

To resume, this large prospective single-blinded real-life study reveals that adequate bowel cleansing can be equally achieved by means of either HV or LV preparation, showing better result with split dosage. However, in the real-life setting the HV preparation is associated with higher PDR and ADR as compared to the LV preparation, due to reduced performances of LV preparation when SD colonoscopes are used. Our results suggest that the HV preparation should still be proposed as one of the preferred options in screening colonoscopy, and that the use of LV preparations should be avoided in average-to-high risk patients if HD scopes are not available. Looking forward to large multi-center real-life studies, we believe that 4L PEG should be still considered the reference standard for new RCTs assessing both the bowel cleansing and the ADR in screening colonoscopy.

ARTICLE HIGHLIGHTS

Research background

Colonoscopy is a key procedure for the diagnosis of several colorectal pathologies and for prevention of colorectal cancer. The diagnostic yield of colonoscopy is strongly influenced by quality of bowel preparation. In the last years, several low-volume (LV) preparations have been introduced with the aim to improve patients' adherence and compliance.

Research motivation

LV preparations have demonstrated similar cleansing effects compared to standard, high-volume (HV) preparation in randomized controlled trials. However, few real-life studies have compared these two types of preparation in terms of clinically relevant outcomes such as lesions detection.

Research objectives

Primary aim of our study was to compare the real-life efficacy of a standard HV preparation (4 L polyethylene glycol) and of a LV preparation (2 L polyethylene glycol with bisacodyl), either in terms of adequate bowel preparation rate (defined as Boston Bowel Preparation Scale score ≥ 2 in all bowel segments) or in terms of lesions detection. Secondary aim was to compare patients' self-reported adherence and tolerability.

Research methods

A prospective study was conducted from 1 December 2014 to 31 December 2016, enrolling all the consecutive outpatients referred for colonoscopy in a single endoscopy center in Italy. Patients were free to choose one of the two proposed preparations (HV or LV). A questionnaire was administered to the patients to collect comorbidities, type of preparation chosen, adherence to preparation and tolerability. Indications for colonoscopy, type of scope used (high-definition, HD, or standard-definition, SD), Boston Bowel Preparation Scale (BBPS) score for each colonic segment, histology of all the lesions resected or biopsied were collected.

Research results

LV was chosen by 52% of patients (50.8% of men, 54.9% of women). HD scopes were used in 33.4% of patients, without difference in the two groups (P = 0.605). There was no difference between HV and LV preparations in terms of adequate bowel preparation, even if mean global BBPS score was higher for HV preparation when compared to LV. Compared to LV, HV preparation resulted higher in polyp detection rate (PDR) but not in advanced adenoma detection rate (AADR) and cancer detection rate. Considering the type of colonoscope used, we observed lower PDR, adenoma detection rate (ADR) and AADR with LV preparation with SD colonoscopes, without differences between the two preparations with HD instruments.

Research conclusions

Despite similar adequate bowel preparation rate among the two preparations compared, we observed higher PDR, ADR and AADR with HV preparation compared to LV. The difference is mainly observed when SD endoscopes are used. The two preparations were stated as equally tolerated by the patients, but self-reported adherence was higher with LV.

Research perspectives

In the last years we have observed an increasing trend towards the use of LV preparations to increase patients' satisfaction. However, primary aim of bowel preparation is to minimize the risk of missing colorectal lesions. Further studies, either randomized controlled trials or real-life studies, are warranted to compare efficacy in lesions detection of new LV products to standard HV preparation.

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SYSTEMATIC REVIEWS

Application of robotic technologies in lower gastrointestinal tract endoscopy: A systematic review

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Abstract

BACKGROUND

Conventional optical colonoscopy is considered the gold standard investigation for colorectal tract pathology including colorectal malignancy, polyps and inflammatory bowel disease. Inherent limitations exist with current generation endoscopic technologies, including, but not limited to, patient discomfort, endoscopist fatigue, narrow field of view and missed pathology behind colonic folds. Rapid developments in medical robotics have led to the emergence of a variety of next-generation robotically-augmented technologies that could overcome these limitations.

AIM

To provide a comprehensive summary of recent developments in the application of robotics in lower gastrointestinal tract endoscopy.

METHODS

A systematic review of the literature was performed from January 1, 2000 to the January 7, 2021 using EMBASE, MEDLINE and Cochrane databases. Studies reporting data on the use of robotic technology in *ex vivo* or *in vivo* animal and human experiments were included. In vitro studies (studies using synthetic colon models), studies evaluating non-robotic technology, robotic technology aimed at the upper gastrointestinal tract or paediatric endoscopy were excluded. System ergonomics, safety, visualisation, and diagnostic/therapeutic capabilities were assessed.

RESULTS

Initial literature searching identified 814 potentially eligible studies, from which 37 were deemed suitable for inclusion. Included studies were classified according to the actuation modality of the robotic device(s) as electromechanical (EM) (n = 13), pneumatic (n = 11), hydraulic (n = 1), magnetic (n = 10) and hybrid (n = 2) mechanisms. Five devices have been approved by the Food and Drug Administration, however most of the technologies reviewed remain in the early phases of

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Grade C (Good): 0
Grade D (Fair): 0
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testing and development. Level 1 evidence is lacking at present, but early reports suggest that these technologies may be associated with improved pain and safety. The reviewed devices appear to be ergonomically capable and efficient though to date no reports have convincingly shown diagnostic or therapeutic superiority over conventional colonoscopy.

CONCLUSION
Significant progress in robotic colonoscopy has been made over the last couple of decades. Improvements in design together with the integration of semi-autonomous and autonomous systems over the next decade will potentially result in robotic colonoscopy becoming more commonplace.

Key Words: Robotics; Colonoscopy; Endoscopy; Automation; Actuation; Propulsion

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Core Tip: Robotic technologies have the potential to transform lower gastrointestinal tract endoscopy into a quicker, safer, more reliable and less painful procedure. In the long term, benefits for patients, endoscopists and the wider healthcare industry are foreseeable, though these have yet to be convincingly demonstrated in human trials. Most studies to date have employed *ex vivo* modelling and high quality level 1 evidence is currently lacking in this field. Robotic technologies are evolving with such rapidity at the moment, that future robo-endoscopic systems are likely to look and behave very differently to conventional master-slave systems currently in use. Exciting developments in 3D printing, soft robotics, autonomous functionality and augmented reality are likely to converge to lead to the development of truly next generation robotic endoscopy devices.

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INTRODUCTION

Conventional optical colonoscopy represents the gold standard investigation for lower gastrointestinal (LGI) tract pathology including colorectal cancer (CRC), polyps and inflammatory bowel disease[1]. Current generation colonoscopes consist of a semi-rigid flexible scope containing fibre optic bundles with a camera at the distal end allowing visualisation of the colonic lumen. The scope tip can be manoeuvred in two directions *via* twin-wheels located on the control shaft of the scope, where buttons controlling air insufflation, suction and irrigation mechanisms are also located. Passage of instruments through a working channel running along the body of the scope also allows the endoscopist to perform diagnostic and therapeutic interventions. Typically, a standard scope will have a diameter of 11-13 mm with a length of approximately 160 cm[2,3]. Though this model has undergone subtle refinements in recent years, the basics of the technology remain largely unchanged. While being a familiar, well developed and effective tool for LGI tract diagnosis and therapy, current technologies in optical colonoscopy remain imperfect and are subject to a number of inherent limitations. These include the limited field of view, challenges identifying and treating mucosal lesions proximal to haustral folds, procedure-related pain, and risk of perforation. Pain during colonoscopy is multifactorial in origin, most often resulting from gas distension, looping of the scope and stretching of the mesocolon[4]. Loop formation and mucosal scope trauma have the potential to cause significant iatrogenic injury to the bowel, especially in areas affected by disease[4,5] In addition, colonoscopy is associated with a long learning curve [typically > 200 procedures are required before 90% caecal intubation rates (CIR) are achieved[6,7]] and poor user ergonomics, which have been shown to result in musculoskeletal injury for the endoscopist[8].

Patient discomfort during LGI endoscopy is primarily responsible for 94.6% of colonoscopies being performed under intravenous sedation in Great Britain, and 96% in the United States[9]. However sedation does not improve CIR, increases discharge times and is costly[10]. Therefore, the development of better tolerated methods for endoscopic assessment of the large bowel with reduced sedation requirements is an urgent priority. The most serious complications associated with colonoscopy are perforation and bleeding, which occur with a frequency of 3-8 *per* 10000 and 1.6 *per* 1000 colonoscopies, respectively[1]. Though these are infrequent endpoints, addressing current physical limitations with the optical colonoscope may help to further diminish their likelihood[11]. Future technologies for colorectal tract assessment would ultimately benefit from being safer and better tolerated whilst simultaneously maximising on outputs in terms of key performance indicators such as achieving CIR ≥ 95% and adenoma detection rates (ADR) of ≥ 20%[1]. Recent advances in medical robotics offer the potential to overcome the disadvantages of conventional colonoscopy, and engineers have been seeking to develop robotic prototypes capable of endoluminal exploration and visualisation since the early 1990s[12]. In particular, the concept of 'front-wheel' actuation, in contrast to the 'rear wheel' pushing mechanism used in conventional colonoscopy has generated considerable interest, as this may possibly reduce procedural pain, the need for sedation and the incidence of iatrogenic colonic injury[13]. Robotic systems may offer a wider field of view and implementation of higher degrees of motional freedom may enhance manoeuvrability and luminal views, leading to improved ADR. The introduction of semi-automated and even fully automated robotic endoscopic platforms has the potential to flatten the learning curve and minimise endoscopist fatigue[14].

The successful application of robotic devices in coronary artery bypass procedures or valvular surgery, and in advanced bronchoscopy, highlight the potential utility of this advanced technology in circumstances where the operator is performing fine tasks within a restricted working environment[15,16]. The same should apply in endoscopy, though comparatively LGI endoscopy has been slow to embrace robotic technologies potentially because of perceived cost barriers, and a lack of understanding of how the technology can improve on the existing formula. Herein we provide a comprehensive narrative review of the state-of-the-art of robotics in lower GI endoscopy.

MATERIALS AND METHODS

Search strategy

Systemic review principles were adhered to in accordance with Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA) guidelines[17] An electronic literature search was undertaken using EMBASE, MEDLINE and Cochrane Central Register of Controlled Trials (CENTRAL) databases (from January 1, 2000 to January 7, 2021). The following MeSH terms were used: "robot", "robotic", "robot assist", "colonoscopy", "flexible sigmoidoscopy", "proctoscopy". Original work reviewing the use of robotic technology in lower GI endoscopy (colonoscopy, flexible sigmoidoscopy or proctoscopy) utilising *ex vivo* or *in vivo* studies in animal and human colons were included. There was no limitation on language and type of bowel pathology studied (polyp, CRC, inflammatory bowel disease *etc*.). Studies evaluating non-robotic technology, robotic technology aimed at the upper gastrointestinal tract, robotic-assisted endoscopy for minimally invasive surgery, robot assisting devices for conventional colonoscopy (such as the The EndoDrive® (ECE Medical Products, Erlangen, Germany) or the Endoscopic Operation Robot)[18] and paedia-tric endoscopy were excluded.

Data extraction

Two authors (HKSIS and EA) independently performed literature searches and determined eligibility of studies. Once consensus was reached on studies meeting predefined inclusion criteria, the following data were extracted from included studies: First author's name, country in which the study was performed, month and year of publication, study design, components of the robotic endoscopic platform, size/length of the endoscopic capsule or flexible scope, illumination method, visualization method, actuation method, data transmission method, aim of robot intention (visualization, diagnosis, treatment, other), degree of robot navigational assistance, type of colon model and results were collected.

