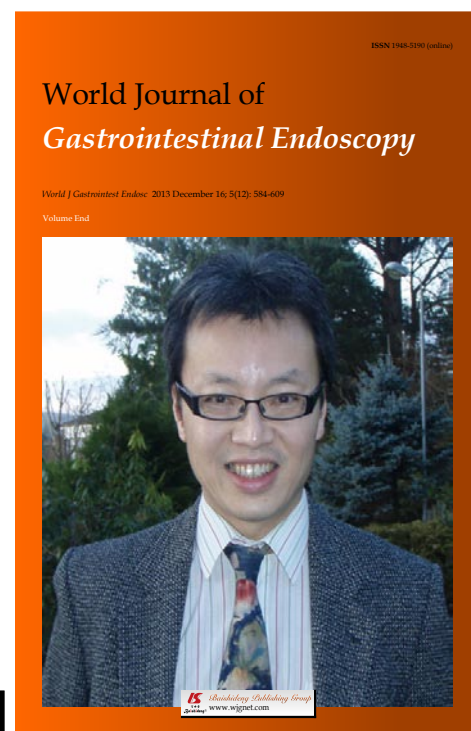
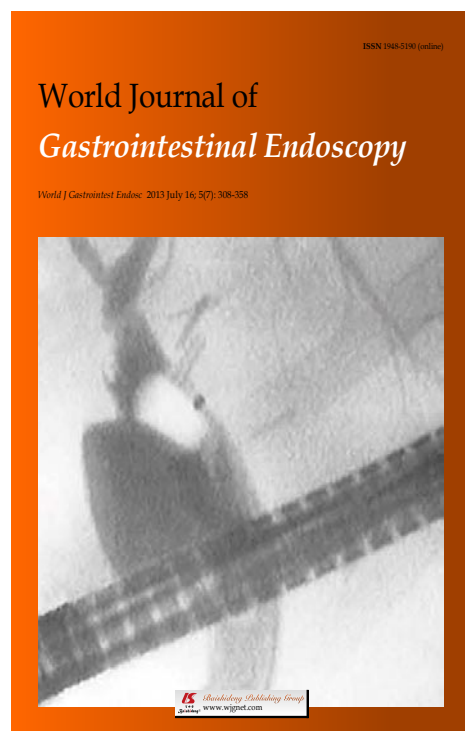
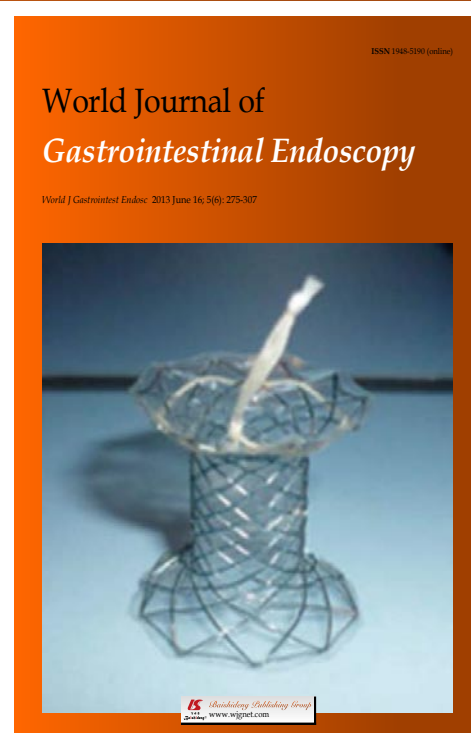
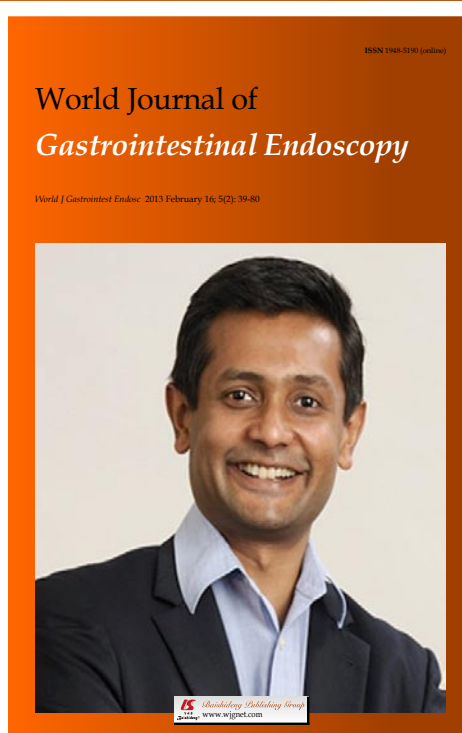


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Use of anesthesia on the rise in gastrointestinal endoscopy

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Abstract

Conscious sedation has been the standard of care for many years for gastrointestinal endoscopic procedures. As procedures have become more complex and lengthy, additional medications became essential for adequate sedation. Often time's deep sedation is required for procedures such as endoscopic retrograde cholangiography which necessitates higher doses of narcotics and benzodiazepines or even use of other medications such as ketamine. Given its pharmacologic properties, propofol was rapidly adopted worldwide to gastrointestinal endoscopy for complex procedures and more recently to routine upper and lower endoscopy. Many studies have shown superiority for both the physician and patient compared to standard sedation. Nevertheless, its use remains highly controversial. A number of studies worldwide show that propofol can be given safely by endoscopists or nurses when well trained. Despite this wealth of data, at many centers its use has been prohibited unless administered by anesthesiology. In this commentary, we review the use of anesthesia support for endoscopy in the United States based on recent data and its implications for gastroenterologists worldwide.

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Key words: Propofol; Ketamine; Conscious sedation;

Deep sedation; Anesthesiology; Gastrointestinal endoscopy

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INVITED COMMENTARY ON HOT ARTICLES

The fiberoptic endoscope, patented in 1956, has revolutionized the diagnosis and treatment of gastrointestinal disorders^[1]. Since its introduction, the indications for use of the gastroscope and colonoscope have grown exponentially, and newer endoscopic tools including the side viewing and double balloon endoscopes with the ability to perform endoscopic therapy have further expanded these indications. According to a national survey of the general population in 2010, 54.6% of Americans underwent colon cancer screening with colonoscopy at least once within the past 10 years^[2]. This number is expected to rise further given recent evidence suggesting a 53% reduction in colon cancer mortality from colonoscopy and polypectomy^[3]. Additionally, colonoscopy has become the standard diagnostic tool for the investigation of other colonic complaints including rectal bleeding, change in bowel habits, abnormal radiological findings, anemia, and abdominal pain.

Healthcare expenditures in the United States have been climbing significantly, and the use of anesthesia services for endoscopy is no exception. In 2010, healthcare costs exceeded \$2.6 trillion dollars, which is twice the amount spent in 2000, and ten times the national cost in 1980^[4]. In the wake of escalating health care costs, attention at the national level has been given to cost-cutting measures in all healthcare sectors. One area of potential cost-savings is minimizing overuse of medical services. For example, Korenstein *et al*^[5] reviewed recent

literature related to the overuse of procedures, tests, and medications between 1978 and 2009. They found evidence of overuse in 18.4%-60.8% of colonoscopies and 5.2%-23.0% of upper endoscopies. Likewise, the burgeoning use of anesthesia support for gastrointestinal procedures has further escalated the overall cost for endoscopy. In this article, we summarize a recent important study that examines the actual trends in sedation utilization across the United States in the past few years reported by Liu *et al*^[6] and discuss selected aspects of anesthesia support for endoscopy.

Liu *et al*^[6] recently reported on the overall utilization of anesthesia services for gastrointestinal procedures in the United States and assessed temporal changes and geographic patterns. The authors analyzed data from insurance claims paid by medicare and commercial health insurers for services provided between 2003 and 2009. The authors used data from the Medicare Limited Data set which is a nationally representative sample comprised of 5% of the general population. Data about commercial insurers were taken from the MarketScan data set which holds information from approximately 150 commercial health plans, about 40 million commercially insured individuals, who comprise 20% of the population covered by employer-sponsored healthcare plans. They evaluated all patients who underwent outpatient upper and lower endoscopy over the 6 year period. Exclusion criteria included patients younger than 18 years of age and patients with incomplete claims data for the 6 mo prior to the endoscopy. They calculated the number of upper and lower gastrointestinal endoscopies, the proportion of procedures which used anesthesia services, the average and aggregate payments for these services, and the proportion of anesthesia services utilized for patients deemed low-risk for conscious sedation. They defined low-risk patients as those with American Society of Anesthesiologists (ASA) physical status 1 or 2. Patients without an associated ASA physical status classification in the insurance claim were assigned one based on a predictive statistical model. They estimated the patient's likelihood of having an ASA physical status of 3 or higher based on age, gender, comorbid medical conditions, and any inpatient hospitalization within the 3 mo prior to the procedure. Pertinent comorbidity contributing to anesthesia risk included cardiopulmonary conditions such as cardiac arrest, congestive heart failure, chronic obstructive pulmonary disease, coronary artery disease, asthma, and cystic fibrosis. A number of other additional medical conditions were used as predictors like cerebrovascular disease, hypertension, peripheral artery disease, *etc.*

They found that 26.6% of 1.1 million Medicare patients had anesthesia services billed for either an upper endoscopy or colonoscopy. Of the 5.5 million privately insured patients, about 28.6% of patients had billed for anesthesia services. For medicare patients, the number of procedures per million patients remained steady at 136 718 from 2003 to 2009. While the number of gastrointestinal procedures per million for privately insured patients grew, however, by more than 50% from 33 599

in 2003 to 50 816 in 2009. Over that same time period, the percentage of procedures utilizing anesthesia services for endoscopy rose in both cohorts. The proportion of medicare patients undergoing gastrointestinal endoscopy with anesthesia support grew from 13.5% in 2003 to 30.2% in 2009. Similarly, anesthesia support for procedures among privately insured patients grew from 13.6% to 35.5% in the same time period. Marked geographic variations were also found. The lowest region was the West with 14% of medicare patients and 12.6% of privately insured patients utilizing anesthesia in 2009, while the highest was the Northeast region with 47.5% of medicare patients and 59% of privately insured patients billing for anesthesia services for endoscopy.

The most significant finding in this study was the large number of patients deemed as low-risk who received anesthesia services for their procedures. Overall of the studied patients, approximately two-thirds of the medicare patients with ASA physical status level < 3 and more than three-quarters of commercially insured patients had anesthesia support for their procedures. This represents an almost doubling of the Medicare patients over the course of the study, increasing from 13 989 per 1 million in 2003 to 25 069 per 1 million in 2006. For privately insured patients, the increase was more dramatic rising from 3938 to 15 108 per 1 million patients, representing an almost 4 fold increase.

This study has much strength. It is one of the most exhaustive studies published utilizing a large population of both government and privately insured patients. With a total of 6.6 million patients across the United States, it covers a variety of racial, socioeconomic, and geographic backgrounds. The authors were able to overcome the possible lack of information inherent to studies examining records of specific hospitals because insurance billing information enabled them to evaluate all available records regardless of healthcare system. The major weakness was the definition of high and low risk patients. The basic assumption was that patients with ASA physical status > 2 are at higher risk for complications and would thus benefit from anesthesia services. There are, however, few studies which compare the risk of complications associated with moderate sedation *vs* deep sedation in these particular patient groups although prior studies show a link between cardiopulmonary complications and ASA class with conscious sedation^[7]. Secondly, only 14.1% of the study population had ASA physical status documented. As noted above, the investigators used a calculated predictive model for the rest of their population. This mathematical model utilized a number of diagnoses and criteria to determine the patient's risk but provided no evidence to confirm the accuracy of this statistical model. Lastly, this study excluded children under the age of 18, hospitalized patients, patients covered by Medicaid, and those paying out of pocket. These populations, particularly self-paying patients, could alter the percentage of patients necessitating anesthesia services.

The increasing use of anesthesia support by anesthesia specialists for both diagnostic and therapeutic endos-

copy revolves around the use of propofol. Since its introduction in the 1980's, its use has slowly expanded into endoscopic sedation principally because of its pharmacologic properties: it is a very short acting sedative agent without analgesic effect resulting in both sedation and amnesia^[8]. A wealth of data including randomized controlled trials has shown that non anesthesiologist administered propofol (NAAP) is both safe and effective^[9-14]. This data has been generated worldwide including from Asia^[15,16]. For example, randomized trials comparing NAAP to meperidine and midazolam combinations have shown no difference in hypoxemia, bradycardia, or need for airway interventions^[9]. Indeed, these studies show the safety of NAAP is comparable to endoscopist administered standard sedation. Most studies do demonstrate NAAP sedation is superior to standard sedation regarding time to sedation as well as speed of recovery. Patient satisfaction with propofol is variable from equivalent to slightly superior to the standard regimens. It should be stressed, however, that the reporting of the use of NAAP comes from centers with much experience in its administration and only after a rigorous training program for administering staff.

Despite this apparent efficacy and safety, the use of propofol by non-anesthesiologists is a highly charged area both in the United States and abroad^[17,18]. In the United States, the labeling on propofol states that "it should be administered only by persons trained in the administration of general anesthesia". Recently, the United States Food and Drug Administration denied a change in this labeling thus essentially preventing the use of gastroenterologist administered propofol for endoscopic procedures. Increasingly, anesthesia societies suggest that patients undergoing deep sedation which can occur during endoscopy require a similar level of care to those undergoing general anesthesia^[19,20]. More recently, many institutions such as our own have established policies where other agents resulting in deep sedation such as ketamine are being withheld from the gastroenterologists purview thus essentially forcing the use of anesthesia services for complex patients that in the past were safely managed by the gastroenterologist.

For many years, the standard of care for endoscopic procedures was sedation with benzodiazepines and narcotics, referred to as conventional or conscious sedation. However, with the availability of propofol, much literature has been dedicated to the increasing use of propofol and monitored anesthesia care (MAC) sedation in gastrointestinal endoscopy as compared to conventional sedation^[21-25]. In addition, many gastroenterologists favor the use of propofol because of more rapid patient recovery and better patient tolerance^[21].

Without question, a major reason for the increasing use of NAAP for gastrointestinal procedures is a financial one. Because it provides for quicker sedation, recovery, and discharge, gastroenterologists are able to be more efficient in providing endoscopy to patients. Vargo *et al*^[26] showed the gastroenterologists were able to perform three colonoscopies under propofol sedation in the time

it takes to perform two colonoscopies with conventional sedation. This significant improvement in efficiency translated into measurable decreases in the operating costs, nurse requirements, and bed requirements in the recovery area. In addition, the payment to anesthesiologists by private insurance as documented by Liu *et al*^[6] is another economic driver and perhaps one reason for the increasing interest in performing endoscopic procedures by the anesthesiology community. However, Cohen *et al*^[27] postulated that the cost of anesthesia services used for every endoscopic procedure annually could amount to \$8 billion per year and other models support this large financial cost^[28]. This is based on an average cost of \$400 for anesthesia with endoscopy, although this number is somewhat variable. No study to date documents whether the expediency benefits of anesthesia care provides sufficient economic cuts to offset its additional cost if used for all 20 million endoscopic procedures performed annually in the United States.

Although anesthesia administered propofol is increasingly used worldwide, other options for sedation exist but are overlooked and perhaps underused in the general community. One such practice is the use of unsedated procedures^[29-31]. Dumortier *et al*^[29] studied 1100 patients in 3 institutions in France who underwent unsedated transnasal upper endoscopies. These patients underwent EGD for various indications with either a 5.9 mm or 5.3 mm endoscope. They found the procedure was feasible in 93.9% of patients. In those that failed, the cause was unsuccessful insertion in 62.7% of the times, patient refusal in 19.4% of the times, and pain in 17.9% of the times. Characteristics associated with failure were young age, female sex, and the need for larger endoscopes. A similar study was performed for unsedated colonoscopy. Petrini *et al*^[30] performed 2091 colonoscopies between June 6, 2006 and December 7, 2006 in an ambulatory endoscopy center in California. These patients were given the option to have the procedure with or without sedation. 578 patients (27.6%) started without any sedation. Of these patients, 470 (81.1%) completed the exam without any sedation. Cecal intubation rates were similar in the sedated and unsedated groups, 99.1% and 97.4% respectively. Most importantly, about 97.4% of the patient who underwent unsedated colonoscopies were satisfied with their comfort level and would be willing to undergo their next colonoscopy without any sedation. The time to cecum in these patients was not significantly different in the sedated and unsedated patients, 9.71 min *vs* 9.87 min respectively. It, however, was significantly different for those who required sedation after the procedure started with a mean cecal intubation time of 15.24 min. This significant delay in time would prevent many gastroenterologists from pursuing this option seriously unless there was some way to predict the patient that would not tolerate unsedated procedures.