RESULTS

A total of 814 records were identified through initial literature searching. Duplicates and obviously irrelevant abstracts were excluded at title and abstract level, leaving 62 articles, which were reviewed fully. Twenty-five articles were further excluded because they were: Review articles (n = 13); studies evaluating robotic devices using *in vitro* synthetic colon/other (n = 4); assessing robot assistance devices coupled to a standard colonoscope (n = 2); evaluating swallowable wireless capsules without active actuation mechanisms (n = 4); evaluating surgical rather than endoscopic platforms (n = 2). A total of 37 studies were included in the final qualitative analysis (Figure 1). For ease of interpretation of this review, studies have been classified according to mode of actuation, that is the principle active method of robotic motion for each technology. Modes of actuation were defined as EM (n = 13), pneumatic (n = 11), hydraulic (n = 1), magnetic (n = 10) and hybrid (n = 2).

EM actuation

EM actuation is where electrical energy is used to bring about mechanical motion. This is usually brought about by a tether (containing wires) attached to the robotic device and to an external power source. Wireless devices without a tether will require an internal battery to provide power which takes up space. The tether will provide additional weight and friction as it slides along the mucosa which the robot will need to overcome. Either way considerable power is usually required[19,20]. A summary of studies investigating this mode of actuation is provided in Table 1.

Two EM actuation robotic endoscopic systems were developed and received Food and Drug Administration (FDA) approval, though these are now no longer commercially available[19]. The Invendoscope SC40 (Invendo Medical, Kissing, Germany) is a motorised colonoscope, controlled by a joystick and actuated by an inverted sleeve mechanism and a driving unit with 8 wheels. It is 18 mm in diameter and has a visualisation module and a 3.2 mm working channel (Figure 2). Two trials on humans have been carried out to evaluate this platform. The first, in 34 healthy volunteers showed a CIR of 82%, with 92% of patients 'pain free' and no acute complications were reported [21]. The purported strength of this system was the combination of a highly flexible endoscope shaft with the proprietary 'inverted sleeve' technology, which the developers believed could permit potentially 'painless' colonoscopy, as no direct forces are applied against the intestinal walls while the device passes through narrow intestinal convolutions. Invendo medical Gmbh was acquired by Ambu A/S with plans to release a single use robotic colonoscope in 2021[19,22]. Another study in 61 asymptomatic individuals with an average risk of CRC willing to undergo CRC screening found a CIR of 98.4%, with a median caecal intubation time (CIT) of 15 min. Only 4.9% of patients required sedation[23]. The Neoguide Endoscopy System (Neoguide Endoscopy System Inc., Los Gatos, CA United States) has a scope diameter of 14-20 mm and consists of 16 actuator segments under EM control to bring about movement. It also contains a tip position sensor, an external position sensor and a 3.2 mm working channel. A trial on 10 individuals undergoing CRC screening or routine diagnostic colonoscopy showed a CIR of 100% with a median CIT of 20.5 min. Adenomas were successfully removed with snare or forceps and there was no evidence of complications at 30 d follow up[24]. With this platform, the position and angle of the scope's tip are encoded into a computer algorithm. As the scope moves forwards, the algorithm directs each successive actuator segment to assume the same shape/position that the tip had for that given insertion depth. The insertion tube thus changes its shape at different insertion depths in a "follow-the-leader" manner, which should minimise discomfort. Neoguide Endoscopy System Inc. was acquired by Intuitive Surgical Inc. and the technology translated to robotic lung biopsy[19]. Several other non-certified EM actuation devices have been developed and below these have been categorised further based on their distinct physical properties which bring about motion.

Legs: A 12-legged capsule was developed by Valdastri *et al*[25], comprising two motors, a bidirectional communication platform and a human machine interface (HMI) capable of semi-autonomous intrinsic EM actuation (Figure 2). The capsule measures 12.8 mm in diameter and 33.5 mm in length. The device was designed to strike a versatile balance between size and ability to traverse the bowel. The device was tested in a porcine gut model and was able to traverse the complete length of the colon (140 cm) at an average speed of 5 cm/min[25]. Though a little slower in terms of pace, this device highlights the potential for miniaturisation of devices in robotic endoscopy.

Table 1 Summary of the included studies reviewing robotic lower gastrointestinal endoscopy devices with electromechanical actuation

Ref.	Design and actuation components of evaluated robotic system(s)	Endoscope and/or capsule dimensions	Mode(s) of actuation	Mode(s) of illumination and luminal visualisation	Capabilities evaluated	Degree of robot navigational assistance	Study methodology	Main findings
Rösch *et al* [21], 2008 (Germany)	InvendoscopeTM SC40 (Invendo Medical, Kissing, Germany): Colonoscope with an inverted sleave mechanism, propulsion connector, endoscope driving unit, hand-held control unit, 3.2 mm working channel	18 mm diameter, 170-200 cm length.	Electromechanical	Three white LEDs, CMOS vision chip with a field of view of 114 degrees	Visualisation	Direct Robot control	*In vivo*: *n* = 34 Human, heathy volunteers	CIR of 82%. Pain free procedure in 92% of cases. Mean pain score 1.96/6. 0% required sedation. No complications
Groth *et al* [23], 2011 (Germany)	InvendoscopeTM SC40 (Invendo Medical, Kissing, Germany): Colonoscope with an inverted sleave mechanism, propulsion connector, endoscope driving unit, hand-held control unit, 3.2 mm working channel	18 mm diameter, 170-200 cm length	Electromechanical	Three white LEDs, CMOS vision chip with a field of view of 114 degrees	Visualisation, Diagnosis, Treatment	Direct Robot control	*In vivo*: *n* = 61 Human, Asymptomatic individuals at average risk of CRC willing to undergo CRC screening	CIR of 98.4%. Sedation required in 4.9%. Median CIT of 15 min. Mean pain/discomfort score: 2.6. 32 of 36 polyps successfully removed with snare or forceps. 1 flat polyp required referral for conventional colonoscopy and 3 polyps seen on introduction could not be found on withdrawal
Eickhoff *et al* [24], 2007	The NeoGuide Endoscopy System (NeoGuide Endoscopy System Inc., Los Gatos, CA United States): Scope with 16 actuator segments, steering dials to control the tip and Tip position sensor. External position sensor, support arm, 3.2 mm working channel, video processor and control unit. Computed 3D mapping of the colon	173 cm in length, 14-20 mm in diameter	Electromechanical	Conventional CCD camera	Visualisation, safety and ease of use	Semi-autonomous	*In vivo*: *n* = 10 Humans requiring screening or diagnosis	CIR is 100%. Median CIT is 20.5 min. Adenomas successfully removed with snare or forceps. No acute colonic trauma (bleeding, perforation, submucosal petechiae). No complications at 30 d follow up. Detection and correction of looping is 100%. Physician satisfaction is 100%
Valdastri *et al*[25], 2009 (Italy)	Legged capsule consisting of two leg sets (six legs each with hooked round tips), 2 motors, bidirectional communication platform, HMI in LabVIEW	11 mm diameter by 25 mm long	Electromechanical	No camera in this prototype	Locomotion and safety	Semi-autonomous	*Ex vivo*- Porcine colon between two fixtures and 140 cm porcine colon placed in an abdominal phantom	Porcine colon between two fixtures: The 12-legged capsule distended the colon in a uniform manner. Maximum pulling force of the capsule on the colon wall: 0.2 N. Porcine colon in abdominal phantom: Capsule was able to traverse the complete length of the colon, Average speed was 5 cm/min
Lee *et al*[26], 2019 (Korea)	Legged robotic colonoscope, reel controller with external motor, Bowden cable and control system. The robot has 6 legs covered with silicone	Robot: 16 mm diameter (33 mm with legs deployed) by 49 mm in length. Bowden cable: 5 mm diameter by 1 m length	Electromechanical	Not described	Locomotion and safety	Autonomous	*Ex vivo*: Excised porcine colon	Locomotion velocities: Straight path: 9.5 mm/s. Incline at 30 degrees: 7.1 mm/s. Incline at 60 degrees: 5.1 mm/s. No mucosal damage or perforations
Trovato *et al* [27], 2010 (Japan)	Robotic colonic endoscope consisting of a front body with a clockwise helical fin, DC motor and rear body with an anti-clockwise helical fin; Reinforcement	170 mm in length, 30 mm in diameter	Electromechanical	Not described. No Visualisation module in this prototype	Locomotion and safety	Semi-autonomous	*Ex vivo*: < 1 m Swine colon (6 specimens) attached to the inside of a cylindrical plastic	*Ex vivo*: Best travelled distance around 70 cm. Average velocity with Fixed input (15 trials): 21.47 mm/min. Average velocity with SARSA (18 trials): 40.71 mm/min (P = 0.02).

	learning algorithm (Q-learning and State-Action-Reward-State-Action)						tube. *In vivo*: Swine colon–10 trials, 5 min each	Average velocity with Q-learning (21 trials): 36.05 mm/min (P = 0.039). Robot with learned algorithms are more likely to pass through bends/tight passages. *In vivo*: Speed 11 mm/min. Best travelled distance is 55 mm. No acute mucosal damage
Kim *et al* [28], 2010 (Korea)	Paddling-based capsule endoscope: Capsule with camera module, DC motor and 6 paddles. Tether consisting of 4 cables extend from the capsule to the external controller	Capsule: 15 mm in diameter and 43 mm in length. Tether: 2 m	Electromechanical	A camera module with 125 degree field of view and which transmits images at 10 frames *per* second	Locomotion and safety	Semiautonomous	*Ex vivo*: Porcine colon set up in 2 positions (sloped 27.5 degrees, straight length 35 cm or sloped 37.5 degrees, straight length 62 cm). *In vivo*: 1 pig–8 trials	*Ex vivo*: Velocity in sloped 27.5 degrees, straight length 35 cm colonic segment: 36.8 cm/min. Velocity in sloped 37.5 degrees, straight length 62 cm colonic segment: 37.5 cm/min. *In vivo*: Mean velocity: 17 cm/min over 40 cm length. Complications: Pinpoint erythema on colonic mucosa seen
Wang *et al* [29], 2006 (China)	Worm like robotic endoscope system consisting of a microrobot, controller and personal computer. The microrobot consists of a head cabin with the visualisation module and 3 mobile cells connected to the controller by an electric cable. Each mobile cell contains a linear electromagnetic driver	9.5 mm in diameter, 120 mm in length	Electromechanical	CCD camera and lights	Locomotion	Semi-autonomous	*Ex vivo*: Porcine colon	Robot travels the colon length (112 cm) in 7.3 min. Robot able to move forward, backward or remain static based on controller commands
Wang *et al* [30], 2007 (China)	Worm like robotic endoscope system consisting of a microrobot, controller and personal computer. The microrobot consists of a head cabin with the visualisation module and 3 mobile cells connected to the controller by an electric cable. Each mobile cell contains a linear electromagnetic driver. Additional deflection mechanism after the head cabin controls the camera's pose	10 mm in diameter, 110 mm in length	Electromechanical	CCD camera and lights	Locomotion	Semi-autonomous	*Ex vivo*: Porcine colon	Robot travels the colon length (112 cm) in 7.3 min
Wang *et al* [31], 2017 (China)	Worm like robotic endoscope consisting of a head cabin and three independent segments; each segment is composed of a linear locomotor with micromotor, turbine-worm and wire wrapping-sliding mechanism. The robot is entirely covered by an external soft bellow	13 mm diameter, 105 mm in length	Electromechanical	Not described	Locomotion and safety	Semi-autonomous	*In vivo*: Porcine colon	Greater speed in straight rather than curved paths. Speed ranges from 1.62-2.2 mm/s. Robot travels the entire colon in 119 s. Distance is not specified. No breakage or damage to the colonic mucosa
Naderi *et al* [32], 2013 (Iran)	Robot with a camera, 2 clampers, 5 discs and 15 springs allowing bending and steerability, 3 motors; Driving kit, HMI in MATLAB and Joystick	19 mm in diameter, 180 mm in length.	Electromechanical	Camera	Locomotion and safety	Semi-autonomous	*Ex vivo*: Sheep colon, 2 positions: Straight or with an 84 degree bend	Velocity: Straight path: 18.4 cm/min. Curved path: 10.5 cm/min. No significant trauma
Lee *et al*[26], 2019 (Korea)	3 elastic PTFE caterpillars with worm gear, steering module, camera module, flexible shaft with steering knobs and wires, external motor and controller	130 mm in length, 55 mm maximum diameter	Electromechanical	LED lamps and camera	Locomotion and visualisation	Direct robot operation	*Ex vivo*: 1 m excised porcine colon placed in an abdominal phantom. *In vivo*: 1 mini pig	*Ex vivo*: Velocity of the robotic colonoscope: 3.0 mm/s; CIR is 50%; CIT is 8.55 min. *In vivo* : Failed caecal intubation with difficulty travelling through fluid and faecal material
Formosa *et*	Endoculus- treaded (4) robotic capsule	2 m tether	Electromechanical	CMOS camera with	Locomotion,	Direct robot	*Ex vivo*: 40 cm excised	*Ex vivo*: Able to move in forward/reverse

al[34], 2020 (United States)	endoscope consisting of an inertial measurement unit, two motors, air/water channels, a tool port, flexible tether connected to a control board and laptop with controller		adjustable LEDs	visualisation and channel function	operation	porcine colon. *In vivo*: 1 pig	directions at 40 mm/s and whether the colon was collapsed or inflated. Also able to pass tight haustra and make turns. *In vivo*: Camera, insufflation, irrigation and biopsy tools functioned as expected