It is not yet clear which option best maximizes patient safety, patient and provider satisfaction with the endoscopy experience, and cost saving. The desire to use propofol over benzodiazepines and narcotics is obvious

because it shortens the endoscopy time, while improving the experience for both the patient and the endoscopist. The use of an anesthesiologist for more complicated procedures is intuitive particularly in those with significant comorbidity (ASA Class 4 or greater) or risk factors for complications. However, we previously found that even in these patients the use of standard conscious sedation supplemented with low dose ketamine was highly effective and safe^[32] and such a sedative cocktail may be of benefit in regions of the world where an anesthesiologist is not available. Certainly the lack of formal training in the use of sedatives in gastrointestinal fellowship does affect the practices of gastroenterologists in the community. Thus the utilization of anesthesia services for MAC and propofol may stem from lack of experience with the use of sedatives such as propofol or the desire to avoid the legal liability it involves. It also allows the endoscopist to abdicate the responsibility of sedation and monitoring to another trained medical staff, allowing them to focus on the endoscopy solely. That being said, the most recent recommendations from the ASGE standards of practice committee in 2008^[33] suggest that the use of anesthesia services for MAC or propofol sedation in gastrointestinal endoscopy is indicated only for patients undergoing prolonged or therapeutic endoscopic procedures that require deep sedation, patients with anticipated intolerance to conventional sedation, patients with severe comorbidities (ASA physical status class III or higher), and patients with higher risk of airway obstruction due to some anatomical variant. Similar guidelines have been published by the American Society of Anesthesiologists Task Force^[34].

In addition to the discussion regarding sedation, technical factors may play a role in the decision to use conscious sedation *vs* propofol-based sedation. Methods to reduce discomfort during endoscopy, principally colonoscopy, such as the use of carbon dioxide insufflation^[35], water aided colonoscopy^[36] as well as an ultrathin colonoscopy^[37,38].

More studies are needed to prove improved safety or decrease in healthcare costs before anesthesia can become the new standard for endoscopic procedures. However the “cat may be out of the bag” given the widespread use of propofol, the increasing pressure from consumers, the burgeoning use of narcotics and other medications making conscious sedation more difficult, and stringent regulations on the use of drugs such as ketamine and propofol by the government and anesthesia societies.

Ultimately, the decision to use conscious sedation, nurse-administered propofol sedation, or anesthesia provided propofol will be dictated by the expertise of the physician and the local environment. In areas of the world where the use of NAPS and ketamine are not restricted, these could be used more liberally with the assurance that the providers are well experienced in the pharmacology of the medications and rescue. Ketamine is a wonderful addition to conscious sedation and should be used more. At our institution, however, despite our experience with using ketamine and its remarkable safety, we are now limited by our hospital policy such that we cannot provide

deep sedation and must rely on anesthesia support for difficult to sedate patients. Like much we do in medicine, sedation for endoscopic procedures is an art.

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Diagnosis and management of gastric antral vascular ectasia

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Abstract

Gastric antral vascular ectasia (GAVE) is an uncommon but often severe cause of upper gastrointestinal (GI) bleeding, responsible of about 4% of non-variceal upper GI haemorrhage. The diagnosis is mainly based on endoscopic pattern and, for uncertain cases, on histology. GAVE is characterized by a pathognomonic endoscopic pattern, mainly represented by red spots either organized in stripes radially departing from pylorus, defined as watermelon stomach, or arranged in a diffused-way, the so called honeycomb stomach. The histological pattern, although not pathognomonic, is characterized by four alterations: vascular ectasia of mucosal capillaries, focal thrombosis, spindle cell proliferation and fibrohyalinosis, which consist of homogeneous substance around the ectatic capillaries of the lamina propria. The main differential diagnosis is with Portal Hypertensive Gastropathy, that can frequently co-exists, since about 30% of patients with GAVE co-present a liver cirrhosis. Autoimmune disorders, mainly represented by Reynaud's phenomenon and

sclerodactyly, are co-present in about 60% of patients with GAVE; other autoimmune and connective tissue disorders are occasionally reported such as Sjogren's syndrome, systemic lupus erythematosus, primary biliary cirrhosis and systemic sclerosis. In the remaining cases, GAVE syndrome has been described in patients with chronic renal failure, bone marrow transplantation and cardiac diseases. The pathogenesis of GAVE is still obscure and many hypotheses have been proposed such as mechanical stress, humoral and autoimmune factors and hemodynamic alterations. In the last two decades, many therapeutic options have been proposed including surgical, endoscopic and medical choices. Medical therapy has not clearly shown satisfactory results and surgery should only be considered for refractory severe cases, since this approach has significant mortality and morbidity risks, especially in the setting of portal hypertension and liver cirrhosis. Endoscopic therapy, particularly treatment with Argon Plasma Coagulation, has shown to be as effective and also safer than surgery, and should be considered the first-line treatment for patients with GAVE-related bleeding.

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Key words: Gastric antral vascular ectasia; Bleeding; Watermelon stomach; Argon plasma coagulation

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INTRODUCTION

Gastric antral vascular ectasia (GAVE) is an uncommon but often severe cause of upper gastrointestinal (GI) bleeding, responsible of about 4% of non-variceal up-

per GI hemorrhage^[1]. This disease was first described in 1953 by Ryder *et al*^[2], but deeply investigated only 25 years later, in 1978, by Van Vliet *et al*^[3]. Since then, a better but still incomplete knowledge of this condition has been reached; however, the exact prevalence is not known, the pathogenesis remains unclear and the best therapeutic approach has not yet been defined. The aim of this paper is to review the current findings about GAVE and to contribute to a better understanding of this often misdiagnosed disease and critically review the current therapeutic options.

MORPHOLOGICAL ASPECTS

GAVE is characterized by a pathognomonic endoscopic pattern, mainly represented by red spots either organized in stripes radially departing from pylorus, defined as watermelon stomach, or arranged in a diffused way, the so called honeycomb stomach^[4] (Figures 1 and 2).

GAVE is typically located in the gastric antrum, however it may be rarely found also in other areas of the GI tract, including cardia^[5,6], duodenum, jejunum^[7] and rectum^[8,9]. The involvement of the proximal part of the stomach is almost rare and generally located within a diaphragmatic hernia^[10]. At the endoscopic ultrasound (EUS), the gastric antrum appears hypertrophic with a spongy appearance of the mucosa and submucosa and a well-preserved muscularis propria^[11,12].

The histological pattern, although not pathognomonic, is characterized by four alterations: vascular ectasia of mucosal capillaries, focal thrombosis, spindle cell proliferation (= smooth muscle cell and myofibroblast hyperplasia) and fibrohyalinosis, which consist of homogeneous substance around the ectatic capillaries of the lamina propria^[13-15] (Figures 3 and 4). In 1989, Gilliam *et al*^[14] proposed a score system to diagnose GAVE, which considered only two histological criteria: the co-presence of ectasia and/or fibrin thrombi and spindle cell proliferation (Gilliam's score). Subsequently, a third parameter, fibrohyalinosis, was added to improve both sensibility and specificity^[15]. This latter score, called "GAVE score", showed a higher diagnostic accuracy (80%) to differentiate GAVE from Portal Hypertensive Gastropathy, which may be present in patients with co-existing portal hypertension. Table 1 summarizes both the histological scores, the Gilliam's score and the GAVE score.

GAVE VS PORTAL HYPERTENSIVE GASTROPATHY: DIFFERENTIAL DIAGNOSIS

Patients with portal hypertension often present an endoscopic pattern called portal hypertensive gastropathy (PHG), which needs to be distinct from the GAVE pattern, since they represent two separate entities in the setting of liver cirrhosis. The differential diagnosis is mainly based on the endoscopic appearance and, in the doubtful

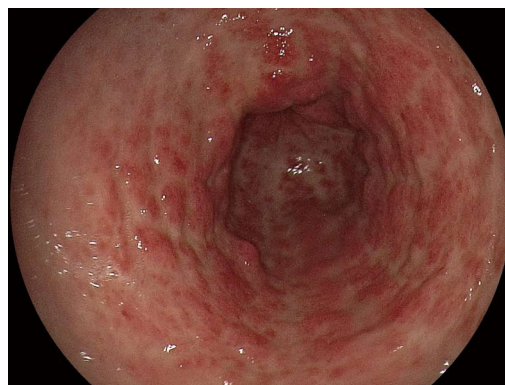


Figure 1 Endoscopic appearance of gastric antral vascular ectasia: Red spots radially departing from pylorus and involving the gastric antrum.



Figure 2 Videocapsule image of gastric antral vascular ectasia.

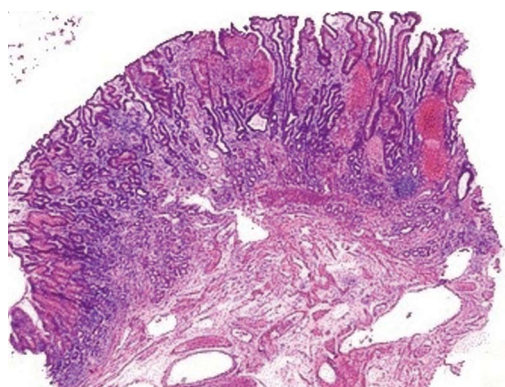


Figure 3 Gastric biopsy showing prominent vascular congestion with thrombosis of the vasculature. The surrounding glands appear regenerative and the vessels in the submucosa are dilated and sclerotic.

cases, by the histological pattern.

PHG occurs only in patients with portal hypertension and typically involves the fundus and the corpus of the stomach; the endoscopic pattern is characterized by a combination of four main characteristics: a mosaic-like pattern, presence of red point lesions, cherry red spots and black-brown spots^[16]. The histological findings may clarify the uncertain cases by the assessment of the "GAVE score", indeed, a GAVE score > 3 is considered highly diagnostic for the presence of GAVE (Table 1)^[15].

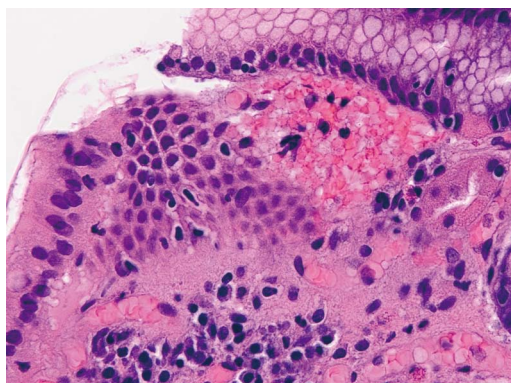


Figure 4 Higher magnification of one of the thrombosed vessels.

Table 1 Histological score systems for diagnosis of gastric antral vascular ectasia

Gastric antral vascular ectasia score (range 0-5)			Gilliam's score (range 0-4)
Score	Fibrin thrombi and/or vascular ectasia	Spindle cell proliferation	Fibrohyalinosis
0	Both absent	Absent	Absent
1	One present	Increased	Present
2	Both present	Marked increased	-

The main aspects to consider in the differential diagnosis between GAVE and PHG are summarised in Table 2. The importance to distinguish these two clinical entities is mainly related to the different therapeutic approach; the reduction of portal pressure by using drugs (beta-blockers, somatostatin, octreotide), trans-jugular intra-hepatic porto-systemic shunt (TIPS) or surgery (portocaval shunts) are not effective for the treatment of GAVE^[17,18].

GAVE AND ASSOCIATED DISEASES

GAVE syndrome can complicate the course of many diseases (Table 3). Autoimmune disorders, mainly represented by Reynaud's phenomenon and sclerodactyly, are co-present in about 60% of patients with GAVE^[10]; other autoimmune and connective tissue disorders are occasionally reported such as Sjogren's syndrome^[19], systemic lupus erythematosus^[20], primary biliary cirrhosis and systemic sclerosis^[21]. In this latter case, it has been reported that GAVE can even represent the presenting syndrome, preceding the development of the autoimmune disorders by several months^[21].

About 30% of patients with GAVE co-present a liver cirrhosis^[22-24], whatever etiology (viral, autoimmune, toxic-metabolic). In the remaining cases, GAVE syndrome has been described in patients with chronic renal failure^[10], bone marrow transplantation^[25] and cardiac diseases^[10,26].

Non-cirrhotic patients more frequently present the typical endoscopic watermelon-, striped-pattern and are mainly represented by middle-aged women whereas the honeycomb-, diffuse-pattern prevails in patients with liver failure^[1,4,27]. However, the endoscopic appearance is

Table 2 Differential diagnosis between portal hypertensive gastropathy and gastric antral vascular ectasia

Features	Portal hypertensive gastropathy	Gastric antral vascular ectasia
Site	Fundus-corpus	Antrum
Endoscopic pattern	Combination of: Mosaic-like pattern Red point lesions Cherry red spots Black-brown spots	Red spots organised: Striped-pattern (watermelon-stomach) Diffused-pattern (honeycomb-stomach)
Histological pattern	Not specific	Highly specific
Response to β -Blockers/transjugular intrahepatic portosystemic shunt/portocaval shunts	Present	Absent

Table 3 Gastric antral vascular ectasia and associated diseases

Associated disease	Prevalence (%)	Ref.
Autoimmune diseases	60	
Raynaud's phenomenon		[10]
Sclerodactyly		[10]
Sjogren's syndrome		[19]
Systemic sclerosis		[21,32]
Primary biliary cirrhosis		[10,32]
Systemic lupus erythematosus		[20]
Liver cirrhosis and/or portal hypertension	30	[22-24]
Others	10	
Chronic renal failure		[10]
Bone marrow transplantation		[25]
Cardiac diseases		[10,26]

not related to the patient's outcome^[4] but could reflect a different pathogenesis.

PATHOGENESIS

GAVE syndrome is an acquired disease rather than a congenital alteration. The pathogenesis of GAVE is still obscure and many hypotheses have been proposed such as mechanical stress, humoral and autoimmune factors and hemodynamic alterations.

Mechanical stress represented by strong gastric peristalsis has been supposed to induce prolapse and trauma of antral mucosa and intermittent obstruction of blood vessels, which can lead to fibro-muscular hyperplasia and vascular ectasia^[28]. These latter are typical findings of GAVE and other gastrointestinal lesions due to repeated traumas and mucosal prolapse (i.e., stomas and prolapsed haemorrhoids)^[13]. Furthermore, a subset of patients with liver cirrhosis and GAVE has been shown to have antropyloric dysfunction with abnormal antral motor response to meals^[29].

Many authors have assumed a pivotal role of humoral factors as gastrin, vasoactive inhibitory peptide (VIP), 5-hydroxytryptamine, glucagon, catecholamines, prostanoïd and other undefined vasoactive substances. GAVE syndrome has been associated with both increased^[28] and decreased levels of gastrinemia^[15] and these conflicting data reduced the importance initially ascribed to this

hormone, which was hypothesised to induce spindle cell proliferation, hyperplasia, prolonged sphincter relaxation and also capillary and venous dilatation. A possible role of both VIP and 5-hydroxytryptamine has been proposed after the evidence of the presence of actively proliferating neuroendocrine cells surrounding the ectatic vessels in the lamina propria of patients with GAVE^[30]. The release of these substances seems to be responsible for the local vasodilatation and the tendency to bleed. On the other hand, glucagon and catecholamines do not seem to play any role in the pathogenesis of GAVE, since concentrations of these metabolites have shown to be similar in cirrhotics with or without GAVE. However, prostaglandin E₂, a prostanoid with vaso-dilatator and acid-inhibitory effect, showed significantly higher levels in patients with GAVE^[31].

Up to 60% of patients with GAVE have also an autoimmune associated disease and show the presence of autoantibodies^[10], therefore an autoimmune pathogenesis has been suggested. Indeed, several autoantibodies have been detected in patients with GAVE; Watson *et al*^[32] found that all patients with systemic sclerosis and GAVE were positive for antinuclear antibodies and, in some cases, were also positive for anti-centromere antibodies. This antibody was subsequently demonstrated to recognize a specific and formerly unknown centromeric protein, involved in the cell growth process^[33]. Garcia *et al*^[34] and Valdez *et al*^[35] found in the sera of a patients with GAVE an antinucleolar antibody that specifically recognized a RNA helicase II (RH-II). It has been speculated that these autoantibodies could cross-react with specific proteins present in the vessels of the gastric mucosa and sub-mucosa inducing the typical alterations. However, the exact role played by these autoantibodies is still unknown and only the development of an animal model will probably provide further information.