LEDs: Light emitting diodes; CMOS: Complementary metal-oxide-semiconductor; CIR: Caecal intubation rate; CIT: Caecal intubation time; CCD: Charged coupled device; HMI: Human machine interface.

A legged colonoscope consisting of six legs covered in silicone and a Bowden cable connecting the device to an external motor and control system was tested in excised porcine colon of varying paths to determine locomotive efficacy and safety. It was able to travel at decreasing velocities of 9.5 mm/s, 7.1 mm/s and 5.1 mm/s on straight, 30 degree curved and 60 degree curved paths, respectively. No mucosal damage or perforations were observed during testing[26]. The diameter of the device is 16 mm without the legs deployed and 33 mm when they are.

Fins: A novel capsular device, 170 mm in length and 30 mm in diameter, consisting of a front body with a clockwise helical fin and rear body with an anti-clockwise helical fin was developed by a team in Japan. The bodies are connected by a DC motor and the device is computationally reinforced with learning algorithms to improve effectiveness of motion through iterative learning. It was tested in *ex vivo* and *in vivo* porcine colon models and *ex vivo* trials demonstrated improved movement performance with learned algorithms. *In vivo* trials showed an average speed of 11 mm/min with no acute mucosal damage[27].

Paddles: A tethered capsule endoscope containing a camera module, DC motor and 6 paddles measuring 15 mm in diameter was evaluated in *ex vivo* porcine colon as well as in an *in vivo* porcine model (Figure 2). At a slope of 27.5 degrees (length: 32 cm) and 37.5 degrees (straight length: 62 cm), impressive forward motion speeds of 36.8 cm/min and 37.5 cm/min were achieved. The mean velocity reached in the *in vivo* model over a distance of 40 cm was 17 cm/min. A degree of minor paddle-trauma was noted on the mucosa which may present a safety concern[28].

Worm-like: Wang *et al*[29,30] created two similar earth-worm like robotic endoscopes. The initial system consisted of a microrobot, controller and user interface. The microrobot in turn consists of a head cabin with the visualisation module and 3 mobile cells connected to the controller by an electric cable. Each mobile cell contains a linear electromagnetic driver[29,30]. The microrobot was able to travel along the porcine colon length (112 cm) in 7.3 min[29,30]. The worm-like device is pictured in Figure 2.

Later, a similar microrobot was created by the same team with two notable design adjustments: Each segment with this updated prototype is composed of a linear locomotor with its own micromotor, turbine-worm and wire wrapping-sliding mechanism, and the microrobot is entirely covered by an external soft 'bellow'. The soft bellow acts to increase the friction gradient between the robot and the colonic

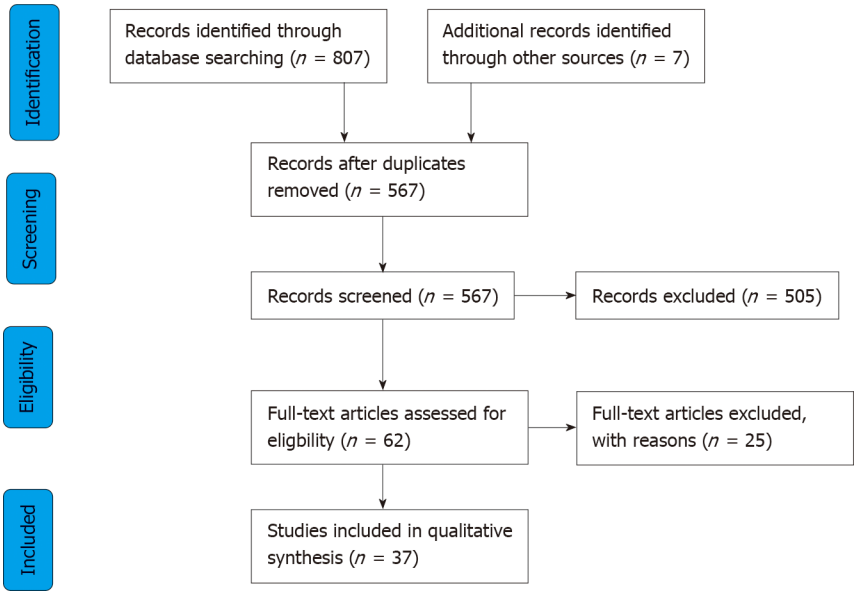

Figure 1 PRISMA flow diagram.

mucosa which should improve locomotion ability. This device was tested in *in vivo* porcine experiments and demonstrated average speeds of up to 2.2 mm/s, with no mucosal damage reported[31].

A robot with a camera, two clampers, three motors, 5 discs and 15 springs was created to allow worm-like flexible movement. It could be driven using a joystick and is 19 mm in diameter and 180 mm long. Motion ability and safety were tested in sheep colon in a straight or curved (84 degree bend) path. The device travelled at 18.4 cm/min and 10.5 cm/min in straight and curved colonic segments, respectively. No mucosal trauma was seen[32]. Overall worm-like devices appear safe with a variable speed.

Caterpillars: A robot with 3 elastic caterpillars, designed to expand the colonic lumen while causing little trauma was able to travel at 3 mm/s and achieve caecal intubation 50% of the time at 8.55 min in porcine colon placed within a human abdominal phantom[33]. Unfortunately, in an *in vivo* experiment, the robot failed to achieve caecal intubation as it had difficulty travelling through fluid and faeces[33].

Treads: A treaded (4 treads) robotic capsule with two motors, connected *via* a flexible tether to a control printed circuit board and laptop (Figure 2) was tested in excised porcine colon and was able to move in forward and reverse directions at 40 mm/s even with the bowel wall collapsed[34]. The treads allow traction between the device and the colonic mucosa to allow effective locomotion. It was also able to pass tight haustra and make turns due to the presence of the second motor and resulting increased degrees of locomotion freedom. The device also had a visualisation module and channels for air, water and tools. Camera, insufflation, irrigation and biopsy tools all functioned effectively during *in vivo* porcine testing[34].

Electropneumatic actuation

Electropneumatic (EP) actuation involves the use of pressurised gas to bring about motion. The Aer-o-scope (GI View Ltd, Ramat Gan, Israel), Endotics [ERA Endoscopy S.r.l., Peccioli (Pisa), Italy] and Sightline Colonosight systems (Stryker GI, Dallas, Tex, Haifa, Israel) are all examples of FDA approved EP robotic systems with a visualisation module and channels for insufflation, suction and irrigation.

The Aer-o-scope system works by generating a gas (carbon dioxide) pressure gradient between a rectal balloon inflated in the anus and a balloon located at the tip of the scope. Safety mechanisms ensure that the pressure in the colon does not exceed 54 m bar. The scope is only 5.5 mm in diameter (Figure 3). *In vivo* studies on healthy human volunteers (n = 12) or those requiring CRC screening (n = 56) have reported CIR ranging from 83%-98%, average CIT of 23 min and no acute complications other than mild mucosal petechiae in some instances[35,36]. Four of twelve patients required sedation[35]. In those undergoing CRC screening, the polyp detection rate was 87.5% and mucosal visualisation was rated as 'excellent' by participating endoscopists[30].

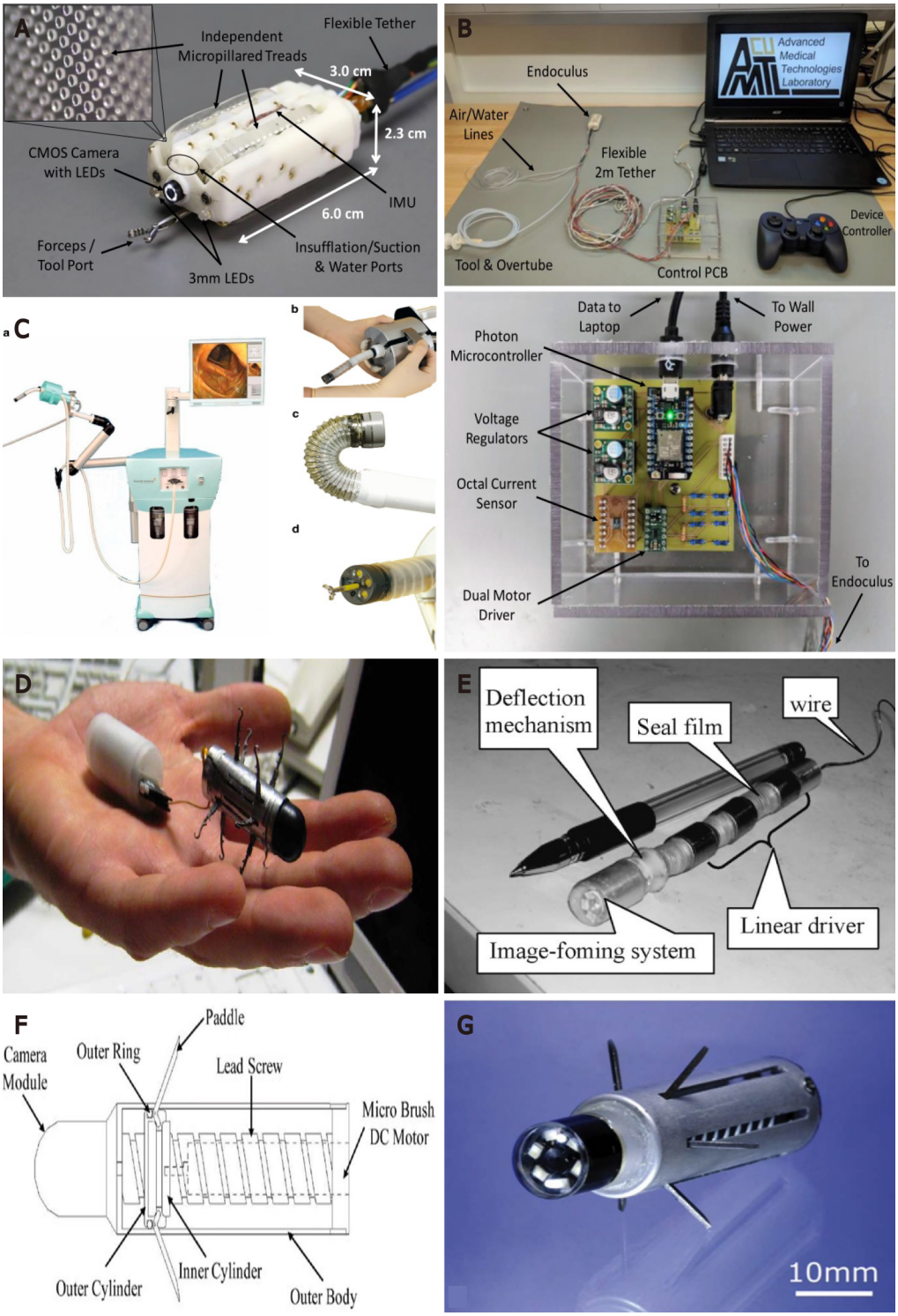

Figure 2 Examples of electromechanical robotic devices. A: The treaded "Endonculus" tethered robot in isolation; B: The treaded "Endonculus" robot with its full operational set up and printed circuit board.Citation for A and B: Formosa GA, Prendergast JM, Edmundowicz SA, Rentschler ME. Novel Optimization-Based Design and Surgical Evaluation of a Treaded Robotic Capsule Colonoscope 2020; 36: 545-552. Copyright© The Authors 2020. Published by IEEE. C: The Invendoscope System with the tip in the driving motor, in full flexion and with a biopsy forceps in the working channel. Citation: Groth S, Rex DK, Rösch T, Hoepffner N. High cecal intubation rates with a new computer-assisted colonoscope: a feasibility study. *Am J Gastroenterol* 2011; 106: 1075-1080. Copyright© The Authors 2011. Published by American College of Gastroenterology. D: The six legged capsule device by Valdastri *et al*[25]. Citation: Valdastri P, Webster RJ, Quaglia C, Quirini M, Menciassi A Dario P. A New Mechanism for Mesoscale Legged Locomotion in Compliant Tubular Environments. *IEEE Transactions on Robotics* 2009; 25: 1047-1057. Copyright© The Authors 2009. Published by IEEE. E: A worm-like endoscope prototype. Citation: Wang K, Yan G. Micro robot prototype for colonoscopy and *in vitro* experiments. *J Med Eng Technol* 2007; 31: 24-28. Copyright© The Authors 2007. Published by Taylor & Francis Ltd. F: Cross-sectional paddled capsular device; G: Complete paddled capsular device. Citation for F and G: Kim HM, Yang S, Kim J, Park S, Cho JH, Park JY, Kim TS, Yoon ES, Song SY, Bang S. Active locomotion of a paddling-based capsule endoscope in an *in vitro* and *in vivo* experiment (with videos). *Gastrointest Endosc* 2010; 72: 381-387. Copyright© The Authors 2010. Published by Elsevier.

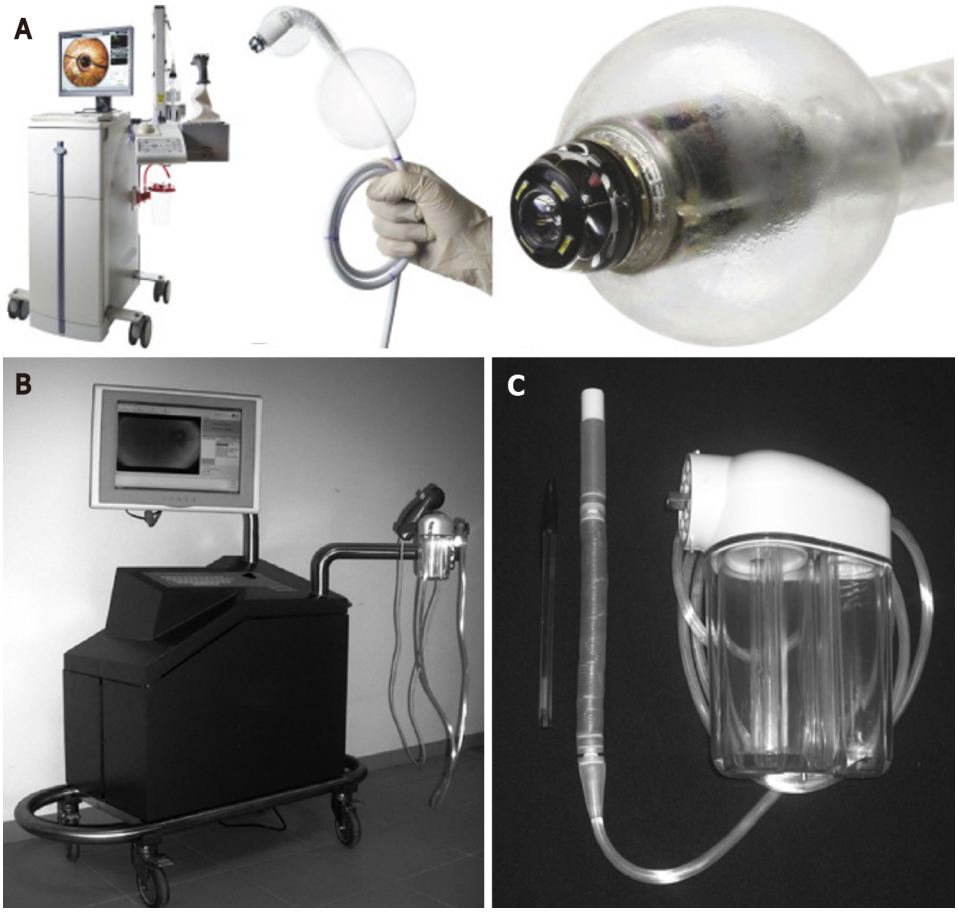

Figure 3 Examples of pneumatic robotic devices. A: The Aer-O-scope system. Citation: Gluck N, Melhem A, Halpern Z, Mergener K, Santo E. A novel self-propelled disposable colonoscope is effective for colonoscopy in humans (with video). *Gastrointest Endosc* 2016; 83: 998-1004.e1. Copyright© The Authors 2016. Published by ELSEVIER open access. B: and C: The Endotics System. Citation: Cosentino F, Tumino E, Passoni GR, Morandi E, Capria A. Functional evaluation of the endotics system, a new disposable self-propelled robotic colonoscope: *in vitro* tests and clinical trial. *Int J Artif Organs* 2009; 32: 517-527. Copyright© The Authors 2009. Published by SAGE Publications, Ltd.

The Aer-o-scope provides a 360 panoramic vision system in addition to a complementary metal-oxide-semiconductor (CMOS) camera which allows improved visualisation. In an *In vivo* study with 12 anaesthetised pigs with surgically simulated colonic 'polyps' the Aer-o-scope visualised 94.9% of polyps compared to 86.8% achieved with standard optical colonoscopy ($P = 0.002$)[37].

The Endotics system consists of a flexible probe with a head, body and tail, EP connector and a workstation (Figure 3). Two clampers located at the proximal and distal ends of the probe aid movement. *Ex vivo* testing using porcine colon has suggested that the stress exerted on the colonic wall using this device is 90% less than in standard colonoscopy[38]. This should in theory translate into a reduced need for analgesia and sedation. In fact, two human trials showed that Endotics was less painful on a scale of 1 to 10 (0.9 *vs* 6.9)[38] and did not require any sedation (0% *vs* 19.7%, $P < 0.001$)[39] compared to conventional colonoscopy[38,39]. This device can achieve CIR as high as 92.7% within 29 min[40]. Diagnostically, in individuals with a family history of CRC and/or polyps, the Endotics System showed a sensitivity, specificity, positive predictive value and negative predictive value of 93.3%, 100%, 100% and 97.7%, respectively[39]. The Endotics system has also demonstrated a short learning curve: Two blocks of consecutive patients underwent LGI endoscopy using the Endotics platform with improvements in CIR (85.2% *vs* 100%), intubation time (55 min *vs* 22 min, $P = 0.0007$) and withdrawal time (21 min *vs* 16 min)[40]. Importantly, in an evaluation of 102 patients previously having undergone failed colonoscopy, 95 patients (93.2%) underwent successful caecal intubation with the Endotics system[41].

The Sightline ColonoSight system consists of a reusable scope covered by a disposable sleeve and connected to an air pressure engine[42]. Shike and colleagues evaluated the performance of this system in 178 human study participants and reported a CIR of 90% with a mean CIT of 11.2 min. Scope advancement with this device is facilitated by self-propulsion of the instrument affected by an air-pressure-

powered engine and LED illumination eliminates the need for fiber optics and an external light source.

Other non-certified EM actuation robotic devices include the "EndoCrawler" which consists of longitudinal and circumferential rubber bellow pneumatic actuators joined in four segments with a bending tube to allow steering between the first two segments [43]. When pressurised air enters the bellow, it extends longitudinally. It has a central hollow cavity for insufflation, irrigation, suction and instrument channels as well as charged coupled device cables to pass through. It has undergone *ex vivo* testing in human cadaveric colon which demonstrated clear visualisation capabilities and an average speed of 200 mm/min. *In vivo* assessment using a live porcine model also demonstrated some encouraging findings, though difficulties were encountered when attempting to negotiate sharp bends. These issues notwithstanding, this early prototype again demonstrates the potential for self-propulsive, remotely controlled robotic devices for endoluminal assessment[43].

In 2017, a simple colonoscopy robot consisting of the robot (tip with camera, latex tubing and anal fixture) with an external pneumatic circuit was developed. Locomotion feasibility and safety was tested in porcine colon. The device was able to traverse the entire length of the colon in 71.4% of trials, able to traverse the entire length of colon with additional bends in 90.9% of trials, had an average speed of 28 mm/s with an average CIT of 54.2 s. The maximum propulsive force was 6 N *i.e.*, an acceptable pressure on the colonic mucosa however balloon rupture led to damage including tearing of the porcine colon[44].

A further pneumatic device consisting of three segments, each containing two soft pneumatic balloons and two rigid connectors was developed and tested in excised pig colon. The balloons are twisted in the proximal and distal gripper segments but linear in the middle propulsion segment. A camera and channels for air flow and instruments are built in. The unactuated device is 22 mm in diameter. The robot travelled at 1 mm/s and was able to clearly visualise the colonic mucosa[45].

A summary of all studies evaluating robotic EM actuation systems for LGI endoscopy is provided in Table 2.

Hydraulic actuation

Hydraulic actuation uses a pressurised fluid medium such as water to progress through the colon. A meta-analysis of randomised controlled trials has previously shown that water immersion colonoscopy does significantly decrease pain scores and sedation rates without affecting the diagnostic quality or completeness of colonoscopy when compared with air intubation[46].

The "Hydraulic Colonoscope" system consists of a colonic vehicle (CV) connected to external pumps and valves *via* a tether. The CV contains a magnetic tracker and is surrounded by a balloon which may be inflated or deflated to create an appropriate seal with the colonic wall. The pump system is used to pump water into the colon behind the CV. An anal port prevents water from escaping the colon. Motion ability was trialled in porcine colon and compared to conventional colonoscopy. The device was able to reach the caecum in all attempts. There was no difference in the CIT or caecal pressure between the device and colonoscopy. However, significant differences were found in the maximum force exerted on the colon (0.63 N *vs* 2.2 N, $P = 0.004$), maximum anal pressure (1.53 kPa *vs* 4.53 kPa, $P = 1 \times 10^{-7}$) and mean anal pressure (0.05 kPa *vs* 1.5 kPa, $P = 0.0003$) between the device and conventional colonoscopy, respectively[47] (Table 2).