It is now evident that portal hypertension does not play a role in the GAVE development, since it is not present in up to 70% of patients, and the reduction of portal hypertension does not affect the course of the disease^[17]. Moreover, it has been shown that liver transplantation despite persistent portal hypertension induces complete disappearance of the antral vascular lesions^[36]. It could be speculated that liver failure, at least in a subset of patients, and not portal hypertension, could have a role in the pathogenesis of GAVE altering the metabolism of not yet identified substances.

Finally, GAVE syndrome could have a multifactorial pathogenesis, with the driven process strictly related to the different clinical settings (i.e., autoimmune or liver failure setting), thus explaining the dissimilar endoscopic appearance (watermelon- or honeycomb-pattern).

THERAPEUTIC OPTIONS

In the last two decades, many therapeutic options have been proposed including surgical, endoscopic and medical choices and the best approach is still to be defined.

Surgery

The surgical approach, most commonly represented by antrectomy, has a clear clinical efficacy in the management of GAVE-related bleeding, since none of the patients surgically treated has recurrence of bleeding in the post-operative period^[37]. However, this approach has significant mortality and morbidity risks, especially in the setting of portal hypertension and liver cirrhosis. Novitsky *et al*^[37] reviewed 45 reported surgical cases and found that antrectomy was the most frequently performed surgical approach (89% of cases) with a 30-d mortality rate of 6.6% and the principal cause of death was multiorgan failure. As previously mentioned, portocaval shunts, including TIPS, have no role in the treatment of GAVE syndrome^[17].

Medical therapy

A wide variety of drugs have been used to try to control GAVE-related bleeding, however no one has clearly shown satisfactory results in order to consider medical therapy as a valid alternative to an invasive approach.

Hormonal therapy - estrogen-progesterone - has been shown to control bleeding related to GI vascular malformations, including GAVE, by undefined mechanisms^[38,39]. However, since the vascular lesions persist despite cessation of bleeding, a dose-reduction is usually related to bleeding relapse^[40-42]. Moreover, the long-term treatment with hormonal-therapy can induce severe side effects, such as menorrhagia and gynaecomastia, and increase the risk of endometrial and breast cancer^[43].

Ocreotide, a long-acting somatostatin analogue, has been shown to effectively control chronic bleeding related to vascular abnormalities. Nardone and co-workers treated 3 patients with GAVE-related bleeding with ocreotide (0.1 mg subcutaneous three times a day) for 6 mo, obtaining a transient reduction of bleeding in one case and cessation in the others two patients, with partial and total regression of the lesions^[44]. This result can be partly explained by several effects exerted by this hormone such as the inhibitory effect on both neuroendocrine cells surrounding the ectatic vessels and on smooth muscle cells, and the anti-angiogenic effect. However, other authors have not confirmed these results^[45] and the role played by ocreotide needs to be further investigated in larger sample size studies.

Few case-reports have suggested a potential benefit from the use of tranexamic acid but reported severe side effects (central venous stasis retinopathy; deep venous thrombosis and pulmonary embolism) limit its use^[46-48].

A case-report showed complete resolution of GAVE with intravenous infusion of methylprednisolone and cyclophosphamide in a patient with associated systemic sclerosis and pernicious anaemia^[49]; but, such result has not been yet confirmed in larger series.

In conclusion, drug therapies have no definite role in the cure of GAVE-related bleeding and should be considered an experimental therapeutic approach in the setting of controlled clinical trials.



Figure 5 Argon plasma coagulation treatment of gastric antral vascular ectasia in patient with transfusion-dependent anaemia.

Endoscopic treatment

The endoscopic treatment principally represented by laser photoablation and, more recently, by Argon Plasma Coagulation (APC) has shown a similar and safer effect as surgery.

Neodymium-yttrium-aluminum garnet (Nd: YAG) laser coagulation has been successfully used to control GAVE-related bleeding. All series have confirmed the efficacy of this endoscopic thermal therapy by reducing or abolishing the need of blood transfusions in about 50% to 80% of cases, with a mean of 3 treatment sessions (range 1-10)^[50-53].

The most serious complication described after laser therapy, even if rare, is represented by gastric perforation. Two weeks after almost all laser therapy sessions, a gastric ulceration is frequently observed, even when the laser treatment session has been performed with an energy power sufficient to induce only superficial scarring without deep tissue necrosis^[54]. Another complication observed after repeated treatment sessions, is pyloric stenosis, that can induce either delayed gastric emptying or true obstruction^[54,55]. Up to 8% of patients developed this complication, that can be resolved by balloon dilation^[55]. Moreover, after multiple, high energy, laser therapy sessions, patients may develop hyperplastic polyps, even after 20 mo of follow-up^[56]. These polyps can reach large dimensions and induce recurrent anaemia without evidence of recurrence of vascular abnormalities^[56]. Their development is thought to be secondary to reactive foveolar hyperplasia and no focal malignancy has been detected. However, Bernstein and co-workers presented a case-report of a multifocal gastric cancer developed after repeated sessions of laser therapy over a five-year period^[57].

Other important disadvantages of laser endoscopic therapy are the high cost and the need of a long training period, since most severe complications, such as perforation and death, happen more frequently when the endoscopist is not sufficiently skilled with the procedure^[51,54].

Argon plasma coagulation (APC) is a noncontact technique with a controllable depth of coagulation (0.5-3 mm). High-frequency current is applied to the tissue

through ionized and electrically conductive gas, called argon plasma; the diverging gas flow allows an axial, radial and retrograde application (Figure 5). In comparison to Nd: YAG laser therapy, APC is easier to use, more manageable, cheaper and, most importantly, safer; nevertheless, randomized trials comparing the two endoscopic procedures are lacking.

The complications are rare and mostly mild. The most frequently reported complication is represented by intestinal gas distension related to argon flow, which can leave the patient with a feeling of discomfort after the endoscopic session. Wall emphysema and intestinal pneumatosis have been described, but these conditions are usually reversible^[58]. More serious adverse events described after APC treatment are asymptomatic antral stenosis^[59] and upper GI hemorrhage. One severe case of sepsis, which conducted to death due to infectious peritonitis, has also been described^[60]. The risk of intestinal perforation is very low and limited to very thin-walled structures (i.e., caecum)^[58,61]; notably, no case of perforation during APC treatment of GAVE has been described.

The largest case series of APC treatment reported an efficacy ranging from 90%^[60] to 100%^[62], with no further need for blood transfusions and an increase of hemoglobin level from 2.3 g/dL^[62] to 5.5 g/dL^[58] in almost all patients. The setting of argon gas flow usually ranges between 0.8 L/min and 2.5 L/min, the electrical power from 40 W to 100 W and, generally, a mean of 2.5 sessions are needed to achieve complete eradication^[58,62,63].

Several other endoscopic therapies have been proposed in the last years, such as cryotherapy, band ligation and radiofrequency ablation.

A small, prospective pilot study, based on 12 patients, investigated the efficacy of cryotherapy for the treatment of GAVE-related bleeding achieving a complete response to treatment (i.e., no need for blood transfusion) in 50% of cases^[64]. Cryotherapy is based on the rapid decrease of temperature due to the rapid expansion of carbon dioxide (CO₂) released by the spray catheter; such sudden decrease of temperature causes superficial necrosis of the mucosa and of the superficial submucosal, with eradication of antral teleangiectasias, and subsequent re-epithelialization. The need for specialized equipment and for specific training, represents Cryotherapy's main limitations; furthermore, the need of an overtube placed to enable passive venting of CO₂, might add technical difficulty and risk to the procedure.

Several case-reports and one observational comparative study have reported the use of band ligation for patients with GAVE related bleeding^[65-67]. Based on the small, retrospective study that compared endoscopic band ligation with endoscopic thermal therapy, band ligation showed a significant higher rate of bleeding cessation, fewer treatment sessions required to achieve cessation of bleeding, a greater increase in hemoglobin values and reduction of the need for transfusions^[67]. The higher efficacy compared to standard thermal therapy is probably due to a more reliable eradication of the abnormal

vasculature in the mucosa and submucosal.

Finally, a pilot study has investigated the role of radiofrequency ablation for the treatment of GAVE^[68]; 6 patients with transfusion-dependent GAVE-related bleeding were enrolled and after 1 to 3 treatments, all but one no longer needed transfusions during the 6 mo follow up, without reporting adverse events.

Although cryotherapy, endoscopic band ligation and radiofrequency ablation have provided encouraging results, well-performed, larger, prospective studies are needed before providing any definitive conclusion.

CONCLUSION

GAVE is an infrequent but severe cause of upper gastrointestinal bleeding, characterized by a pathognomonic endoscopic pattern of red spots organized either in stripes or randomly distributed in the gastric antrum. GAVE can develop in the setting of many diseases, mainly represented by autoimmune diseases and liver cirrhosis. Although many hypotheses, such as mechanical stress, humoral/immunological factors and haemodynamics alterations, have been proposed, the pathogenesis of GAVE remains still obscure and probably different pathways occur in different clinical settings. The therapy is limited to surgical or endoscopic approach, since most drug therapies have shown conflicting results. Surgery has the advantage to be a definitive therapy but with high morbidity and mortality risks, especially in patients with severe co-morbidities, such as liver cirrhosis. Endoscopic therapy, particularly treatment with APC, has shown to be as effective and also a safer than surgery, and should be considered the first-line treatment for patients with GAVE-related bleeding.

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Percutaneous endoscopic gastrostomy tube replacement: A simple procedure?

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Abstract

Replacement of gastrostomy tube in patients undergoing percutaneous endoscopic gastrostomy (PEG) is generally considered as a safe and simple procedure. However, it could be associated with serious complications, such as gastrocutaneous tract disruption and intraperitoneal tube placement, which may lead to chemical peritonitis and even death. When PEG tube needs a replacement (e.g., occlusion or breakage of the tube), clinicians must realize that the gastrocutaneous tract of PEG is more friable than that of surgical gastrostomy because there is no suture fixation between gastric wall and abdominal wall in PEG. In general, the tract of PEG begins to mature in 1-2 wk after placement and it is well formed in 4-6 wk. However, this process could take a longer period of time in some patients. Accordingly, this article describes three major principles of a safe PEG tube replacement: (1) good control of the replacement tube along the well-formed gastrocutaneous tract; (2) minimal insertion force during the replacement, and, most importantly; and (3) reliable methods for the confirmation of intragastric tube insertion. In addition, the management of patients with suspected intraperitoneal tube placement (e.g., patients having

abdominal pain or signs of peritonitis immediately after PEG tube replacement or shortly after tube feeding was resumed) is discussed. If prompt investigation confirms the intraperitoneal tube placement, surgical intervention is usually required. This article also highlights the fact that each institute should have an optimal protocol for PEG tube replacement to prevent, or to minimize, such serious complications. Meanwhile, clinicians should be aware of these potential complications, particularly if there are any difficulties during the gastrostomy tube replacement.

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Key words: Percutaneous endoscopic gastrostomy; Gastrostomy tube replacement; Gastrostomy tube exchange; Gastrostomy tube reinsertion; Complication; Peritonitis; Prevention; Management

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INTRODUCTION

Gastrostomy is indicated when an individual requires long-term prepyloric feeding^[1-5]. With an advent of endoscopic procedure, percutaneous endoscopic gastrostomy (PEG) has become more preferential than open gastrostomy thanks to its less invasiveness and better cost-effectiveness^[6-11]. Moreover, PEG was associated with significantly faster time to start feeding^[12,13]. A PEG tube is usually made of silicone or polyurethane^[14-18], thereby making it very durable and less likely to be damaged by gastric secretion compared to a latex tube^[19]. In general, the tract of PEG begins to mature in 1-2 wk after placement and it is well formed in 4-6 wk^[20,21]. However, this process

could take a longer period of time in patients with severe malnutrition, immunosuppression, or ascites^[22-26]. If a PEG tube is dislodged within a month after placement, it is advised that a repeat endoscopy be performed to replace the tube since the stomach may not well adhere to the abdominal wall, thus resulting in a free perforation^[27-29]. Blindly replacing a new tube in this scenario could cause intraperitoneal placement and consequent peritonitis^[30].

When PEG tube needs a replacement (e.g., occlusion or breakage of the tube^[31-34], or accidental dislodgement of PEG tube^[35-37]), clinicians must realize that the gastrocutaneous tract of PEG is more friable than that of surgical gastrostomy because there is no suture fixation between gastric wall and abdominal wall in PEG. Although the incidence of intraperitoneal tube placement in patients with mature gastrocutaneous tract (PEG performed > 30 d) remains unknown, peritonitis after PEG tube replacement has been reported sporadically and it was associated with significant morbidity and mortality^[38-46].

PRINCIPLES OF GASTROSTOMY TUBE REPLACEMENT

Although there is no guideline or consensus regarding PEG replacement protocols^[47-54], the principles of any PEG tube replacement should include (1) good control of the replacement tube along the well-formed gastrocutaneous tract; (2) minimal insertion force during the replacement, and, most importantly; and (3) reliable method for the confirmation of intragastric tube insertion. Replacing a new tube along the proper tract can be achieved by using a leveler to measure the depth and direction of the tract, exchanging a PEG tube over a relatively short guide wire with or without the assistance of fluoroscopy (the railroad technique, or the modification of Seldinger technique)^[55-60], or inserting a new tube under a direct endoscopic view^[61,62]. Replacing an old PEG tube with a balloon-tip tube, rather than a mushroom-tip tube or a disc-tip tube, may minimize the risk of gastrocutaneous tract disruption^[63-66]. Additional caution should be devoted when replacing PEG tubes in individuals who have non-straight gastrocutaneous tract, who have narrow stoma site, and who have less co-operation.

There are several ways to confirm a proper PEG tube replacement such as aspirating gastric or bilious fluid from the tube, listening to a gurgling sound when flushing air through the replacement tube, and performing a water/saline irrigation test (no resistance or pain when filling the tube with sterile water/saline). These methods are simple but somehow unreliable to indicate whether or not the tube insertion is getting into the stomach. The gold standard to confirm tube position is however to obtain a water-soluble contrast examination through the replacement tube^[67-69], or to visualize the internal bolster or balloon *via* an upper gastrointestinal endoscopy^[70].



Figure 1 Patient (A 60-year-old woman) developed sudden abdominal pain immediately after percutaneous endoscopic gastrostomy tube replacement. Fluoroscopy of the upper abdomen demonstrated the leakage of water-soluble contrast from a disc-tip gastrostomy tube into the peritoneal cavity (figure courtesy of Dr. Asada Methasate and Dr. Cherdasak Iramaneerat).

STEPWISE APPROACH TO PATIENTS WITH SUSPECTED INTRAPERITONEAL TUBE PLACEMENT

When intraperitoneal tube placement is suspected (e.g., patients having abdominal pain or signs of peritonitis immediately after PEG tube replacement or shortly after tube feeding was resumed), prompt investigation should be performed, either with a water soluble contrast study (Figure 1) or computed tomography scan of the abdomen^[41], and tube feeding must be discontinued immediately. In case this situation occurs in an endoscopy room, gastroscopy may show an absence of PEG tube in the stomach which confirms the malposition of gastrostomy tube.

If the investigation reveals gastrostomy tube located in the peritoneal cavity, surgical intervention is usually required such as an exploratory laparotomy with peritoneal lavage for chemical peritonitis (Figure 2). The initial site of gastrostomy may be reused, or closed and a new gastrostomy site be created distal to the former one. Broad-spectrum antibiotics should be given intravenously until clinical grounds and laboratory parameters of infection/inflammation return to normal, mostly within 5-7 d. In a lesser extent of the consequence (i.e., a stable patient with minimal symptoms and signs of peritonitis), non-operative management may be justified^[41]. This conservative approach includes the removal of the gastrostomy tube, nasogastric tube decompression, intravenous administration of broad-spectrum antibiotics, and close monitoring of hemodynamic and abdominal signs. A new PEG tube may be placed by endoscopy at a new site in the stomach whenever the patient is completely stabilized.