Magnetic actuation

Magnetic actuation is brought about externally through magnetic fields created either by an external permanent magnet (EPM) or electromagnetic coils[48]. Control of this field is crucial for locomotion as controlling the field allows movement of the device in a particular direction and orientation. The main advantage of external magnetic actuation is that it allows a 'front-wheel' motion without the need for large internal actuating motors. When an EPM is used, small internal permanent magnets (IPMs) incorporated into the luminal robot are required to generate the magnetic field. A power supply is generally not required. The resulting device is therefore less bulky and more likely to reduce pain and the need for sedation. Additionally, there is more scope to incorporate other subsystems. The EPMs can be moved manually and the magnetic field controlled directly by the user to cause luminal device movement. However, movement is non-linear and therefore complex. Other disadvantages include the ongoing need for insufflation and the continuous contact between the device and the colonic mucosa due to the continuous attraction between the EPM and IPM[48]. The magnetic fields generated may also interfere with nearby equipment as

Table 2 Summary of the included studies reviewing robotic lower gastrointestinal endoscopy devices with pneumatic or hydraulic actuation

Ref.	Design and actuation components of evaluated robotic system(s)	Endoscope and/or capsule dimensions	Mode(s) of actuation	Mode(s) of illumination and luminal visualisation	Capabilities evaluated	Degree of robot navigational assistance	Study methodology	Main findings
Vucelic *et al*[35], 2006 (Israel)	Aer-O-scope (GI View Ltd, Ramat Gan, Israel): Workstation and Disposable unit consisting of a rectal introducer, supply cable, scanning balloon, scope and rectal balloon. The supply cable connects the disposable unit to the workstation with its joystick and is able to transmit air, water and suction	5.5 mm diameter, 2.5 m length	Pneumatic	White LED, 360 panoramic vision system with CMOS camera with a field of view of 57 degrees	Visualisation and safety	Semi-autonomous	*In vivo*: n = 12 Human, healthy volunteers	CIR is 83%. Median CIT is 14 min with an average procedure duration of 23 min. Analgesia required in 2 patients. 4 patients had submucosal petechial lesions. No complications at 30 d follow up
Gluck *et al*[36], 2016 (Israel)	Aer-O-scope (GI View Ltd, Ramat Gan, Israel): Workstation and Disposable unit consisting of a rectal introducer, supply cable, scanning balloon, scope and rectal balloon. The supply cable connects the disposable unit to the workstation with its joystick and is able to transmit air, water and suction	5.5 mm diameter, 2.5 m length	Pneumatic	White LED, 360 panoramic vision system with CMOS camera with a field of view of 57 degrees	Visualisation and safety	Semi-autonomous	*In vivo*: n = 56 Human, CRC screening	CIR is 98.2%. Mean withdrawal time is 14 min. Polyp detection rate of 87.5%. 0 patients had submucosal damage. No complications at 48 h follow up. Rated as excellent visualisation by endoscopists
Gluck *et al*[37], 2015 (Israel)	Aer-O-scope (GI View Ltd, Ramat Gan, Israel): Workstation and Disposable unit consisting of a rectal introducer, supply cable, scanning balloon, scope and rectal balloon. The supply cable connects the disposable unit to the workstation with its joystick and is able to transmit air, water and suction	5.5 mm diameter, 2.5 m length	Pneumatic	White LED, 360 panoramic vision system with CMOS camera with a field of view of 57 degrees	Visualisation and detection	Semi-autonomous	*In vivo*: n = 12 pigs with surgically simulated colonic 'polyps'	A total of 36 Aer-O-scope and 24 colonoscopy procedures were performed. The Aer-o-scope visualised 94.9% of polyps compared to 86.8% with colonoscopy. This was significant (P = 0.002). Miss rates for polyps was 5.1% with Aer-O-scope and 13.2% (P = 0.002) with conventional colonoscopy. This significant difference is true for > 6 mm polyps
Cosentino *et al*[38], 2009 (Italy)	Endotics System [ERA Endoscopy S.r.l., Peccioli (Pisa), Italy]: Workstation with console and disposable flexible probe. The probe has 2 clampers to aid locomotion and a head (contains the camera, LEDs and channels for suction, irrigation and insufflation) a body and a tail	23-37 cm in length, 17 mm in diameter	Pneumatic	LED light source and CMOS camera with a field of view of 110 degrees	Visualisation and Safety	Semi-autonomous	*Ex vivo*: n = 1 porcine colon fixed to a human adult abdominal phantom. *In vivo*: n = 40 Humans, with a family Hx of CRC, known previous polyps and FOB positive requiring investigation	*Ex vivo*: The stress pattern was 90% less than with colonoscopy. *In vivo*: CIR was 27% for the endotics system compared to 82% with colonoscopy. The mean CIT was 57 min. The endotics system was described as less painful (0.9 *vs* 6.9). The endotics system has a higher diagnostic accuracy as it detected 2 polyps and 2 angiodysplastic lesions not identified with colonoscopy
Tumino *et al*[39], 2010 (Italy)	Endotics System (ERA Endoscopy S.r.l., Peccioli (Pisa), Italy): Workstation with console and disposable flexible probe. The probe has 2 clampers to aid locomotion and a head (contains the camera, LEDs and channels for suction, irrigation and insufflation) a body and a tail	25-43 cm in length, 17 mm in diameter	Pneumatic	LED light source and CMOS camera with a field of view of 110 degrees	Visualisation, sensitivity and specificity	Semi-autonomous	*In vivo*: n = 71 Humans, with a family Hx of CRC or polyps	Endotics system versus colonoscopy: CIR: 81.6% *vs* 94.3%. The average time for procedure completion: 45 min *vs* 23 min (P < 0.001). Patients requiring sedation: 0% *vs* 19.7% (P < 0.001). Endotics system for detecting polyps: Sensitivity: 93.3%; Specificity: 100%; Positive predictive value:

								100%; Negative predictive value: 97.7%
Trecca *et al*[40], 2020 (Italy)	Endotics System [ERA Endoscopy S.r.l., Peccioli (Pisa), Italy]: Second generation system- Workstation with console and disposable flexible probe. The probe has 2 clampers to aid locomotion and a head (contains the camera, LEDs, chromoendoscopy and channels for suction, irrigation and insufflation) a body and a tail	23-37 cm in length, 17 mm in diameter	Pneumatic	LED light source, chromoendoscopy and CMOS camera with a field of view of 140 degrees	Learning curve, visualisation and diagnostic accuracy, safety	Semi-autonomous	*In vivo*: n = 55 Humans, requiring diagnosis, CRC screening or surveillance. Training progress was evaluated by comparing two consecutive blocks of patients i.e. group A (first 27) and group B (last 28)	CIR is 92.7%. Median CIT is 29 min. Median withdrawal time is 18 min. Polyp detection rate: 40%; Adenoma detection rate: 26.7%; Advanced neoplasm: 0%; Complication: 1.8%-bleeding with polypectomy; Successful polypectomy and hot biopsy coagulation for bleeding. Mean VAS pain/discomfort: 1.8. Learning curve assessment, Group A *vs* Group B: CIR: 85.2% *vs* 100%. Median CIT: 55 min *vs* 22 min (P = 0.0007). Median withdrawal time: 21 min *vs* 16 min
Tumino *et al*[41], 2017 (Italy)	Endotics System (ERA Endoscopy S.r.l., Peccioli (Pisa), Italy): Workstation with console and disposable flexible probe. The probe has 2 clampers to aid locomotion and a head (contains the camera, LEDs and channels for suction, irrigation and insufflation) a body and a tail	25-43 cm in length, 17 mm in diameter	Pneumatic	LED light source and CMOS camera with a field of view of 110 degrees	Visualisation and performance	Semi-autonomous	*In vivo*: n = 102 Humans, previously failed caecal intubation on colonoscopy	CIR was 93.1% and therefore had a 95% performance. Mean CIT was 51 min
Shike *et al*[42], 2008 (Italy/Israel/United States)	Sightline ColonoSight (Stryker GI, Dallas, Tex, Haifa, Israel): A reusable scope with LEDs and camera at the tip and steering dials proximally. Tips is covered by a disposable sleeve with 3 working channels for suction, irrigation, insufflation and instruments. Electropneumatic unit, control unit and video monitor	Not described	Pneumatic	LED light source and camera	Visualisation, diagnosis and treatment	Semi-autonomous	*In vivo*: 2 pigs–To assess safety in terms of bacterial transmission to the reusable scope with a disposable sleeve covering. *In vivo*: 178 Humans, healthy volunteers and various clinical indications for colonoscopy	*In vivo*, Pigs: E.coli and E. Fergusonii from scope handle, shaft and tip before the procedure: Nil growth. E.coli and E. Fergusonii from scope handle, shaft and tip after the procedure: Nil growth. E.coli and E. Fergusonii from sheath covering after the procedure: Heavy growth. *In vivo*, Humans: CIR is 90%. Mean CIT is 11.2 min. Diagnoses of diverticulosis, polyps, colitis, haemorrhoids, normal or other was given. Successful polypectomy, biopsy and argon plasma coagulation. No complications at 2 wk follow up
Ng *et al*[43], 2000 (Singapore)	EndoCrawler: Longitudinal and circumferential rubber bellow actuators joined in four segments with a bending tube to allow steering between the first two segments and vision module; Central hollow cavity for instruments, insufflation, irrigation and suction channels and CCD cables. These exit the proximal end as a flexible cable similar to a colonoscope; LabWindows user interface and joystick	28 mm in diameter, 420 mm length	Pneumatic	CCD camera and light source	Locomotion and visualisation	Direct robot operation	*Ex vivo*- Cadaveric colon. *In vivo*-Pig	*Ex vivo*: Clear visualisation of colonic wall. Speed: 200 mm/min however required external pushing and couldn't progress beyond bends unless the head was deflected away from the colonic wall. *In vivo*: 'Red out' images throughout most of the robot's journey. Average speed: 150 mm/min with external pushing. Unable to progress beyond an acute bend
Dehghani *et al*[44], 2017 (United States)	Pneumatically driven colonoscopy robot consisting of the robot (tip with camera, latex tubing, tethered camera and anal fixture) and external pneumatic circuit and electric circuit with laptop	Not described	Pneumatic	Camera	Locomotion feasibility and safety	Semi-autonomous	*Ex vivo*: 1.5 m porcine colon in human phantom. Tests repeated 5-14 times depending on analysis performed	Able to traverse the entire length 71.4% (10/14 trials). Able to traverse the entire length with additional bends 90.9% (10/11 trials). Robot speed of 28 mm/s (5 trials). Average CIT is 54.2 s. (5 trials). Maximum propulsive force is 6 N (44 mmHg) which is less than the safe intraluminal pressure of 80

								mmHg. Balloon rupture led to damage including tearing of the porcine colon
Chen *et al*[45], 2019 (China)	Soft endoscopic device which consists of two gripper segments and one propulsion segment. Each segment contains two soft pneumatic balloons and two rigid connectors. The balloons are twisted in the gripper segments but linear in the propulsion segment. The connectors contain inner channels for air flow and instruments; Lab view interface. Air compressor with regulators, pressure sensors, valves and air pipes connected to the endoscopic device and a power source	The unactuated device is 95 mm in length and 22 mm in diameter.	Pneumatic	CCD camera	Locomotion and visualisation capability	Semi-autonomous	*Ex vivo*: Pig colon-one end fixed to a pipe, the other free. Colon placed in a horizontal position	Velocity to traverse the colon: 1 mm/s. Clear visualisation of the colonic mucosa
Coleman *et al*[47], 2016 (United Kingdom)	Hydraulic colonoscope system: A CV connected to extra-corporeal pumps and valves *via* a tether. The CV contains a magnetic tracker and is surrounded by a balloon which is flexible and may be inflated or deflated. The pump system is used to pump water into the colon behind the CV; Anal port and control system on HMI	CV dimensions not described. Tether: 1.8 m long, 6 mm in diameter	Hydraulic	No camera in this prototype however a dummy with a diameter if 11 mm and length of 25 mm is incorporated to simulate its presence	Comparison of CV locomotion under manual control or automatic control to colonoscopy	Direct or semi-autonomous	*Ex vivo*: Two 120 cm porcine colon placed in human abdominal phantom–6 trials *per* manual control, automatic control and colonoscopy	100% CV reached the caecum. CV *vs* colonoscopy: CIT: 3.95 *vs* 4.91 min (P = 0.43). Maximum force to the colon: 0.63 *vs* 2.2 N (P = 0.004). Maximum anal pressure: 1.53 *vs* 4.53 kPa ($P = 1 \times 10^{-7}$). Mean anal pressure: 0.65 *vs* 1.5 kPa (P = 0.0003). No difference in maximum or mean caecal pressure. Manual CV versus Auto CV: CIT: 2.11 *vs* 5.79 min (P = 0.02). Mean anal pressure: 1.86 *vs* 1.31 kPa (P = 0.03). No difference maximal anal pressure and maximum or mean caecal pressure

LEDs: Light emitting diodes; CMOS: Complementary metal-oxide-semiconductor; CIR: Caecal intubation rate; CIT: Caecal intubation time; CCD: Charged coupled device; HMI: Human machine interface; CV: Colonic vehicle.

they are permanent and cannot be turned on or off[3]. Electromagnetic coils can improve control over the magnetic field however they do require a power supply[19]. We have further classified these devices into whether or not they are wireless or tethered.