CONCLUSION

This article emphasizes the potential serious complication for PEG tube replacement, an intraperitoneal placement

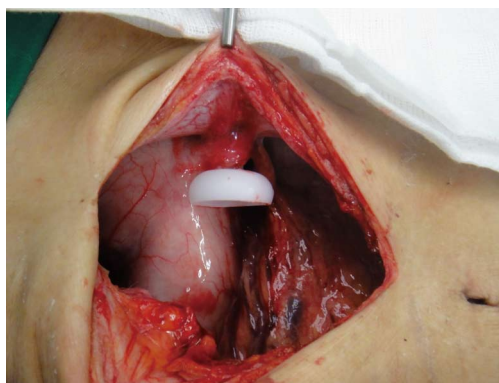


Figure 2 Intraoperative findings of the aforementioned patient showed an intraperitoneal gastrostomy tube, and the separation of mature gastrocutaneous tract close to the stomach (figure courtesy of Dr. Asada Methasate and Dr. Cherdasak Iramaneerat).

and its subsequent peritonitis, which could be associated with significant morbidity and even mortality. Each institute should have an optimal protocol for PEG tube replacement to prevent, or to minimize, such a serious complication. Meanwhile, clinicians should be aware of this complication, particularly if there are any difficulties during the gastrostomy tube replacement.

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Endoscopic management of chronic pancreatitis

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Abstract

Chronic pancreatitis (CP) is a common gastrointestinal illness, which affects the quality of life with substantial morbidity and mortality. The management includes medical, endoscopic and surgical approaches with the need for interaction between various specialties, calling for a concerted multidisciplinary approach. However, at the time of this publication, guidelines to establish care of these patients are lacking. This review provides the reader with a comprehensive overview of the studies summarizing the various treatment options available, including medical, surgical and endoscopic options. In addition, technological advances such as endoscopic retrograde cholangiopancreatography, endoscopic shock wave lithotripsy and endoscopic ultrasound can now be offered with reasonable success for pancreatic decompression, stricture dilatation with stent placement, stone fragmentation, pseudocyst drainage, and other endoscopic interventions such as celiac plexus block for pain relief. We emphasize the endoscopic op-

tions in this review, and attempt to extract the most up to date information from the current literature. The treatment of CP and its complications are discussed extensively. Complications such as biliary strictures, pancreatic pseudocysts, and chronic pain are common issues that arise as long-term complications of CP. These often require endoscopic or surgical management and possibly a combination of approaches, however choosing amongst the various therapeutic and palliative modalities while weighing the risks and benefits, makes the management of CP challenging. Treatment goals should be not just to control symptoms but also to prevent disease progression. Our aim in this paper is to advocate and emphasize an evidence based approach for the management of CP and associated long term complications.

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Key words: Chronic Pancreatitis; Biliary strictures; Pseudocysts; Endoscopic management; Pain; Pancreatic stones

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INTRODUCTION

Chronic pancreatitis (CP) is debilitating illnesses, with a prevalence estimated between 4% to 5%^[1]. The chronicity of CP and the frequent acute exacerbations significantly impact patients' quality of life. Alcohol is the most common etiology of CP in the western world. Sarles *et al*^[2] reported that 60% to 70% of patients with CP have a 6 to 12 year history of alcohol abuse. Other common etiologies of CP include autoimmune pancreatitis, hypercalcemia, as well as idiopathic CP^[3].

CP is characterized by irreversible damage that leads to fibrosis and necrosis of the pancreatic tissue^[4]. This

destruction of the pancreatic tissue manifests as abdominal pain, the most common presenting symptom of CP^[5-9]. Steatorrhea and diabetes are other common presenting symptoms seen with the loss of endocrine and exocrine function of the pancreas^[10]. Medical, endoscopic and surgical methods are available for management of CP. Medical management revolves around pain medications, fluid hydration and pancreatic enzyme supplementation surgery seem to be efficacious, at least in the short and mid term but is associated with high morbidity and mortality^[11-13]. Technological advances such as endoscopic retrograde cholangiopancreatography (ERCP), endoscopic shock wave lithotripsy (ESWL) and endoscopic ultrasound (EUS) can now be offered with reasonable success for pseudocyst drainage, stricture dilatation with stent placement, and other endoscopic interventions such as celiac plexus block or neurolysis for pain relief^[14]. However, choosing amongst the various therapeutic and palliative modalities while weighing the risks and benefits, makes the management of CP challenging.

This review is focused on the current management of CP with emphasis on pain control and treatment of complications. We aim to provide the reader with the most up-to-date evidence on endoscopic modalities available for CP.

MANAGEMENT OF CP

Pain is the most common presenting symptom of CP, and ranges from mild discomfort to severe pain that often requires hospitalization. The origin of pain is much debated; and the consensus at this time is that the etiology of pain is multifactorial^[4,15-17]. It can be caused by pancreatic duct obstruction, which subsequently leads to ductal hypertension^[9]. Pancreatic duct obstruction can be frequently caused by complications of CP such as pancreatic duct strictures, pseudocysts, intraductal stones, and sphincter stenosis^[9].

Medical management

Alcohol abuse is the most common cause of CP in the United States, and the association of binge drinking with acute exacerbation of abdominal pain in CP is well known. Therefore emphasis on alcohol cessation with offering resources on alcohol cessation such as support groups is the first step to manage CP. In addition to alcohol, smoking has also been shown to be an independent risk factor for both acute and CP^[18], and smoking cessation is equally important in patients with CP. If the avoidance of exacerbating factors fails to control flare-up of abdominal pain, pain medications should be considered for symptom relief.

Acetaminophen and non-steroidal anti-inflammatory agents should be used for pain relief, if there are no contraindications. Narcotics should never be the first line for control of pain and offering narcotics as first line of pain medication poses a real risk of addiction^[16]. Pancreatic enzymes and antioxidants have also been shown

to relieve pain in CP. Isakson and co-workers showed a 30% reduction in pain after treatment with oral enzyme preparations in a small number of patients with CP^[19]. The mechanism through which enzymatic preparations work is presumed to be *via* a negative feedback pathway involving the pancreas, specifically involving the cholecystokinin pathway^[20]. In recent years, this theory has been challenged by conflicting evidence^[21].

It is well documented that in CP there is a decreased absorption of vitamins and minerals^[22]. Deficiencies lead to increase in oxygen free radicals. There is some data to suggest that removal of oxygen free radicals may have an increased therapeutic effect in controlling pain^[23].

Endoscopic management

Advances in understanding the pathogenesis of CP combined with progress in technology have led to an emerging role of endoscopy in the management of CP. Experts believe that endoscopic management has an important role in patients^[24] as a primary therapeutic measure in poor surgical candidates where medical management fails. Recent evidence by Dite *et al*^[25] suggests that surgical outcomes were more durable than endoscopic therapy in patients with a dilated pancreatic duct (PD), stones and/or strictures^[25]. Cahen *et al*^[26] recently reported better outcomes in pain control after surgery than with endoscopic intervention. Although these studies indicate surgery might be a better intervention than endoscopy, it needs to be pointed out that neither one of those studies came from centers using routinely ESWL, which is now incorporated into the management of patients with pancreatic stones^[27]. Finally, endoscopy remains a highly effective intervention in patients with severe comorbidities and can also serve as a bridge to surgery^[28].

PANCREATIC STRICTURES

Pancreatic strictures can be caused by prior stones, recurrent inflammation or fibrosis^[29]. In cases of pancreatic stricture, where malignancy is suspected it is crucial to obtain cross sectional imaging followed by endoscopic ultrasound with fine needle aspiration (EUS-FNA) of any pancreatic masses. In the absence of a definitive mass, pancreatic brushing should be performed, keeping in mind that the threshold for referral to surgery in those cases should be low^[30-32].

The management of benign strictures includes dilatation and stenting (Figure 1). The number of strictures, the location of the strictures and the length of the stricture play key roles in determining the efficacy of endotherapy.

Symptomatic patients with a single stricture in the main PD in the head of the pancreas are the best candidates for ERCP with stenting^[33]. It is generally accepted that patients with multiple strictures along the main PD, the so-called “chain of lakes” appearance, are not good candidates for endotherapy^[33].

Table 1 summarizes the results of endotherapy in ref-

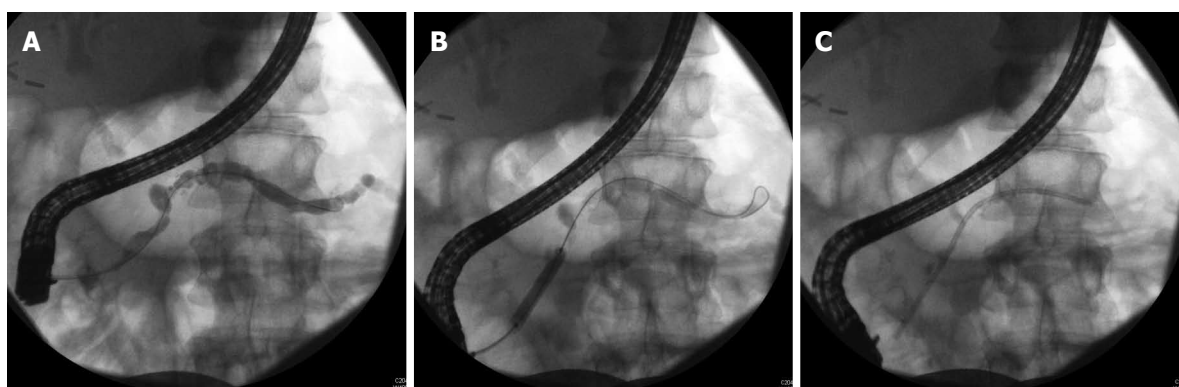


Figure 1 Management of benign strictures includes dilation and stenting. A: Distal pancreatic stricture in a patient with chronic pancreatitis; B: Dilation of the distal pancreatic stricture; C: Placement of a pancreatic stent (8.5 Fr x 12 cm).

Table 1 Summary of endotherapy in treatment of pancreatic strictures

Study	No. of patients	Tech success (%)	Average follow up time (mo)	Percent improvement in pain (%)
Weber <i>et al</i> ^[103]	19	89.4	24	89.4
Costamagna <i>et al</i> ^[40]	19	83.3	38	84
Eleftherladis <i>et al</i> ^[39]	100	70	69	70
Rosch <i>et al</i> ^[35]	1018	88	60	85
Eisendrath <i>et al</i> ^[104]	100	100	69	70
Layer <i>et al</i> ^[105]	66	NA	36	50
Cremer <i>et al</i> ^[106]	75	NR	37	94

NR: Not reported; NA: Not applicable.

erence to pancreatic strictures. Wilcox^[34] summarized the available studies on this topic. The 15 series analysis has a total of 1500 patients. Among the 1500 patients, benefit was seen in 31%-100% of patients with a wide follow-up time period from 8-72 mo. An important finding from these studies was that complete stricture resolution is not needed for the resolution of pain.

The technique of stenting the PD in the event of strictures involves dilation prior to stenting. Dilation can be performed by wire guided balloons (4-6 mm), bougie or with a Soehendra stent retriever. Polyethylene pancreatic stents are then deployed for main pancreatic duct MPD stricture as large as possible to mimic a “pancreatico-duodenostomy”^[12,27,33,35,36].

Pain relief is seen in 70%-94% of patients after stent placement (Table 1). Ductal decompression is indicated if the main PD above the stricture is significantly dilated (large duct disease). The strategy remains that the stents are prophylactically exchanged every three months^[37]. In some cases, the stent can get clogged, however it will continue to remain effective by what is known as the “wick” effect^[38].

It is important to note, however, that after stent removal the rate of recurrence of a main PD stricture is high. In fact, Eleftherladis *et al*^[39] reported the stricture relapse rate after a 2 year follow up period was as high as 38%, with these patients require repeat stenting.

Although the approach of multiple stents for PD strictures seems promising^[40-42], to our knowledge, at the time of writing, there have been no studies comparing

single and multiple stenting procedures for PD strictures caused by CP.

For patient in whom conventional ERCP is not feasible or fails, access and decompression of the main pancreatic duct using EUS-guided pancreatography has increased the success for PD drainage^[30-32,43-45]. This constitutes a minimally invasive alternative to surgery in patient with altered anatomy or severe stone burden not responding to ESWL.

PANCREATIC STONES

Obstruction of the PD by calcified stones leads to increased pressure upstream from the stone causing increased intraductal hypertension. The data surrounding pancreatic stone removal is clear. Endoscopic therapy alone was found to be successful in 72% of patients with a 68% symptomatic improvement^[35,46,47]. ESWL can relieve the elevated intraductal pressure by fragmentation of intraductal stone.

Upon fragmentation the stones can pass spontaneously^[48,49], therefore ERCP is not obligatory unless there is an associated stricture. The primary limitation of ESWL is that it cannot be used to fragment larger stones. In such cases, laser lithotripsy might be more effective^[50-53].

In 2007, Dumonceau *et al*^[54] compared ESWL alone with ESWL in conjunction with endoscopic drainage of the main PD for pain relief. Two years after intervention, they noted a similar decrease in the number of pain episodes per year. As such, it was concluded that

Table 2 Studies that evaluated endoscopic shock wave lithotripsy with endoscopic retrograde cholangiopancreatography for chronic pancreatitis

Study	Total patients	No. of patients in any amount of pain at follow up	Duct clearance	Mean follow up time (mo)
Sauerbruch <i>et al</i> ^[107]	8	8	8	11
Den Toom <i>et al</i> ^[108]	8	8 (7 pain relief)	8	17
Sauerbruch <i>et al</i> ^[109]	24	24	24	24
Delhaye <i>et al</i> ^[60]	123	88	123	
Schneider <i>et al</i> ^[110]	50	39	48	20
Van der Hul <i>et al</i> ^[111]	17	17	17	30
Wolf <i>et al</i> ^[112]	12	9	12	19-22
Schreiber <i>et al</i> ^[113]	10	7	10	12
Johanns <i>et al</i> ^[114]	35	23	16	NA
Ohara <i>et al</i> ^[115]	32	7	24	44
Matthews <i>et al</i> ^[116]	19	13	19	6 mo-6 yr
Costamagna <i>et al</i> ^[117]	35	32	35	6
Adamek <i>et al</i> ^[49]	80	80	NA	NA
Brand <i>et al</i> ^[55]	48	17	48	7
Karasawa <i>et al</i> ^[118]	24	12	24	12
Kozarek <i>et al</i> ^[36]	40	28	NA	2.4 yr
Rubenstein <i>et al</i> ^[119]	23	NA	23	NA

¹Pain relief was not a primary end point. NA: Not applicable.

ESWL alone was a safe and effective modality of treatment in reducing pain in CP with stone only disease and addition of endoscopic measures added costs to patient care, with no significant reduction in pain relief^[54]. Endotherapy in conjunction with ESWL has been shown to increase stone clearance rates and to improve long-term outcomes^[36,49,55-60] in patients with stone and stricture disease. In one study Kozarek *et al*^[36] were able to show that surgery was avoided in 80% of patients who underwent ESWL, with decrease in narcotic use and reduction in hospitalizations (Table 2).

PANCREATIC PSEUDOCYSTS

A total of 20%-40% of patients with CP can develop this complication^[61]. Intraductal hypertension within the main PD, or the rupture of a branching duct can lead to formation of pseudocysts. Pseudocysts^[62] who fail to resolve spontaneously and are symptomatic require drainage. Drainage is indicated if there is pain, infection or evidence of obstruction^[61,63,64].

The modality employed for drainage is also important. There are two major routes of endoscopic drainage-transmural and transpapillary. The route chosen depends on the size, possible communication between the pseudocyst and the pancreatic duct. There appears to be a trend in the literature for transmural drainage versus transpapillary^[65] with an attempt to seal any possible leak or draining a proximal duct by crossing a stricture^[65]. Several studies place the technical success of transmural drainage of pseudocyst at 85%-100%. The recurrence rate range from 10%-15% with complications between 10%-34%^[63,66-68].

In recent years, EUS-guided pseudocyst (EGPD) drainage has gained in popularity since it allow to avoid intervening vessels and target more challenging collections safely when compared to conventional transmural drainage

techniques (CTDT)^[69-71]. Our team^[64] and others^[72] have demonstrated that EUS-guided drainage and conventional transmural drainage techniques have fairly comparable rates of success and similar rates of complications if non bulging collection and patient at higher risk of bleeding are selectively drained using EGPD.

ENDOTHERAPY ON BILIARY DUCT STRICTURES

Benign strictures can also form within the biliary ductal system in CP, and if left untreated can lead to jaundice, cholangitis and biliary cirrhosis^[41,73]. Traditionally benign biliary strictures in CP are treated by surgery, but as with all surgeries the procedure is invasive and can involve significant morbidity especially if patients have other accompanying co-morbidities such as CP and/or liver disease. Morbidity and mortality of surgical treatment of post-operative biliary strictures is low, with mortality rates ranging from 0%-2.2%, whereas post-operative morbidity rates approaching almost 43% in some studies^[74-76]. The multiple stent placement technique was initially popularized by Costamagna *et al*^[40] for the treatment of postoperative strictures. In their study, stricture resolution was observed in 95% of patients at stent removal, and at follow up (average time of 38 mo after stent removal) 84% of patients were pain free and only 10.5% (2 patients) had recurrence of stricture.

They reported good long term results in treatment of post-operative biliary strictures by insertion of plastic stents after greater than a ten year follow up. While, success is dependant on the number of sessions and the number of stents placed, it appears that this maybe a reasonable first-line option^[42]. Several groups have studied biliary strictures and endoscopic approach to treatment, and in all cases average stricture resolution was reported between 10%-33% (Table 3)^[57,77-83].

Table 3 Summary of studies that evaluated efficacy of endoscopic biliary polyethylene stents for treatment of common bile duct strictures

Study	Total patients	Success rate (%) -short term	Stricture resolution (%)	Stent occlusion (%)	Stent migration (%)	Follow up time (mo)
Deviere <i>et al</i> ^[85]	25	100	3 (12)	32	40	14
Barthet <i>et al</i> ^[83]	19	100	2 (11)	0	5	18
Smits <i>et al</i> ^[82]	58	100	16 (28)	62	7	49
Kiehne <i>et al</i> ^[81]	14	100	2 (16)	36	NA	NA
Vitale <i>et al</i> ^[80]	25	100	20 (80)	12	8	32
Farnbacher <i>et al</i> ^[79]	31	100	10 (32)	29	23	24
Eickhoff <i>et al</i> ^[78]	39	100	12 (31)	33	10	58
Average	30	100	30	29.14	17.16	32.5

NA: Not applicable.

Uncovered metal stents have also been evaluated. Since biliary strictures related to CP can be difficult to treat with plastic stents, there have been several studies that examined the use of uncovered self-expanding metal stents (USEMS) in patients with primarily CP^[84-87]. Deviere *et al*^[85] deployed USEMS in patients ($n = 20$) with CP, and initially demonstrated relief of cholestasis for up to 33 mo for 18 patients. Repeat ERCP 3 mo later demonstrated that the stent was embedded within the bile duct wall. All subsequent studies confirmed that uncovered metal stents proved to be problematic due to epithelial hyperplasia, occlusion, and the inability to easily remove the stent without overwhelming evidence of improved patency or stricture resolution^[88]. This lack of removability also predisposes the patient to chronic inflammation and a potential for cholangiocarcinoma.

Covered metal stent, partially or fully covered have been used, with stricture resolution for partially covered metal stent^[89] noted to be about 77% in CP, whereas fully covered metal stents provided a success rate of 83%^[90]. Given the limitations noted with uncovered stents, and in an effort to improve patency, partially covered self-expanding metal stents (PCMS) were assessed in this biliary stricture related to CP. They were noted to be easier to remove, offering the option of temporary placement^[91-93]. Cantù *et al*^[94] placed PCMS in patients with CP and associated common duct stricture who failed prior plastic stent therapy. All the patients responded initially but with a median follow up of 22 mo (range 12-33 mo), 7 patients developed stent dysfunction, requiring re-intervention. Stent patency, however, decreased over time, from 100% at 12 mo to 37.5% at 36 mo and none of the PCMS were removed during the study period, demonstrating that PCMS left in place over time decrease in patency, requiring additional endoscopic interventions^[94]. Another similar study deployed PCMS in 6 patients with limited patency (2/6) at 35 mo (range 33-37 mo) follow up. In addition, this study compared uncovered ($n = 18$) to PCMS and found longer patency with uncovered stents (mean 46 mo *vs* 20 mo, $P = 0.002$), although overall follow up was much longer for uncovered stents (mean 61 mo), which could account for the significant difference^[86].

Kahaleh *et al*^[95] performed the largest series of pa-

tients ($n = 79$) with partially covered metal stents coated with Permalume (Wallstent, Boston Scientific, Natick, MA). Sixty five patients had stent left in place for a median of 4 mo (range 1-28 mo) and removed once successful treatment was confirmed. Follow up after stent removal was a median of 12 mo (range 3-26 mo). Three patients developed a stricture at uncovered proximal portion, 3 failed primary therapy and 2 developed duodenal edema preventing SEMS insertion, resulting in 90% success (59/65). Successful resolution of the stricture was noted to be lowest with strictures related to CP (17/22, 77%)^[95]. As a follow up to this study, Sauer *et al*^[96] further analyzed long term response of those patients. Notably, migration occurred with 15 stents, as well as intimal hyperplasia and stent embedment into the mucosa in 7 patients each respectively^[96].

Fully-covered self-expandable metal stents

With limitations related to partially covered metal stents namely epithelial hyperplasia at the uncovered portions and migration, fully covered metal stents (FCSEMS) were then tried in this indication (Figure 2). Cahen *et al*^[97] published a series of 6 patients with strictures resulting from CP receiving FCSEMS (Hanaro; M.I.Tech Co., Ltd., Seoul, South Korea), with 66% resolution, however 2 stents were unable to be removed requiring plastic stents placement through the other metal stent. More recently, Mahajan *et al*^[98] analyzed a FCSEMS with anchoring fins (Viabil, Conmed, Utica, NY) to treat benign biliary strictures. A total of 44 patients (28 men, median age 53.5 years) were included. Etiologies included 19 CP. Complications were observed in 6/44 (14%) patients after placement, and 4/44 (9%) patients after removal, mainly pain and post ERCP pancreatitis. Lower rate of resolution was seen with CP (58%) and moderate difficulty in deploying and removing the stent due to its anchoring fins proved to be limitations in its widespread use. The anchoring fins also caused ulceration and bleeding with stent extraction^[98].

A follow up study came from the same group with 55 patients and subsequent mean stent time of 126 ± 74 d and follow up of 524.2 ± 297.7 d. The success rate was 67% for those with CP and 71% for other etiologies^[96].

The data that we are seeing in literature on FCSEMS

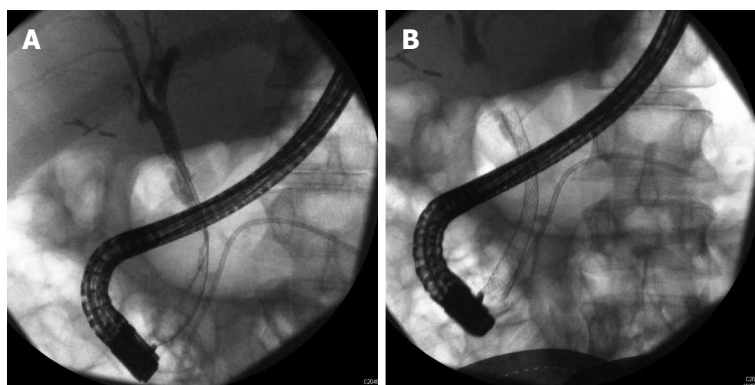


Figure 2 Fully-covered self-expandable metal stents. A: Distal biliary stricture in the setting of chronic pancreatitis; B: Placement of a fully covered metal stent (10 mm x 60 mm) draining the bile duct.

are promising, but larger randomized control trials are needed to evaluate this treatment modality. It is conclusive however, that endotherapy in treatment of biliary strictures is a good option for high risk surgical patients and for those who prefer a less invasive approach.

EUS-GUIDED CELIAC PLEXUS BLOCK

Celiac plexus block (CPB) is performed via a gastric approach using EUS-guidance and has high success rates and relatively low complication rates. EUS-guided CPB is preferred over CT-guided CPB not only because there are fewer side effects^[98] but also because of clarity obtained via EUS. CPB can be performed by injection of anesthetics and/or steroids. Celiac plexus neurolysis, used for pain secondary to malignancy, is similar but involves injection of pure ethanol which results in complete destruction of the celiac plexus. EUS allows for live imaging of the celiac space which improves visualization. EUS guided celiac plexus block improves pain in about 50% of patients for a period of 3-6 mo^[98]. In a prospective randomized study, Gress *et al*^[98,99] compared EUS to CT-guided CPB for the treatment of CP pain and discovered that about 50% of patients in the EUS group had significant pain reduction. In addition, about 40% (8 wk group) and 30% (24 wk group) of the EUS-guided CPB had continued benefit. This, when compared to 12% (12 wk) in the CT-guided CPB, clearly suggest superiority of the EUS method.

Several retrospective and prospective studies have put the success rate as high as 95%^[98-101]. While technical success has been high, long term pain relief are disappointing. Short-term pain improvement was approximately 50%, whereas long term pain relief at 24 wk was only 10%. A similar number has been achieved for short-term pain relief by Kaufman *et al*^[102].

Given the low long-term success rates, EUS-guided celiac block should be considered as a temporary measure. It should be considered in acute flares of chronic pain in those patients with limited options.

Surgical options

Advances in understanding the pathogenesis of CP com-

bined with progress in technology have led to an emerging role of endoscopy in the management of CP. Experts believe that endoscopic management has an important role in patients^[24] as a primary therapeutic measure in poor surgical candidates where medical management fails. Recent evidence by Díte *et al*^[25] suggests that surgical outcomes were more durable than endoscopic therapy in patients with a dilated PD, stones and/or strictures. Cahen *et al*^[26] recently reported better outcomes in pain control after surgery than with endoscopic intervention. Although these recent studies that indicate surgery as a better intervention than endoscopy, endoscopy is a highly effective intervention especially in patients who are high-risk surgical candidates especially if combined to ESWL. Delhaye *et al*^[28], concluded that endotherapy can also serve as a bridge to surgery.

Díte *et al*^[25] analyzed patients with CP secondary to large duct CP and compared endoscopic therapy to lateral pancreatojejunostomy procedure, and found that in the randomized and the non-randomized groups the results were similar. Moreover, on a five year follow up, patients in the surgery group were more likely to be pain free than in the endoscopic group. Cahen *et al*^[26] also reported similar results. The primary difference between the two studies was that in the former study, endoscopic techniques were not optimized. Specifically, it did not involve patients undergoing cumulative stenting, or repeat treatment after recurrence, and it did not include ESWL.

CONCLUSION

CP is a disabling disease with serious complications affecting quality of life. There have been significant advances particularly on the endoscopic front with advent of endoscopic techniques such as pancreatic stenting, ESWL, pseudocyst drainage and EUS-guided access and therapy. A multidisciplinary team approach with judicious and appropriate utilization of the medical, endoscopic and surgical treatment options holds promise to revolutionize patient care. Given the variability in the presentation and patient preferences, treatment should be tailored on a case-to-case basis.

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Endoscopic knot tying: *In vitro* assessment in a porcine stomach model

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Abstract

AIM: To determine if surgical knotting performed *via* endoscopy is an effective closure method for natural orifice transluminal endoscopic surgery.

METHODS: The proposed method was tested on an *in vitro* pig stomach model using standard endoscopy suite materials. A single use laparoscopy trocar (VersaPort Plus manufactured by Tyco Healthcare) was fixed onto a plastic rectangular box in a horizontal position. A fresh pig stomach was tightly attached *via* its esophageal end to the trocar opening on the inner side of the box. The stomach cavity was closed at the duodenal end with Kocher forceps. A standard upper gastrointestinal endoscope fitted at its tip with a transparent plastic cap was introduced into the stomach through the outer trocar opening, so that the passage of the surgical trocar would mimic the passage of an esophagus. The stomach was subsequently inflated, followed by irrigation and washing. A neutral electrode of an electrocautery unit was placed inside the plastic box, un-

derneath the pig stomach. The stomach's outer surface was kept moist using normal saline in order to maintain the natural elasticity and to ensure good contact with the electrode.

RESULTS: The submucosal space on the anterior face of the stomach was accessed using the technique of endoscopic submucosal dissection. First, a site on the anterior face of the stomach was chosen, near the angle. Then, saline was injected into the submucosa with a standard endoscopic needle, so as to create a 20 mm diameter elevation. A linear 15 mm vertical incision was created at its center using a Dual Knife (KD650U manufactured by Olympus). This incision was used to access the submucosal space, and about 10 mm was dissected on both sides of the incision. The endoscope was then pushed through to the outside of the stomach after dilating a small puncture made by the Dual Knife in the *muscularis propria*, which simulated the peritoneoscopy procedure. Then, a 0.025" guidewire (Jagwire/450 cm manufactured by Boston Scientific) was inserted into the puncture, followed by a dilating balloon (Quantum TT manufactured by Cook Medical) that was used to enlarge the aperture orifice. After withdrawing the scope back into the stomach, the procedure continued with guidewires being passed from the submucosal space into the gastric lumen through small orifices on the left and right sides of the mucosal opening. These orifices were made with the Dual Knife, and the guidewires were inserted *via* a guiding catheter (HGC-6 manufactured by Cook Medical). As the guidewires were pulled outside of the stomach, they were replaced with a single surgical suture that had been initially attached to their tip and was now untied. Finally, one loop of this surgical suture was formed on the exterior. One loop end was fixed while the opposite suture end was pulled by biopsy forceps through the endoscope channel as the scope was inserted into the stomach. The loop was advanced until it approached and fixed the two mucosal incision margins. Three alternating loops were made in this manner to create a genuine tight surgical knot.

CONCLUSION: Endoscopic knotting of the gastric wall is feasible, but an *in vitro* survival study is necessary to validate clinical significance.

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Key words: Endoscopy; Endoscopic submucosal dissection; Natural orifice transluminal endoscopic surgery; Suture; *in vitro*

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INTRODUCTION

The concept of natural orifice transluminal endoscopic surgery (NOTES) was introduced in 2004, when Kaloo *et al*^[1] reported a successful transgastric peritoneoscopy performed in an *in vivo* porcine model. Since then, the variety of NOTES interventions using the porcine survival model has expanded to include splenectomy^[2], gastrojejunostomy^[3], hysterectomy^[4], ligation of fallopian tubes^[5], oophorectomy^[6,7], cholecystectomy^[8], appendectomy^[9], hernia repair^[10], pancreatectomy^[11], and lymphadenectomy^[12]. Human trials are currently under way^[13].

From the beginning, two of the main scientific endoscopic societies have been involved in assessing and promoting research related to the NOTES procedures, namely the North American Natural Orifice Surgery Consortium for Assessment and Research (NOSCAR) group^[14] and the European EURO-NOTES group^[15]. In 2006, NOSCAR published a White Paper outlining twelve critical features that can impact the safety of NOTES to guide its appropriate usage and highlighted the need for increased research and analysis of data^[16]. Gastric (intestinal) closure was designated as a very important area of research, and the group mandated a strict objective of the NOTES procedure to achieve closure with absolutely no leaks.

To date, the reported closure methods for the various NOTES interventions have used dedicated suture and anchor tools^[17], such as T tags^[18], purse string-modified T tags^[19], Eagle Claw VIII^[20], flexible endoscopic stapler^[21], purse string suturing device^[22], and flexible Endostitch^[17]. All of these devices are cumbersome and have not yet received approval for use in clinical settings.

Therefore, this study was designed to investigate the feasibility of performing a surgical suture of a stomach opening by using common endoscopy devices.

MATERIALS AND METHODS

A modified version of the *in vitro* porcine stomach model described by Hon *et al*^[23] was used. Briefly, a trocar with radiolucent sleeve and 10-15 mm seal (Versaport Plus;

Tyco Healthcare, Gosport, United Kingdom) was fixed onto a plastic rectangular box. A fresh pig stomach was tightly attached to the trocar on the inner side of the box *via* the esophageal opening. The duodenum was closed with a pair of Kocher forceps (Figure 1A). A standard gastroscope (GIF 160; Olympus, Rungis, France) fitted with a transparent straight plastic cap was inserted through the trocar (emulating passage through the esophagus) into the lumen of the stomach. The lumen was inflated and the procedure was performed as detailed in the Results.