Wireless capsules

A swallowable wireless capsule with the aim of therapeutic control of bleeding was developed[49]. It consists of a surgical clip, 4 IPMs and a bidirectional communication platform and is able to actively locomote *via* a magnetic link generated by its interaction with an EPM. The EPM is mounted on a passive hydraulic arm that is moved manually by the user. A HMI under direction by the controller controls clip deployment. When tested 10 times in *ex vivo* porcine colon, the clip release occurred 100% of the time and was instantaneous. Moving the capsule was effective and fast although it took 2-3 min to align it appropriately against the mucosa to be clipped. *In vivo* in a pig, 'good' movement and positioning of the device with the EPM was observed. The clip was released successfully onto the desired target and it remained *in situ*. The amount of tissue grasped was also satisfactory. This capsule was 12.8 mm in

diameter and 33.5 mm in length[49].

Another wireless capsule with a set of IPMs, inertial and vision sensors and vision module, with an EPM mounted on a robotic arm was created[50]. The robotic arm was moved intelligently *via* closed loop steering and the HMI (Figure 4). Visualisation, motion feasibility and learning curve were tested in insufflated or collapsed porcine colon (500 mm) placed in a human abdominal phantom. In the collapsed colon, the device was only able to travel very short distances whereas there was a 100% success rate in traversing the whole length when the colon was insufflated with air. The average time required was 10 min. Novice medical doctors were able to drive the EPM in an effective way within 40 trials[50]. Using a robotic arm to steer the EPM was shown to provide better manoeuvrability and lesion detection rates compared to manual steering of the EPM[51].

Carpi and colleagues used the readily available PillCam capsule created by Given Imaging Ltd, Israel to visualise the small bowel and covered it in a magnetic shell to create a simple wireless capsule capable of magnetic actuation. The magnetic link was created between the shell and two EPMs controlled by a magnetic navigation system (Niobe, Stereotaxis, Inc, United States). This navigation system is already clinically in use in the field of robotic cardiology. A remote computer workstation and mouse was used to navigate the capsule. *In vivo* testing in a pig showed simply that such a capsule is capable of travelling through the colon without causing damage[52].

The magnetic controlled capsule endoscopy (MCCE) system (Chongqing Jinshan Science & Technology Group Co, Ltd) consists of an ingestible colon capsule with IPM and battery, an external magnetic manipulator with EPM, and an image transmission system. The capsule measures 27.9 mm in length and 13.0 mm in diameter. It was tested in 52 volunteers for CRC screening. The average time to reach the caecum was 3.63 h. Manoeuvrability of the capsule was good (94.3%) or moderate (5.77%). It was capable of providing good-quality pictures and identified 6 positive findings (polyps, diverticulum) which were confirmed by colonoscopy. All volunteers were able to swallow the capsule and excreted the capsule within 2 d. Complications included 7 mild adverse events (abdominal discomfort, nausea, and vomiting) lasting 24 h only [53].

Tethered capsules

Using the technology from[51] the "Magnetic Air Capsule", a device consisting of a capsule like frontal unit and a compliant multi-lumen tether was created[13]. The incorporation of the multi-lumen tether allows for intervention in addition to basic colonoscopy functions. The frontal unit contains a vision module, an IPM, a magnetic field sensor, and two channels, one for lens cleaning and the other for insufflation/suction/irrigation or instrument passage. The capsule is 11 mm in diameter, 26 mm in length and the tether is 2 m in length. 12 trials in 850 mm porcine colon placed in a human abdominal phantom with attached coloured beads (5 mm) mimicking polyps showed an 85% detection rate. 100% of which were successfully removed with a polypectomy snare. The mean completion time (inspection of the colon as well as removal of the 'polyps') was 11.3 min. Six trials in anaesthetised pigs showed device ability to navigate around bends and folds, retroflexion capability and successful operation of the working channels without a loss of magnetic link. In addition, there was no mucosal damage[13]. Using a similar prototype (Figure 5), visualisation and diagnostic ability was assessed 22 times in 850 mm of porcine colon and compared to that of colonoscopy. CIR for both was 100%. Compared to colonoscopy, pin detection rate was lower (80.9% with *vs* 85.8%) and procedure completion time (visualisation and diagnosis) was significantly longer [556 s *vs* 194 s ($P = 0.0001$)]. There was no difference in intuitiveness score[54].

Further advancement led to the "Magnetic flexible endoscope" (MFE). This tethered robot has a standard visualisation module and working channels for instruments, irrigation and insufflation. Additionally, it has a unique retroflexion control algorithm to improve this repetitive but technically challenging skill. Autonomous retroflexion ability was examined 30 times in an anaesthetised pig. Successful retroflexion manoeuvres with a mean time of 11.3 s were performed 100% of the time. No acute tissue trauma or perforation was seen[55]. A comparison of different degrees of locomotion autonomy was performed recently using the MFE in two pigs[14]. Completion times for Direct robot operation *vs* teleoperation *vs* semi-autonomous operation *vs* colonoscopy showed similar results over distances of 45 cm (9 min 4 s *vs* 2 min 20 s *vs* 3 mins 9 s *vs* 1 min 39 s) and 85 cm (unable to reach marker *vs* 8 min 6 s *vs* 9 min 39 s *vs* 3 min 29 s). Intelligent and semi-autonomous control had NASA Task Load Index[56] mean ratings lower/less demanding than colonoscopy or direct robot operation[14].

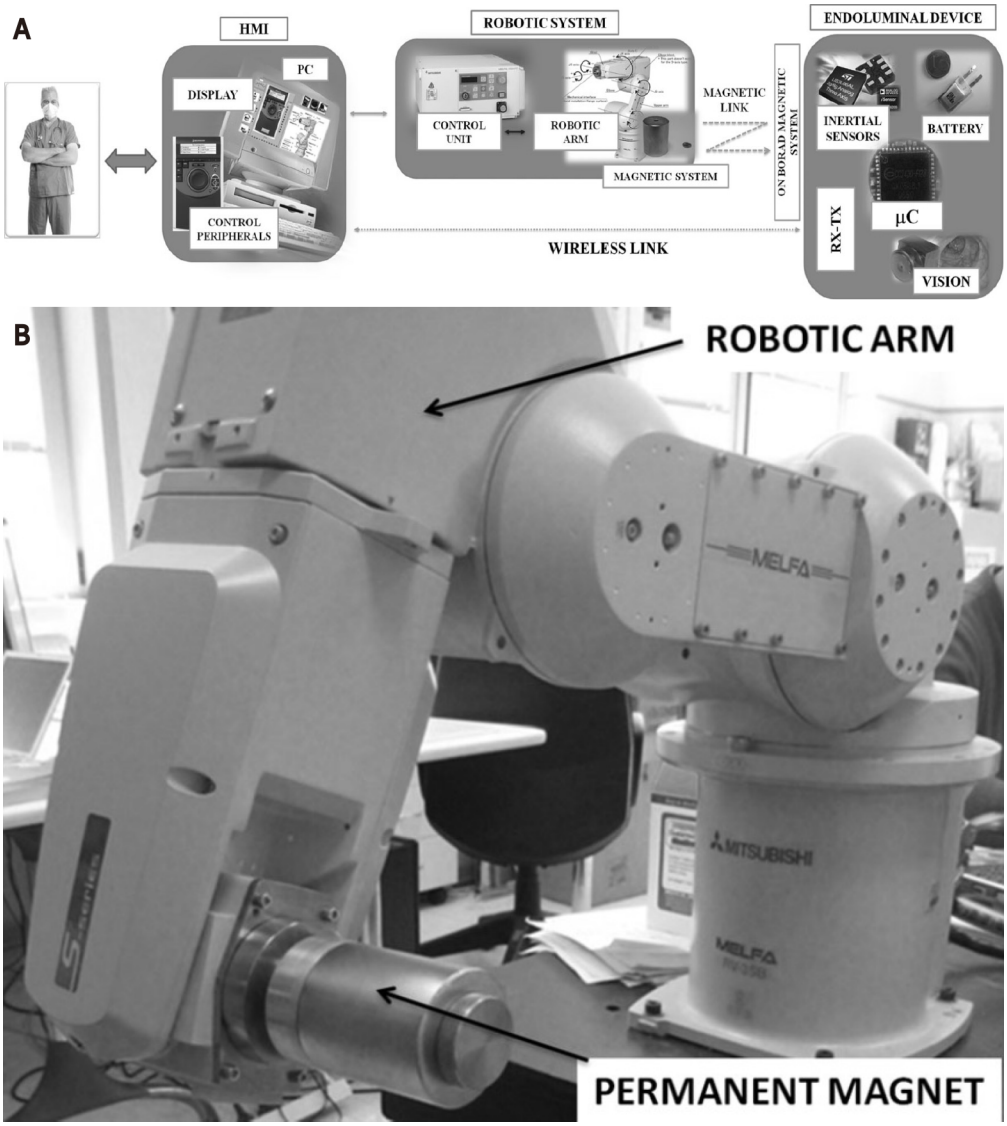

Figure 4 An example of a magnetic device device by Ciuti *et al*[50]. A: The system architecture of the wireless magnetic robot; B: The Robotic arm with external permanent magnet. Citation for A and B: Ciuti G, Valdastri P, Menciassi A, Dario P. Robotic magnetic steering and locomotion of capsule endoscope for diagnosis and surgical endoluminal procedures. Robotica. *Cambridge University Press* 2010; 28: 199-207. Copyright© The Authors 2010. Published by Cambridge University Press.

An Endoo capsule with a permanent magnet, visualisation module, tether with 4 working channels for suction, insufflation, irrigation and instruments was developed in Italy within a European H2020 project[57]. The system consists of an external robot with EPM, a localisation system and medical workstation with a joystick. The workstation and joystick allow the user to control all functions of the Endoo capsule (Figure 5). In addition, the vision system contains 4 green/blue UV-LEDs. Compared to colonoscopy CIR was 67% *vs* 100% at 9.5 min *vs* 3.5 min respectively. Interaction forces between the Endoo capsule and colonic wall as well as polyp detection rates was lower than colonoscopy [1.17 N *vs* 4.12 N; 87% *vs* 91% (P = 0.16)]. The magnetic link was lost an average of 1.28 times *per* complete procedure, but it was restored in 100% of cases[57]. All studies are summarised in Table 3.