RESULTS

The gastroscope-assisted knotting procedure was carried out with the following nine steps: (1) A 20 mm gastric submucosal bleb was created by injecting saline (25G 1-JectS; ABS Bolton Medical, Saint Michel/Meurthe, France) into the anterior inner face of the stomach, near the angle. A 15 mm linear incision was then made at the top of the submucosal elevation using a Dual Knife (KD650U; Olympus) coupled with a standard electro-surgical unit (Erbotom ICC200; ERBE, Tübingen, Germany); (2) The submucosal space was dissected at about 10 mm on both sides of the incision by introducing the cap-fitted endoscope inside the submucosal space (Figure 1B); (3) Peritoneoscopy was performed by the standard technique^[1]. First, the Dual Knife was used to puncture the muscular layer from the submucosal space into the middle of the initial incision. A 0.025" guidewire (Jagwire/450 cm; Boston Scientific, Nanterre, France) was introduced into this orifice, followed by a 10 mm dilating balloon (Quantum TT; Cook Medical, Charenton le Pont, France) that was inflated to facilitate the scope's passage out of the stomach (Figure 1C). Finally, the balloon was deflated and the scope was retracted into the stomach; (4) On one incision side, a puncture was made in the mucosa from the submucosal space towards the lumen. A guiding catheter (HGC-6; Cook Medical) was introduced into this puncture to facilitate introduction of a 0.025" guidewire on the luminal side of the mucosa, traversing into the gastric lumen (Figure 2A); (5) After creating several loops in the stomach with the guidewire from Step (4), the endoscope was withdrawn, leaving the guidewire in place, and then reintroduced near it. The guidewire's distal end was captured with forceps (Radial Jaw; Boston Scientific) and pulled outside of the stomach (Figure 2B). Both ends of the guidewire were now outside the stomach, with the guidewire passing through an orifice from the submucosal space into the gastric lumen; (6) A 120 cm 4-0 surgical suture (Prolene; Ethicon, Issy les Moulineaux, France) was tied to one end of the guidewire. The other end of the guidewire was then pulled out, effectively dragging the surgical wire into the previously occupied position. The extracted guidewire was detached from the in-place surgical wire; (7) Steps (4), (5), and (6) were repeated on the second incision side, with minor modification. At step (6), the submucosal end of the guidewire was tied outside the stomach, with the submucosal end

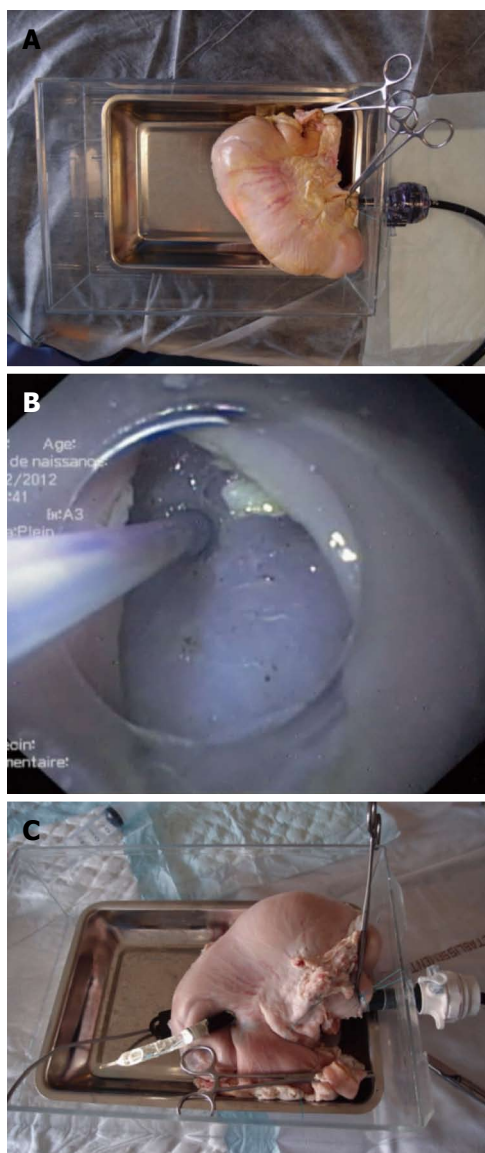


Figure 1 Endoscope. A: The “*in vitro*” pig stomach model with the endoscope in place; B: View over *muscularis propria* from the gastric lumen in the submucosal space created by endoscopic submucosal dissection. *Muscularis propria* is about to be punctured (“peritoneoscopy”); C: Endoscope outside of the stomach simulating peritoneoscopy, with the dilated balloon in the working channel.

of the surgical wire remaining in place on the first incision side. The guidewire was again pulled out, so that the surgical wire passed through both sides of the submucosal incision (Figure 2C); (8) A single loop had formed on the outside, and one wire end was fixed into place. Biopsy forceps were used to pull the other end through the working channel of the endoscope, simultaneously introducing the endoscope into the stomach and pushing the loop with the endoscope tip towards the incision line (Figure 2D). In this manner, the incision mucosal sides were brought towards one another as the loop was tightened. Three alternating loops were made to form the final surgical knot; and (9) The wire ends were cut with a reusable loop cutter (FS-5Q-1; Olympus) (Figure 2E). A photograph of the completed surgical knot is shown in Figure 2F.

DISCUSSION

The aim of this study was purely theoretical, by which we sought to prove that a surgical suture may be created using only commonplace endoscopy suite materials, without metallic clips, to close a hole in the wall of a hollow digestive organ. As such, the study has several important limitations.

Since the study was based on an *in vitro* model, neither the strength of the suture, its resistance nor tightness was evaluated. Moreover, other treatment-related quality parameters, such as infection rate and histological response, were not evaluated. Although infectious complications may be prevented in the *in vivo* model by antibiotic lavage of the stomach before gastric NOTES procedures^[24]. Another limitation is that only a single knot was used to close a 15 mm incision, which would be insufficient for a surgical closure. We speculate that two or more suture wires may be passed through both incision sides and tightened at the end, so as to form two or more surgical knots and increase the fidelity of the closure. However, this may prove unfeasible since surgical wires could tangle or form spontaneous knots inside the stomach, beyond the operator’s control.

Nonetheless, the endoscopic method does have an important safety advantage. The endoscopic surgical suturing reduces the risk of injury to organs adjacent to the stomach, which is a significant concern when using T-tags^[25]. The method itself may also prove useful as a feasibility model for future development of safer suturing devices that work within a previously dissected submucosal space. In fact, some researchers have already attempted to investigate the utility and safety of an artificially generated submucosal tunnel, but the mucosal incision site had been closed with metallic clips^[26]. Testing of this method in an *in vivo* animal model is necessary to better understand not only its clinical significance with NOTES interventions but also to help realize its potential for other applications.

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COMMENTS

Background

Traditionally, surgery has been the only method available for removing pathological tissue from the inner abdomen. Laparoscopic surgery and digestive endoscopy have made diagnostic and therapeutic procedures less invasive. Laparoscopic surgery requires creation of orifices in the abdominal wall to access the peritoneal space, while digestive endoscopy travels along and is confined to the digestive tract. In the last 10 years, however, the natural orifice transluminal endoscopic surgery (NOTES) approach passed the endoscope into the peritoneal cavity through a created orifice in the wall of the digestive tract.

Research frontiers

The NOTES approach has not yet been fully developed. Questions remain about how to prevent peritoneal infection, how to accurately stabilize the endoscope in the peritoneal cavity and obtain a good grip and orientation (triangula-

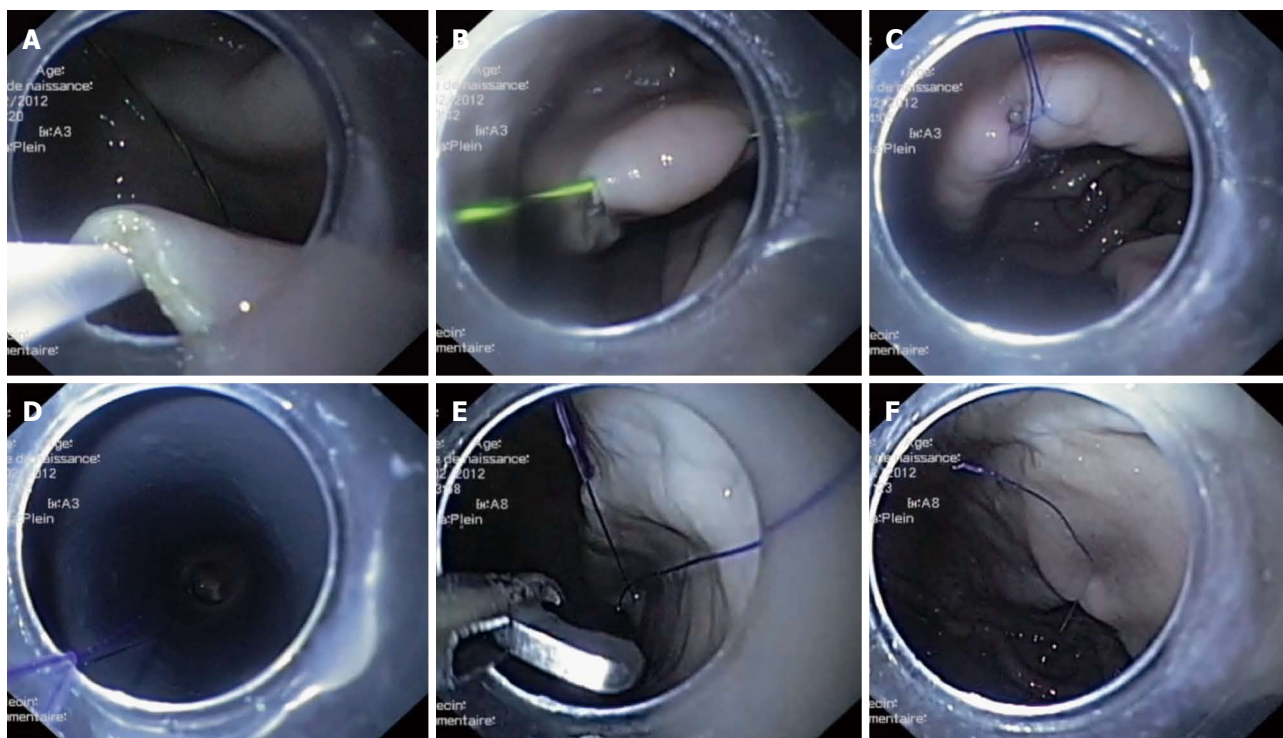


Figure 2 Natural orifice transluminal endoscopic surgery. A: Puncture of the mucosa from the submucosal space on the right side of the incision and passing a guidewire into the gastric lumen; B: The guidewire traverses the mucosa on the right side of the incision, both ends are outside; C: Surgical wire replaces the guidewire first on the right side, then is passed through both sides after replacing the guidewire on the left side; D: A loop formed outside is pushed with the endoscope (here at the rim of the transparent cap) at the mucosal incision so as to tighten the knot; E Cutting the wire ends; F: The final aspect of the surgical knot.

tion), and how to finally close the parietal access point. The simplest way to close the orifice is to use endoscopic metallic clips, which are already used for closing accidental perforations, for hemostasis, or for marking. More elaborate methods have been proposed, including endoscopic suture machines and staplers, or trans-parietal metallic tags tightened together. Yet, these methods are complicated, costly, high risk, and not approved for clinical practice.

Innovations and breakthroughs

The authors have described a method to close the digestive wall orifice with a surgical knot using only common endoscopy suite materials. This approach avoids the use of additional devices and reproduces the gold standard surgical closure method-the surgical knot.

Applications

The method may be used as a model for creating simple suturing devices that work within the submucosal space. It must first be validated by *in vivo* survival animal experiments.

Terminology

NOTES: Natural orifice transluminal endoscopic surgery, a method to perform abdominal surgery by entering the peritoneal space through small orifices made into hollow organs (i.e., stomach, colon, vagina, urinary bladder).

Peer review

The case is interesting and extremely rare. It is well written and is describing a new method of endoscopic suture. It can be accepted for publication an intra operative image during laparotomy would be of added value.

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Primary intestinal follicular lymphoma: How to identify follicular lymphoma by routine endoscopy

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Abstract

A 69-year-old Japanese female was diagnosed with primary intestinal follicular lymphoma. Esophagogastroduodenoscopy with high-definition imaging revealed not only the typical feature of whitish polyps of up to 2 mm in diameter in the duodenal second and third portions, but also more detailed morphology, such as enlarged whitish villi and tiny whitish depositions. These findings appeared to reflect the pathological structures; infiltration of lymphoma cells into the villi were probably seen as enlargement of the villi, and the formation of lymphoid follicles were shown as opaque white spots

or tiny white depositions. Thus, the above features might contribute to the distinct diagnosis of intestinal follicular lymphoma. This case indicates that routine esophagogastroduodenoscopy can visualize microsurface structures, which can be pathognomonic and help to diagnose intestinal follicular lymphoma, even without magnifying endoscopy.

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Key words: Follicular lymphoma; Gastrointestinal endoscope; Duodenal neoplasms; Gastrointestinal lymphoma; Microsurface structures

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INTRODUCTION

The number of patients newly diagnosed with primary intestinal follicular lymphoma is increasing as increasing numbers of endoscopists and gastroenterologists become familiar with this entity. The duodenum is the most frequently affected site, and the representative endoscopic feature, small whitish polypoid nodules up to 2 mm in diameter, is well known^[1]. This feature has been described as “multiple polypoid lesions,” “multiple small polyps,” “multiple nodules” and “multiple granules”^[2,3]. The ongoing development of magnifying endoscopy has provided more detailed endoscopic images of intestinal follicular lymphoma, enabling the identification of features such as enlarged villi, opaque whitish spots, and coiled vascular pattern within the villi^[4-9].

We recently treated a patient with a typical case of primary duodenal follicular lymphoma. Her diagnosis was based on routine esophagogastroduodenoscopy findings without magnifying observations. The endoscopy findings were of a characteristic morphology, including enlarged whitish villi, tiny submucosal whitish depositions and multiple sites of involvement, in addition to the typical macroscopic features of whitish polypoid nodules. This case indicates that routine endoscopy can identify not only well known features such as whitish polyps or nodules, but also more detailed images that help to diagnose this disease, even without magnifying endoscopy.

CASE REPORT

A 69-year-old Japanese female presented to Onomichi Municipal Hospital in April 2012 with intermittent vague abdominal pain that had been present for the previous week. She had been taking betahistine mesilate for the prevention of Meniere's syndrome. The patient had no previous history of gastrointestinal or hematopoietic diseases. Physical examination revealed no abnormalities, and there was no evidence of hepatosplenomegaly or peripheral lymphadenopathy. All laboratory findings, including the levels of lactate dehydrogenase (LDH) and soluble interleukin-2 receptor (sIL-2R), were within the normal ranges.

Esophagogastroduodenoscopy was performed with a high-definition imaging system (CV-260SL, Olympus, Tokyo) and a videoendoscope (GIF-H260, Olympus). Esophagogastroduodenoscopy revealed whitish polyps around the ampulla of Vater (Figure 1A and B). Polyps were also noticed in the third portion of the duodenum (Figure 1C). A close-up view of the lesion in the second portion of the duodenum revealed that the lesion was composed of two components: enlarged whitish villi and tiny submucosal whitish depositions (Figure 2A and B). These structures were more clearly visualized with a narrow-band imaging view (Figure 2C). Based on these endoscopic features, duodenal follicular lymphoma was highly suspected. Biopsy samples contained lymphoid follicles in the duodenal mucosa, and these were comprised of small to medium-sized lymphoid cells which had also infiltrated into the villi (Figure 3). The lymphoid cells were positive for CD20, CD10, and BCL2, but negative for CD3. Small bowel involvement was evaluated by video capsule endoscopy, and whitish polyps were detected as multiple jejunal lesions (Figure 4). A colonoscopy revealed no abnormality.

A bone marrow aspirate and biopsy were performed, and revealed that there was no infiltration of lymphoma cells in the bone marrow. Computed tomography (CT) scans of the neck, chest, abdomen and pelvis detected neither lymphadenopathy nor a thickened gastrointestinal wall (including the duodenum). An 18F-fluorodeoxyglucose positron emission tomography scan showed

no abnormal accumulations of 18F-fluorodeoxyglucose. Consequently, the patient was diagnosed with primary intestinal follicular lymphoma, which was localized to the duodenum and the jejunum. The clinical stage was considered to be stage I, based on the Lugano staging system for the classification of gastrointestinal tract lymphomas^[10,11].

DISCUSSION

The use of high-definition imaging systems is well established in the field of gastrointestinal endoscopy, and such systems are now also widely used as a routine examination tool. High-definition imaging technologies provide high-resolution pictures to reveal more detail than the traditional video endoscopy systems. In the present patient, several key features, such as whitish enlarged villi and tiny whitish depositions under the mucosa, were visualized by high-definition imaging without a magnifying endoscopy system. To our knowledge, this is the first report to describe these microsurface structures as characteristic findings of intestinal follicular lymphoma being detected by routine esophagogastroduodenoscopy without magnifying observation.

Primary intestinal follicular lymphoma is a distinct variant of systemic follicular lymphoma that was established within the last decade^[1,12]. The representative feature in the conventional endoscopic observation is well known as small whitish polypoid nodules that can be up to 2 mm in diameter^[2,3]. More detailed microsurface structures have been reported by several authors, based on magnified endoscopic findings of intestinal follicular lymphoma^[4-9]. Norimura *et al.*^[8] summarized the magnified endoscopic findings of six patients with intestinal follicular lymphoma, and they reported that abnormalities of the villi and the presence of opaque white spots are possible pathognomonic features of this disease. Our patient's endoscopic findings are in concordance with the report by Norimura. We speculate that these findings reflect pathological structures; infiltration of lymphoma cells into the villi are seen as enlargement of the villi, and lymphoid follicle formations are observed as opaque white spots or tiny white depositions. Thus, the above features might contribute to making the definite diagnosis of intestinal follicular lymphoma, although the sensitivity and specificity of these endoscopic features require further investigations.

In the present patient, esophagogastroduodenoscopy revealed multiple lesions, i.e., one lesion in the second portion and another lesion in the third portion of the duodenum. Video capsule endoscopy revealed additional lesions in the jejunum. Multiple sites of the gastrointestinal tract are frequently involved in patients with intestinal follicular lymphoma. Our previous study revealed that 46 out of 54 duodenal follicular lymphoma patients (85.2%) who underwent whole gastrointestinal tract surveillance had extensive involvement of the small

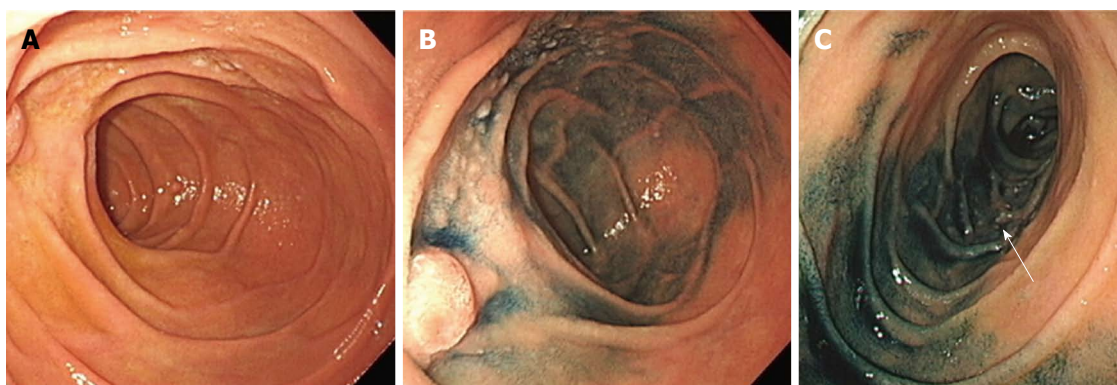


Figure 1 Images obtained during esophagogastroduodenoscopy. A: Normal white-light observation revealed whitish polyps around the ampulla of Vater; B: Indigo carmine spraying increased the contrast of the lesion; C: Whitish polyps were also seen in the third portion (arrow).

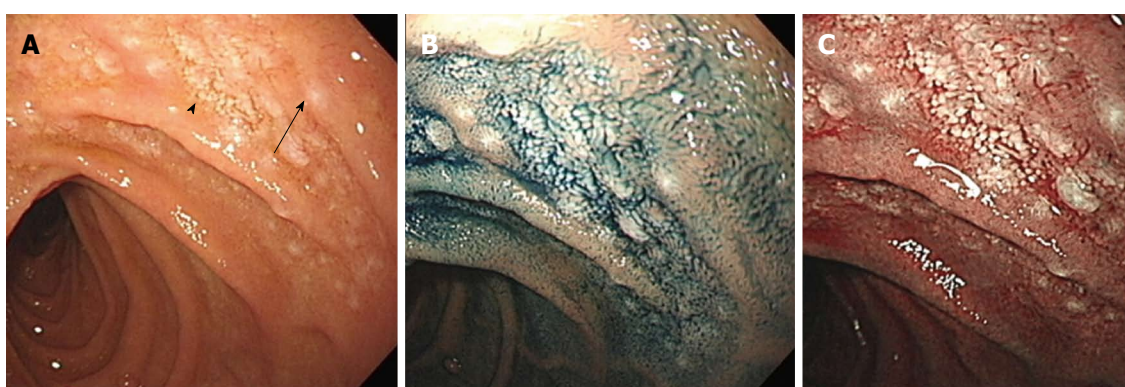


Figure 2 Close-up observation of the follicular lymphoma lesion. A: Enlarged whitish villi (arrowhead) and tiny submucosal whitish depositions (arrow); B: Indigo carmine spraying visualized these microsurface structures more clearly; C: Narrow-band imaging view also emphasized microsurface structures.

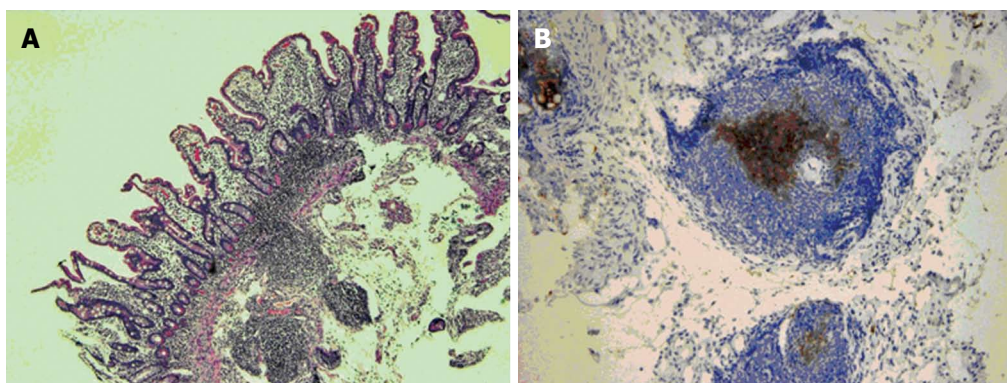


Figure 3 Pathological evaluation of the biopsy samples. A: Monotonous proliferation of small- to medium-sized lymphoid cells which formed lymphoid follicles and infiltrated into the villi; B: The lymphoma cells were positive for CD10 expression.

intestine^[13]. Other researchers also reported that the percentage of patients with multiple lymphoma lesions in the small intestine ranged from 66.7% to 100%^[5,14-17]. Consequently, multiple lesions in the duodenum are another feature that is suggestive of intestinal follicular lymphoma.

Pathologically, the major differential diagnoses of follicular lymphoma include mucosa-associated lymphoid tumors (MALT) lymphoma, mantle cell lymphoma and

reactive lymphoid hyperplasia. Neoplastic cells in low-grade B-cell lymphomas, namely, follicular lymphoma, MALT lymphoma and mantle cell lymphoma, share morphological features to some extent. Such lymphomas are primarily composed of small- to medium-sized lymphoid cells of B cell origin. Generally, subcategorizing low-grade B-cell lymphomas requires immunohistochemical staining. Typical follicular lymphoma consists of CD10-positive neoplastic lymphoid cells. In mantle

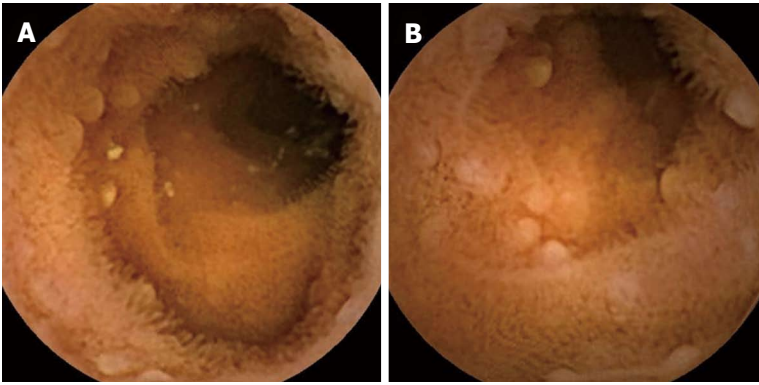


Figure 4 Multiple jejunal involvement revealed by video capsule endoscopy.

cell lymphoma, the lymphoma cells are positive for CD5 and cyclin D1. In contrast, the lymphoma cells in MALT lymphoma are negative for CD10, CD5 and cyclin D1. Therefore, biopsy and immunohistochemical examination should be performed to make the distinct diagnosis of follicular lymphoma, when endoscopists find the aforementioned endoscopic features of small whitish polyps, enlarged whitish villi, tiny submucosal whitish depositions and/or multiple sites of involvement in the intestine.

In conclusion, we present a case of primary intestinal follicular lymphoma. Enlarged whitish villi, tiny submucosal whitish depositions, and multiple sites of involvement, were demonstrated in addition to the typical macroscopic morphology of whitish polyps. Routine esophagogastroduodenoscopy by a high-definition imaging system can provide detailed features, helping to diagnose intestinal follicular lymphoma even without magnifying endoscopy.

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- 15 Morse SS. Factors in the emergence of infectious diseases. Emerg Infect Dis serial online, 1995-01-03, cited 1996-06-05; 1(1): 24 screens. Available from: URL: <http://www.cdc.gov/ncidod/eid/index.htm>

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- 16 Pagedas AC, inventor; Ancel Surgical R&D Inc., assignee. Flexible endoscopic grasping and cutting device and positioning tool assembly. United States patent US 20020103498. 2002 Aug 1

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Factors influencing quality of bowel preparation for colonoscopy

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Abstract

Recent technological advances in colonoscopy have led to improvements in both image enhancement and procedural performance. However, the utility of these technological advancements remain dependent on the quality of bowel preparation during colonoscopy. Poor bowel preparation has been shown to be associated with lower quality indicators of colonoscopy performance, such as reduced cecal intubation rates, increased patient discomfort and lower adenoma detection. The most popular bowel preparation regimes currently used are based on either Polyethylene glycol-electrolyte, a non-absorbable solution, or aqueous sodium phosphate, a low-volume hyperosmotic solution. Statements from various international societies and several reviews have suggested that the efficacy of bowel preparation regimes based on both purgatives are similar, although patients' compliance with these regimes may differ somewhat. Many studies have now shown that factors other than the type of bowel preparation regime used, can influence the quality of bowel preparation among adult patients undergoing colonoscopy. These factors can be broadly categorized as either patient-related or procedure-related. Studies from both Asia and the West have identified patient-related factors such as an increased

age, male gender, presence of co-morbidity and socio-economic status of patients to be associated with poor bowel preparation among adults undergoing routine out-patient colonoscopy. Additionally, procedure-related factors such as adherence to bowel preparation instructions, timing of bowel purgative administration and appointment waiting times for colonoscopy are recognized to influence the quality of colon cleansing. Knowledge of these factors should aid clinicians in modifying bowel preparation regimes accordingly, such that the quality of colonoscopy performance and delivery of service to patients can be optimised.

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Key words: Bowel preparation; Colonoscopy; Risk factors; Quality

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INTRODUCTION

Colorectal cancer (CRC) is recognized as a significant health problem in both developed and developing countries. In 2008, the worldwide estimated number of new cases of colorectal cancers was 1 233 000 with an estimated mortality of 608 700^[1]. In Asia, the incidence of colorectal cancer has been noted to be increasing and is already comparable to that of the West^[2-5]. However, if diagnosed at an early stage, CRC is one of the most preventable and curable malignancies^[6]. Therefore, screening with the ideal modality can potentially alleviate the health burden of CRC^[7,8]. Current recommendations on colorectal screening advocate colonoscopy as the preferred modality^[9,10], in view of its' accuracy in detecting

early lesions and proven efficacy in lowering rates of incident CRC^[11-14]. Advances in technology, such as magnification lenses, narrow band imaging and chromoendoscopy have increased the detection yield for early cancers during colonoscopy^[15-17]. Lesions characterized as early cancers can be endoscopically resected at the same sitting and can be curative^[18,19]. However, the advantages of colonoscopy are not only limited to the detection and treatment of early cancers. Other therapeutic benefits of colonoscopy include endoscopic hemostasis of bleeding lesions, dilatation of benign strictures and stenting of malignant strictures^[20-23].

Despite these advances in diagnostic and therapeutic colonoscopy, the utility of colonoscopy remains dependent on the cleanliness of the colon or the quality of bowel preparation. For instance, adenoma detection rate, being one of the quality indicators of colonoscopy, is recognized to be decreased by poor bowel preparation^[24-26]. Colonoscopy performance is also significantly affected by poor bowel preparation. In a recent study among Asian patients, poor bowel preparation resulted in decreased cecal intubation, prolonged cecal intubation and total colonoscopy time, and increased patient discomfort^[27]. In similar studies in Europe and Australia, poorly prepared patients during colonoscopy had longer, more difficult procedures and a lower diagnostic yield for polyps^[28-30].

GRADING OF BOWEL PREPARATION

Many clinical studies have used the terms “excellent”, “good”, “fair”, and “poor” to rate the quality of bowel preparation^[31-34]. “Excellent” is typically defined as no or minimal solid stool and only small amounts of clear fluid that require suctioning. “Good” is typically used to describe no or minimal solid stool with large amounts of clear fluid that require suctioning. “Fair” generally refers to collections of semisolid debris that are cleared with difficulty. “Poor” generally refers to solid or semisolid debris that cannot be cleared effectively. For practical purposes, an unsatisfactory or inadequate bowel preparation is one which would use a combination of the descriptions of “fair” and “poor”.

BOWEL CLEANSING AGENTS

Several colon cleansing agents and schedules have been utilized and studied for bowel preparation during colonoscopy. The most popular regimes today are based on either polyethylene glycol-electrolyte (PEG) lavage solution or aqueous sodium phosphate solution^[35-38]. PEG is a non-absorbable solution that should pass through the bowel without net absorption or secretion^[39]. Significant fluid and electrolyte shifts are therefore avoided but large volumes (4 L) are still required to achieve a cathartic effect. Sulphate-free PEG (SF-PEG) is more palatable with improved aroma and taste than pure PEG solutions. A reduced-volume (2 L) preparations coupled

with irritant laxatives, such as bisacodyl or magnesium citrate^[40], was developed to increase patient compliance and is recognised to be as effective as the standard 4 L PEG preparation^[41-43]. Aqueous sodium phosphate is a low-volume hyperosmotic solution which contains 48 g (400 mmol) of monobasic sodium phosphate and 18 g (130 mmol) of dibasic sodium phosphate per 100 mL. Sodium phosphate osmotically draws plasma water into the bowel lumen to promote colonic cleansing and significant fluid and electrolyte shifts can occur^[39]. Two meta analyses, comprising 71 trials (10 201 subjects) and 18 trials (2792 subjects) respectively, previously concluded that sodium phosphate-based bowel preparations resulted in a more complete and better quality of bowel preparation compared to 4-L PEG^[44,45], mainly due to the poorer compliance with the latter^[46-49]. However, sodium phosphate is associated with significant fluid and electrolyte shifts due to its hyperosmotic nature and patients with renal impairment, dehydration, on angiotensin-converting enzyme inhibitors, or angiotensin receptor blockers can develop renal failure^[50-52].

The recent American Society for Gastrointestinal Endoscopy, American Society of Colon and Rectal Surgeons, and the Society of American Gastrointestinal and Endoscopic Surgeons consensus statements on bowel preparation evaluated the use of PEG, SF-PEG, low-volume PEG/PEG-3350 with bisacodyl delayed-release tablets, aqueous and tablet preparations of sodium phosphate, the data of which has been summarised in Table 1^[50]. There is little variation in bowel preparation regimens in other countries. The European Society of Gastrointestinal Endoscopy recommended 4 L polyethylene glycol with low-dose sodium phosphate boosts as bowel preparation for colon capsule endoscopy^[53]. Similarly in a bowel preparation study in South Korea, subjects were given PEG solutions in 4 L of water^[54]. In Canada, as described in the position paper of the Canadian Association of Gastroenterology, the most commonly used bowel preparation agents are polyethylene glycol, sodium phosphate, magnesium citrate, and sodium picosulfate, citric acid, and magnesium oxide-containing solutions^[55]. In a colonoscopy practice study in the United Kingdom comprising of 9223 colonoscopies, bowel preparation was performed using sodium picosulfate, polyethylene glycol preparations and sodium phosphate in 36.8%, 20.7% and 15.6% of colonoscopy procedures respectively^[56].