Hybrid actuation

Hybrid actuation involves the combination of different propulsive mechanisms to achieve motion. A wireless endocapsule consisting of a 3 legged mechanism, DC motor, battery and small IPMs was created and tested by Simi and colleagues (Figure 6)[58]. Magnetic and EM mechanisms are combined here: The IPMs interact with an EPM to primarily move and orient the capsule while the legged mechanism is used to extract the capsule out of collapsed areas of the colon when it might otherwise get trapped. Motion feasibility was examined 10 times on 20 cm porcine colon and in 4 anaesthetised pigs. In the *ex vivo* trials, the average time taken to travel 20 cm and

Table 3 Summary of the included studies reviewing robotic lower gastrointestinal endoscopy devices with magnetic or hybrid actuation

Ref.	Design and actuation components of evaluated robotic system(s)	Endoscope and/or capsule dimensions	Mode(s) of actuation	Mode(s) of illumination and luminal visualisation	Capabilities evaluated	Degree of robot navigational assistance	Study methodology	Main findings
Valdastri *et al* [49], 2008 (Italy)	Swallowable wireless capsule with surgical clip, electromagnetic motor, 4 IPMs and a bidirectional communication platform. The EPM on a passive hydraulic arm is controlled manually by the user. A HMI controls clip deployment	Diameter of 12.8 mm and a length of 33.5 mm	Magnetic	No camera in this prototype however 300 mm^3 space was left for future integration. Throughout the experiments the capsule was monitored with a flexible endoscope	Therapeutic clip application for bleeding	Direct robot operation	*Ex vivo*- Porcine colon placed in a model of the abdomen–10 trials. *In vivo*-1 pig	*Ex vivo*: Clip release: 100%; Clip release occurred instantly, and moving of the capsule was effective and fast. It took 2-3 min to position the capsule against the mucosa to be clipped. *In vivo*: Good locomotion and positioning with the EPM. The clip was released successfully onto the desired target. The clip remained in situ. The amount of tissue grasped was satisfactory
Ciuti *et al*[50], 2010 (Italy)	Magnetic wireless capsule with inertial and vision sensors and a set of IPM; External robotic arm with EPM and human machine interface. The working distance is 150 mm. The HMI is used to control the robotic arm and receives input from the capsule	Capsule: 40 mm in length, 18 mm in diameter	Magnetic	CMOS camera and 4 white LEDs	Visualisation, locomotion and learning curve	Intelligent teleoperation	*Ex vivo*: 500 mm porcine colon in human phantom model–40 trials (some insufflated and collapsed colons)	Insufflated colon: 100% of success rate in traversing the entire colon. Short learning curve (descriptive analysis) to drive the robotic arm. The average time required to traverse the colon was approximately 10 min. Collapsed colon: Capsule was able to travel only really short distances and manual assistance was required
Ciuti *et al*[51], 2009 (Italy)	Wired capsule with 3 IPMs and vision module; EPM either controlled manually or robotically *via* a robotic arm controlled by a HMI and controller. The working distance is 150 mm	14 mm in diameter and 38 mm in length	Magnetic	CMOS camera with illumination system	Robotic versus manual steering	Direct or Intelligent teleoperation	*Ex vivo*: 480 mm porcine colon in human phantom model–10 trials each for robot and manual arm steering. *In vivo*: 2 Pigs–5 trials each for robot and manual arm steering	*Ex vivo*: Robot versus manual steering: The mean completion time: 423 s *vs* 201 s ($P < 0.01$). The mean percentage of '4 mm white spherical targets' reached: 87% versus 37% ($P < 0.01$). *In vivo*: Manual steering was usually faster, whereas manoeuvrability was better with robotic movement of the EPM (Descriptive analysis)
Carpi *et al*[52], 2011 (Italy/United States)	PillCam (Given Imaging Ltd, Israel) capsule covered in a magnetic shell; Two EPMs, a magnetic navigation system (Niobe, Stereotaxis, Inc, United States), a remote computer work-station and mouse. Fluoroscopic images were continuously acquired by means of a digital scanner to provide visual feedback regarding capsule manoeuvres	13 mm in diameter and length	Magnetic	Not described	Steering and localisation capability	Intelligent teleoperation	*In vivo*: Pig (Number of pigs and trials not described)	The capsule was freely moved within the colon. No complications
Gu *et al*[53], 2017 (China)	The MCCE system (Chongqing Jinshan Science & Technology Group Co, Ltd): Ingestible colon capsule with IPM and battery, an external magnetic manipulator with an EPM, and an image transmission system	Capsule measures 27.9 mm in length by 13.0 mm in diameter	Magnetic	Not described	Manoeuvrability, visualisation, diagnosis and safety	Direct robot operation	*In vivo*: $n = 52$ Human, CRC screening volunteers. Capsule movement was	Average CIT: 3.63 h. Maneuverability of the capsule was good (94.3%) or moderate (5.77%). MCCE provided good-quality pictures and identified 6 positive findings (polyps, diverticulum) which

							visualised *via* colonoscopy 5 h after ingestion	were confirmed by colonoscopy. 78% reached the rectosigmoid colon in 25 min. All 57 volunteers were able to swallow the capsule and excreted the capsule within 2 d. Complications: 7 mild adverse events (abdominal discomfort, nausea, and vomiting) lasting 24 h. No complications at one week follow up
Valdastri *et al* [13], 2012 (Italy)	MAC consists of capsule-like frontal unit and a compliant multi-lumen tether. The frontal unit contains a vision module, an IPM, a magnetic field sensor, and two channels, one for lens cleaning and the other for insufflation/suction/irrigation or instrument passage. The IPM is controlled by an EPM mounted on a robotic platform. A control device allows the user to directly control the position of the EPM. The working distance is 150 mm. The tether connects to an external control box	Capsule: 11 mm diameter, 26 mm in length. Tether: 5.4 mm diameter, 2 m length	Magnetic	CCD camera with 120 degree field of view and 4 white LEDs	Diagnostic and treatment ability, safety, usability	Intelligent teleoperation	*Ex vivo*: 850 mm porcine colon in human phantom model–12 trials. *In vivo*: 2 Pigs–3 trials each	*Ex vivo*: Mean percentage of 5 mm coloured beads (polyps) detected was 85%. 100% successful removal (polypectomy loop) of identified beads. Mean completion time (inspection and bead removal) was 678 s. Mean bead removal time was 18 s. Good manoeuvrability, low friction from the tether on the colon wall and reliable feedback from the vision module. *In vivo*: No mucosal damage or perforation. Able to navigate around bends and folds, retroflexion of the camera and successful operation of the tools (loop, forceps, retrieval basket, grasper) without loss of magnetic link
Arezzo *et al* [54], 2013 (Italy)	Robotic arm with EPM controlled by HMI and controller; Wired capsule with 3 IPMs, camera, LEDs and magnetic sensor. The working distance is 150mm. The wired sheath allows transmission from the vision module and electric energy	Capsule: 13.5 mm in diameter and 29.5 mm in length. Wired sheath: 2 mm in diameter	Magnetic	CCD camera with 120 degree view and 6 white LEDs	Visualisation and diagnostic ability compared to colonoscopy	Intelligent teleoperation	*Ex vivo*: 850 mm porcine colon in human phantom model–22 trials each for capsule and colonoscope	Robot *vs* colonoscopy: CIR: 100% for both. Pin detection rate: 80.9% *vs* 85.8%. Procedure completion time (visualisation and diagnosis): 556 s *vs* 194 s (P = 0.0001). No difference in intuitiveness score
Slawinski *et al* [55], 2018 (United States/United Kingdom)	MFE with IPM, camera, illumination module, working channel for instruments, channel for irrigation and insufflation, EPM on robotic arm and HMI. Additional sensing, retroflexion and software control systems	Tip: 20.6 mm in diameter and 18.1 mm in length. Body: 6.5 mm in diameter	Magnetic	Camera and illumination module	Retroflexion ability	Intelligent teleoperation with task autonomy	*In vivo*: 1 Pig–30 trials	100% successful retroflexion manoeuvres with a mean time of 11.3 s. No acute tissue trauma or perforation
Martin *et al* [14], 2020 (United Kingdom)	MFE with an IPM, camera, an insufflation channel, irrigation channel, working channel for instruments and localisation circuit; A robotic arm with EPM; Robot operating system and joystick	Capsule: 20.6 mm in diameter and 18.1 mm in length. Tether: 6.5 mm in diameter	Magnetic	Camera and LED	Comparison of different degrees of autonomy for locomotion and novice usability	Direct robot or intelligent teleoperation or semi-autonomous	*In vivo*: 2 Pigs–3 trials for each MFE control and colonoscopy in the first pig and 4 trials for each in the second pig	First porcine model–colon distance of 45 cm: Task completion times for direct robot operation, teleoperation, semi-autonomous operation and conventional colonoscopy were 9 min 4 s, 2 min 20 s and 3 min 9 s and 1 min 39 s, respectively. Second porcine model-colon distance of 85 cm: Task completion times for, teleoperation, semi-autonomous operation and conventional colonoscopy were 8 min 6 s, 9 min 39 s and 3 min 29 s, respectively. It was not possible to reach the marker with direct robotic operation. Intelligent and semi-autonomous had

								NASA task force mean Index ratings lower/less demanding than colonoscopy or direct robot operation
Verra *et al*[57], 2020 (Italy)	Endoo system: An Endoo capsule with a IPM, soft tether connection with 4 working channels for suction, insufflation, irrigation and instruments; An external robot with EPM, force-torque sensor and movable platform, localisation system and medical workstation with a joystick complete the system. The robot with EPM is controlled *via* the workstation but can also be steered manually. The localisation system provides information on the capsule position and orientation	Tether: 160 cm long	Magnetic	Two CMOS cameras with 170 degree field of view, 4 white LEDs and 4 green/blue UV-LEDs	Visualisation, locomotion, diagnosis and safety	Semi-autonomous	*Ex vivo*: 100-120 mm porcine colon in human phantom model	*Ex vivo* Endoo alone: 100% success rate in operating channel (use of polypectomy snares, biopsy forceps and needles). 100% success rate for target approach tests (using these instruments to target a polyp). *Ex vivo* Endoo (21 trials) *vs* colonoscopy (13 trials): Completion rate: 67% *vs* 100%. Interaction forces: 1.17 N *vs* 4.12 N. Polyp detection rate: 87% *vs* 91% ($P = 0.16$). Mean CIT: 9.5 min *vs* 3.5 min. The magnetic link was lost an average of 1.28 times *per* complete procedure, but it was restored in 100% of cases
Simi *et al*[58], 2010 (Italy)	Wireless endocapsule with legged mechanism (3 legs), DC motor, battery, small IPMs which interacts with an EPM. LabVIEW HMI is present and is also compatible with voice commands	14 mm in diameter, 44 mm in length.	Hybrid-Electromechanical and Magnetic	No camera in this prototype however 450 mm^3 space was left for future integration. Throughout the experiments the capsule was monitored with a gastroscope	Locomotion and lumen dilatation	Semiautonomous	*Ex vivo*: 20 cm porcine colon–10 trials. *In vivo*: 4 pigs–10 trials. Capsule was placed 40 cm from the anus and expected to travel towards the anus	*Ex vivo*: Ability to travel 20 cm in 10 min: 70%. Average time to traverse 20 cm and number of leg activations: 4 min and 5 mechanism activations. Average speed: 5 cm/min. *In vivo*: Ability to travel 40 cm in 20 min: 60%. Average time to traverse 40 cm and number of leg activations: 5 min and 5 activations. Average speed: 8 cm/min
Nouda *et al* [59], 2018 (Japan)	Self-propelling capsule endoscope (SPCE) consisting of a silicon resin fin with micro-magnet connected to the PillCam SB2 capsule; External magnetic field generating controller (Minimermaid System), human interface with joystick	45 mm in length and 11 mm in diameter	Hybrid-Mechanical and Magnetic	Camera with 156 degree field of view	Locomotion and safety	Semi-autonomous	*In vivo*: 1 Human	The SPCE could swim smoothly in forward and backward directions but had difficulty bypassing bends. No acute complications

IPM: Internal permanent magnet; EPM: External permanent magnet; HMI: Human machine interface; LEDs: Light emitting diodes; CMOS: Complementary metal-oxide-semiconductor; CIT: Caecal intubation time; CIR: Caecal intubation rate; CCD: Charged coupled device; MCCE: Magnetic controlled capsule endoscopy; MFE: Magnetic flexible endoscope.

number of times the legs were activated was 4 min with 5 activations. The average speed was 5 cm/min. In the *in vivo* trials, the average time taken to travel 40 cm and number of times the legs were activated was 5 min with 5 activations. The average speed was 8 cm/min. The colon was not insufflated with air[58]. In Japan, a self-propelling capsule was created by attaching a silicon resin fin with micro-magnet to the commercially available Pillcam SB2 capsule (Covidien, Dublin, Ireland). In the presence of a magnetic field and water, the fin vibrates and propels the capsule. When placed in the rectum and descending colon of a human subject, it was shown to be able to swim forwards and backwards without causing damage to the mucosa however it had difficulty by-passing the bend of the sigmoid colon[59] (Table 3).

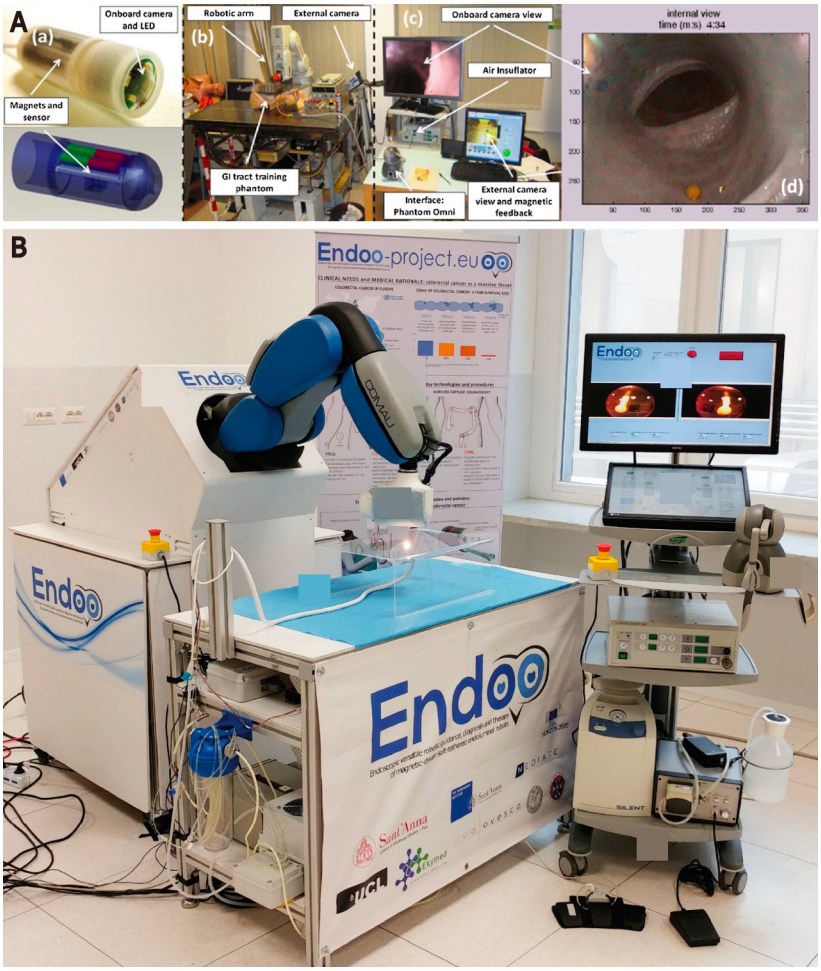

Figure 5 Examples of tethered magnetic robotic devices. A: Shows the overall tethered device and system with an image of the internal view provided by the device camera in Arezzo *et al*. Citation: Arezzo A, Menciassi A, Valdastri P, Ciuti G, Lucarini G, Salerno M, Di Natali C, Verra M, Dario P, Morino M. Experimental assessment of a novel robotically-driven endoscopic capsule compared to traditional colonoscopy. *Dig Liver Dis* 2013; 45: 657-662. Copyright© The Authors 2013. Published by Elsevier. B: Shows the Endoo system with a clear image of the capsule in the lower left corner. Citation: Verra M, Firrincieli A, Chiurazzi M, Mariani A, Lo Secco G, Forcignanò E, Koulaouzidis A, Menciassi A, Dario P, Ciuti G, Arezzo A. Robotic-Assisted Colonoscopy Platform with a Magnetically-Actuated Soft-Tethered Capsule. *Cancers (Basel)* 2020; 12: 2485. Copyright© The Authors 2020. Published by Open access.

DISCUSSION

Medical robotics is realising its potential in a variety of healthcare disciplines, and the last couple of decades have seen increasing demand for robotic platforms designed specifically for endoscopy. In terms of LGI tract 'robo-endoscopy', significant strides have been made over this period, with five devices receiving FDA approval. These devices represent a heterogeneous group in terms of actuation modality (EM or pneumatic), and many studies have been performed using *ex vivo* models. These models, while able to demonstrate proof of concept, cannot effectively capture data on *in vivo* motion ability, pain perception or device safety. Nevertheless, the human data that is available suggests that the evaluated robo-endoscopic systems are able to locomote effectively (*i.e.*, achieve CIR > 90%[23,24,36,40-42]), to locomote safely (*i.e.*, be associated with mild if any mucosal disruption or complications[21,24,35,36,40,42])and to achieve endoscopic tasks with minimal associated pain[21,23,35,39]. Reducing discomfort associated with LGI endoscopy represents a key directive in robotic endoscopy and in two trials, human participants gave the Invendoscope an average pain score of 1.96/6 and 2.6/6, which translated into 0% and 4.9% requiring sedation, respectively[21,23]. When compared to colonoscopy, pain scores and sedation rates were also significantly lower with the Endotics system[38,39]. Early data suggest that the Endotics system may even have superior diagnostic capabilities compared with conventional colonoscopy as indicated by its ability to detect lesions missed on colonoscopy[38]. These reports are certainly encouraging, though overall it is important to appreciate that most devices presented in this review remain in the relatively early phases of translational application, and few have met the goal of

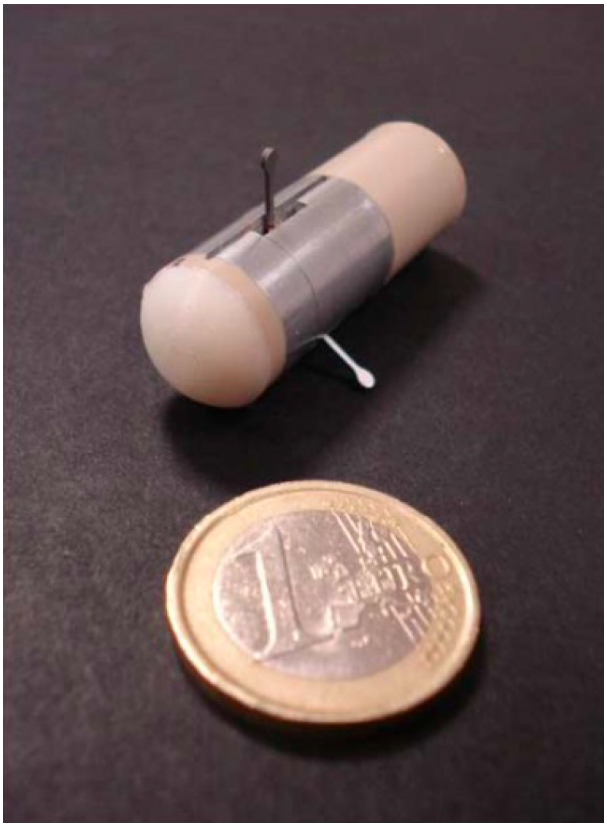

Figure 6 Hybrid robotic device by Simi *et al*[58]. Citation: Simi M, Valdastri P, Quaglia C, Menciassi A, Dario P. Design, Fabrication, and Testing of a Capsule With Hybrid Locomotion for Gastrointestinal Tract Exploration. *IEEE/ASME Trans Mechatron* 2010; 15: 170-180. Copyright© The Authors 2010. Published by IEEE.

clinical deployment outside of academic institutions. An inherent limitation lies in the fact that most systems provide primarily diagnostic functionality, with large scale trials evaluating therapeutic robotic LGI endoscopy currently lacking.

Improved reproducibility, enhanced procedural efficiency and a shorter learning curve have all been suggested as possible areas where robotic endoscopy could make a positive impact. In addition, they may offer a more comfortable system for the user, which may have potential to minimise fatigue and injury and ultimately this may equate to more years of professional service. More intuitive control and visualisation systems have the potential to shorten learning curves. For example, one trial evaluating a robotic endoscopic system suggested that only an average of 30 procedures was required for the user to achieve CIR, CIT and scope withdrawal time comparable to standard colonoscopy performed by an 'expert'[40].

From a broader perspective, it is important to acknowledge that this review has focused entirely on the specific application(s) of robotic systems in LGI endoscopy. However, robotic advances in this area are not made in isolation from advances in other luminal organs such as the upper GI tract or in natural orifice transluminal endoscopic surgery. Thus, it is likely that advances in one field will complement another.

One can anticipate that in the future, as the technology becomes more sophisticated, it should be possible to exploit the 'computational interface' that robotic endoscopy provides further, with the potential for integration of AI based algorithms and novel augmented reality systems for 'smart' therapeutics. It is doubtful whether these next-generation technologies will work to their full capabilities if operating within anything other than a robotic system. It is an exciting time in medical robotics with recent reports confirming the potential for the development of 'soft' robotic systems with in-built autonomic functionality[60]. Such systems are likely to represent the long-term direction of luminal robotics. In the near- to mid-term, the goal will be to continue to stimulate strong collaborative links between GI physicians and medical engineers in order to continue to refine design and functionality.

CONCLUSION

Robotic technologies have the potential to transform LGI endoscopy into a quicker, safer, more reliable and less painful procedure. In the long term, benefits for patients, endoscopists and the wider healthcare industry are foreseeable, though these have yet to be convincingly demonstrated in human trials. Most studies to date have employed *ex vivo* modelling and high quality level 1 evidence is currently lacking in this field. Robotic technologies are evolving with such rapidity at the moment, that future robo-endoscopic systems are likely to look and behave very differently to conventional master-slave systems currently in use. Exciting developments in 3D printing, soft robotics, autonomous functionality and augmented reality are likely to converge over the coming decade to lead to the development of truly next generation robotic endoscopy devices.

ARTICLE HIGHLIGHTS

Research background

Inherent limitations exist with conventional colonoscopy which may be overcome by a variety of next-generation robotically-augmented technologies.

Research motivation

Robotic technologies have the potential to transform lower gastrointestinal (LGI) tract endoscopy with long term, benefits for patients, endoscopists and the wider healthcare industry. High quality evidence is currently lacking in this field.

Research objectives

This review provides a comprehensive summary of recent developments in the application of robotics in LGI tract endoscopy.

Research methods

A systematic review of the literature was performed. Studies reporting on the use of robotic endoscopic technology in *ex vivo* colon models or *in vivo* animal and human experiments were included.

Research results

Of 37 studies were included of varying actuation modality. Five devices have been approved by the Food and Drug Administration, however the majority remain in the early phases of testing and development. Level 1 evidence is lacking at present, but early reports suggest that these technologies may be associated with improved pain and safety.

Research conclusions

Significant progress in robotic colonoscopy has been made over the last couple of decades. The reviewed devices appear to be ergonomically capable and efficient though to date no reports have convincingly shown diagnostic or therapeutic superiority over conventional colonoscopy.

Research perspectives

Future improvements in design together with the integration of semi-autonomous and autonomous systems over the next decade will potentially result in robotic colonoscopy becoming more commonplace.

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