Regardless of the type of bowel preparation used, whether it is PEG or sodium phosphate-based, both types appear to have a similar level of bowel cleansing ability. Modifications of these two common types of bowel preparations, such as adding prokinetic agents to PEG^[57,58], or adding simethicone to sodium phosphate^[59], may provide some improvements in certain instances. However, it is recognized that factors other than the type of bowel cleansing agent used, have an equally, if not more, important role in influencing the quality of bowel preparation in patients undergoing colonoscopy. In gen-

Table 1 Summary of American Society for Gastrointestinal Endoscopy, American Society of Colon and Rectal Surgeons, Society of American Gastrointestinal and Endoscopic Surgeons consensus recommendations on colon cleansing agents for bowel preparation during colonoscopy

Agent	Dosing	Recommendation	Level of evidence
PEG	240 mL every 10 min until rectal output is clear or total of 4 L	Faster, more effective, better-tolerated compared to dietary restriction with cathartics, gut lavage, or mannitol	Grade I A
Sulfate-free PEG	240 mL every 10 min until rectal output is clear or total of 4 L	Better tasting, comparable to PEG in effectiveness and safety, acceptable alternative to PEG	Grade II B
Low-volume PEG/PEG-3350 and bisacodyl	4 bisacodyl delayed-release tablets at noon, after bowel movement or 6 h, 240 mL every 10 min until 2 L is consumed	Equally effective to standard 4-L PEG, better tolerated, acceptable alternative to 4-L PEG	Grade I A
Aqueous sodium phosphate	Two doses of 30 to 45 mL sodium phosphate with 8 oz of liquid 10-12 h apart	Equal alternative to PEG except for pediatric and elderly patients, bowel obstruction, renal failure, congestive heart and liver failure	Grade I A
Sodium phosphate tablets	20 tablets on the evening before the procedure, 12-20 tablets 3-5 h before the procedure	Improved taste and palatability compared to aqueous sodium phosphate, but no improvement in patient tolerance	Grade I A

PEG: Polyethylene glycol-electrolyte.

eral, this can be categorized as either patient-related (*i.e.*, clinical or epidemiological parameters) or procedure-related (*e.g.*, administrative issues relating to bowel preparation or the conduct of colonoscopy) factors. In this review, we will focus on both of these factors and their influence on the quality of bowel preparation among adult patients undergoing colonoscopy.

PATIENT-RELATED FACTORS

Age

Several studies have evaluated advancing age as a risk factor for poor bowel preparation in colonoscopy. In a retrospective United States study of 300 patients, univariate analysis demonstrated that a mean age of ≥ 66 years was predictive of poor colonoscopy preparation^[60]. In two recent Asian studies, age ≥ 60 years were similarly associated with a poor bowel preparation^[27,54]. An increased age is known to be associated with a reduced colonic transit, greater co-morbidity and polypharmacy, all of which are known to impact on colonic cleansing^[39,61-64]. However, in a larger prospective study of 649 patients, the age of patients did not appear to have an impact on the quality of bowel preparation in patients undergoing colonoscopy^[65]. One possible explanation was that the mean age of patients in this study was 56 years, which is significantly lower than other studies which reported on age as a risk factor for poor bowel preparation.

Gender

Studies in both the West^[65,66] and the East^[67] have demonstrated that male gender is an independent predictor of poor bowel preparation. Among 649 American patients, of whom 21.7% had poor bowel preparation, Ness *et al.*^[65] reported that male gender was an independent predictor of poor bowel preparation among other patient-related factors. Chan *et al.*^[67] showed that male patients undergoing colonoscopy were 1.6 times more

likely to have poor bowel preparation compared to female patients, in a study of 501 Asian patients. Lebowitz further reported that male patients had a 1.4 times risk of poor bowel preparation compared to females in yet another American study of 10 921 patients undergoing colonoscopy^[66].

It is well known in most societies that men are less health-conscious compared to women for various reasons^[68-70]. Gender differences in reproductive biology, higher morbidity rates in women than in men, differences in health perceptions and the reporting of illnesses, and a greater likelihood that women seek help for prevention of illness^[71] are some of the explanations for a lesser healthcare attitude amongst men. It is plausible then that this gender difference may have led to a poorer adherence to bowel preparation instructions among male patients undergoing colonoscopy from both Eastern and Western patients.

Co-morbidity

Several studies have managed to explore the association between co-morbidities and adequacy of bowel preparation. A recent study of 300 outpatients undergoing colonoscopy identified the “use of more than 8 active prescription medications”, *i.e.*, a surrogate marker for co-morbidity as a predictor for poor bowel preparation^[72]. Among the common chronic illnesses known, diabetes has been shown to be consistently associated with poor bowel preparation. In a South Korean study of 367 patients, Chung *et al.*^[54] demonstrated that diabetic patients had a 8.6 times risk of poor bowel preparation compared to non-diabetic patients. In yet another study specifically comparing standard PEG bowel preparation between diabetic and non-diabetic patients, Taylor *et al.*^[73] demonstrated that an adequate bowel preparation was found in 97% non-diabetic patients compared to 62% of diabetic patients. Diabetes is known to impair colonic and general gastrointestinal transit^[74,75], and it is this mechanism that is thought to result in a poorer bowel

preparation.

Patients with stroke disease and dementia have additionally been demonstrated to have a higher risk of poor bowel preparation^[65], potentially as a result of an altered gastrointestinal motility as well and their inability to comply with bowel preparation instructions. A single study has additionally identified prior gastrointestinal and pelvic surgery as risk factor for inadequate bowel preparation^[54].

The setting in which patients are referred for a colonoscopy, *i.e.*, either from an in-patient or out-patient setting, is yet another surrogate marker for the impact of co-morbidity on level of colon cleanliness. Inpatient status has been associated with poorer bowel preparation in several studies^[65,67,76], and this has been attributed to prolonged immobility and poor tolerance to purgatives due to co-morbid illness. Even in colonic surgery, an out-patient bowel preparation, as opposed to an in-patient preparation, has been shown to result in a better clinical outcome due increased co-morbidity in the latter^[77].

Socioeconomic status

Bowel preparation regimens need to be adhered to ensure a good quality of preparation during colonoscopy (see later). As standard bowel preparation usually requires a combination of dietary restrictions and several steps of purgative administration, a clear understanding of the process and strict adherence to instructions (usually in a written format) is vital. A poor understanding of this process, and its' importance, has been shown to be more prevalent among patients from a lower socioeconomic background. A recent United States-based study identified poor bowel preparation to be more common among patients who needed English-language interpretation (for bowel preparation instructions) and those on Medicaid insurance (a marker of low socioeconomic status)^[72]. A lower education level, as a marker of lower socioeconomic status, was recently shown to be an independent predictor of poor bowel preparation in an Asian study of 501 outpatients^[67]. In contrast, enhanced education and specific counseling of adult patients on bowel preparation instructions was shown to improve the quality of bowel preparation in an elegant Canadian study of 38 patients^[76].

PROCEDURE-RELATED FACTORS

Adherence to bowel preparation instructions

As mentioned before, a standard bowel preparation usually involves several steps. Regardless of the type of purgative used, non-adherence to these steps alone have been shown to be an important determinant of quality of bowel preparation. Among several other factors which predicted poor bowel preparation, Ness *et al.*^[65] had identified that a failure to adequately follow preparation instructions was associated with a 2.68 odds ratio for predicting poor bowel preparation. In a recent

American study of 300 patients who underwent screening colonoscopy for cancer, Nguyen *et al.*^[72] reported that 86.7% of patients with a poor/inadequate bowel preparation had failed to either complete the bowel preparation or follow written instructions. These findings were similarly reported in a Malaysian study of 501 patients, whereby non-adherence to purgative instructions was associated with a 4.76 risk of poor bowel preparation^[67]. Whilst non-adherence to preparation instructions is an obvious determinant of the quality of bowel preparation, it is generally unreliable as it depends on self-reporting by patients. It is well recognized that many patients are reticent to admit non-adherence or they may not even recognize non-compliance themselves^[65]. Nevertheless, it is important to identify factors contributing to non-adherence of instructions as this provides an opportunity to intervene and enhance quality. A lower socioeconomic status has been identified as one of the main reasons for non-adherence to bowel preparation instructions^[72] and it is likely that male gender may be a contributing factor^[66,67], for reasons outlined previously.

Timing of bowel preparation administration

Several studies have examined the effect of timing of bowel purgative administration (mostly PEG) and its' impact on quality of bowel preparation. In a large study of 317 patients undergoing an afternoon colonoscopy, Church *et al.* demonstrated that a "same-day" administration resulted in a significantly better quality of bowel preparation compared to a "one day before" timing, using the same quantity of PEG solution^[78]. Regardless of the location of the colon, patients with a "same day" bowel preparation had a greater proportion of "excellent grade" cleanliness and a lower proportion of "fair grade" cleanliness compared to patients who had consumed purgatives the day before^[78]. Two other studies examining "day before" *vs* "same day" preparations have managed to demonstrate a similar superior efficacy of the "same day" preparations^[79,80], with an Italian study even suggesting that this timing improved the detection rates of colonic adenomas^[80]. A prolonged duration between purgative administration and timing of colonoscopy is thought to result in proximal colon contamination from the small bowel and hence a poorer colon cleansing ability. In a different study, El Sayed *et al.*^[81] investigated the effect of a split-dose administration of PEG, whereby 187 patients were randomised to either "3 L PEG + dietary restriction one day before" *vs* "2 L PEG + Bisacodyl one day before + 1 L PEG on the same day" of the colonoscopy procedure. Although a little more complicated, the authors were able to demonstrate that the split-dose regime was better tolerated and resulted in better colon cleansing.

Appointment waiting time

The time from booking a routine colonoscopy procedure to the actual appointment date, *i.e.*, the appointment

Table 2 Predictive factors for quality of bowel preparation independent of colon cleansing agent

Patient-related factors	Procedure-related factors
Age > 65 yr	
Male gender	Adherence to bowel preparation instructions
Co-morbidity	Timing of purgative administration
Diabetes	
Stroke disease	
Inpatient status	
Low socioeconomic status	Appointment waiting times

waiting time, may influence the quality of bowel preparation due to individual patient's ability to recall bowel preparation instructions. To date, a single study among Malaysian patients in a public institution has demonstrated that a prolonged appointment waiting time of > 16 wk was associated with a 1.86 risk of poor bowel preparation^[67]. A previous retrospective study in the United States did not identify appointment waiting times as a risk factor for poor bowel preparation, but the mean waiting time was only 4.39 wk in this study^[72]. Whilst most endoscopy units strive to shorten their outpatient waiting times for appointments for index colonoscopies, the increasing demand from colorectal cancer screening together with limited resources in most healthcare systems requires urgent attention.

CONCLUSION

Preferences for either PEG or phosphate-based purgative preparations may differ between populations. Nevertheless, it is apparent that patient-related or procedure-related factors, summarized in Table 2, have a significant influence on the quality of bowel preparation among adults undergoing colonoscopy. Although not all factors can be necessarily addressed, modifying the standard bowel preparation regime for such patients may enhance the quality of bowel preparation, reducing the negative impact of poor bowel preparation on individuals and colonoscopy services as a whole.

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Sedation and monitoring for gastrointestinal endoscopy

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Abstract

The safe sedation of patients for diagnostic or therapeutic procedures requires a combination of properly trained physicians and suitable facilities. Additionally, appropriate selection and preparation of patients, suitable sedative technique, application of drugs, adequate monitoring, and proper recovery of patients is essential. The goal of procedural sedation is the safe and effective control of pain and anxiety as well as to provide an appropriate degree of memory loss or decreased awareness. Sedation practices for gastrointestinal endoscopy (GIE) vary widely. The majority of GIE patients are ambulatory cases. Most of this procedure requires a short time. So, short acting, rapid onset drugs with little adverse effects and improved safety profiles are commonly used. The present review focuses on commonly used regimens and monitoring practices in GIE sedation. This article is to discuss the decision making process used to determine appropriate pre-sedation assessment, monitoring, drug selection, dose of sedative agents, sedation endpoint and post-sedation care. It also reviews the current status of sedation and monitoring for GIE procedures in Thailand.

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Key words: Sedation; Monitoring; Gastrointestinal en-

doscopy; Sedatives; Analgesics

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INTRODUCTION

Sedation always has been a critical component of performing gastrointestinal endoscopy (GIE) procedures. The aim of sedation for these procedures is to increase patient's comfort, to improve endoscopic performance and to increase patient and endoscopist satisfaction. The need for sedation is decided by the type of endoscopy, duration of procedure, degree of endoscopic difficulty, patient physical status and physicians' preferences. The sedation regimen for GIE procedures is still varied. The guidelines established by the American Society of Anesthesiologists (ASA)^[1] and the American Academy of Pediatrics^[2] serve as the standard for institutional policy development in the area of procedural sedation.

The guideline defines terms throughout and in particular: (1) Minimal sedation: a drug-induced state which patients respond normally to verbal commands; (2) Moderate sedation (conscious sedation): a drug-induced depression of consciousness which patients respond purposefully to verbal commands. Spontaneous ventilation is adequate. Cardiovascular function is usually maintained; (3) Deep sedation: a drug-induced depression of consciousness which patients can not be easily aroused but respond purposefully after repeated verbal or painful stimulation. Spontaneous ventilation may be inadequate. Cardiovascular function is usually maintained; and (4) General anesthesia: a drug-induced loss of consciousness which patients are not arousable, even by painful stimulation. Patients often require assistance in maintaining a patent airway. Cardiovascular function may be impaired.

The important component of these guidelines is that the endoscopy team must have the ability to rescue the

patient from deeper than targeted level of sedation. Personnel qualifications and proper monitoring must be adhered to when administering sedative drugs. This article provides an overview of my current knowledge regarding the role of anesthesiologists and non-anesthetic personnel in determining the field of procedural sedation, and the current status of sedation and monitoring for GIE procedure. It also briefly discusses current practice for this procedure in Thailand.

PRE-SEDATION ASSESSMENT

All patients scheduled to receive sedation should have an up-to-date history and relevant physical examination. Many risk factors to be aware of are the history of sleep apnea, alcohol or substance abuse, adverse reaction to sedation and prolonged duration of procedure. Patients should be classified using the criteria of the ASA. Cardiorespiratory problems which could occur during GIE procedure should be carefully evaluated. Pregnancy test is recommended in women of childbearing age who are not sure whether they could be pregnant or not^[3]. Consequently, patients should be informed of possible adverse events, and written consent should be done. High risk patients in which anesthesia consultation may be warranted including known respiratory or hemodynamic instability, obstructive sleep apnea, high risk airway management, ASA physical status > 3, history of sedation-related adverse events, and patients with neuromuscular disease affecting respiratory or brain stem function.

MONITORING DURING SEDATION

Cardiorespiratory-related complications are a leading cause of morbidity and mortality associated with GIE procedure. Both ventilatory depression and oxygen desaturation from the sedative agents used to achieve sedation are thought to be important risk factors for these complications.

Clinical monitoring

Continuous monitoring of patient undergoing sedation is very important for ensuring the safety of the procedure. The physicians need to monitor the patients' status throughout the procedure. Clinical observation of the sedated patients can provide an early warning for potentially dangerous problems. Additionally, continuous venous access must be maintained until the patient has completely recovered, in order to enable the fast administration of resuscitated drugs or antagonist drugs if needed.

Pattern of respiration: Proper breathing is monitored by observing the rate and depth of chest, abdominal movements, and pattern of respiration. Respiratory depression is the main risk of sedation-related adverse events especially in the elderly or in comorbidity patients.

Skin or mucosa color: A change in the skin or mucosa

color can be an indication of alteration in physiologic functions. A more pale color may be due to a drop in blood pressure or a reduction of hematocrit level, while a bluish color may be a sign of hypoxia.

Consciousness: The level of sedation and consciousness can be defined by the patient's ability to respond to verbal commands. In minimal and moderate sedation, the patients can respond purposefully to verbal commands. Many tools such as Ramsay score and Modified Observer Assessment of Alertness/Sedation scale are used for assessment the depth of sedation.

Comfortable level: The facial expression of the patient is also a good indicator of the level of comfort that the patient experiences.

Respiratory monitoring

Pulse oximetry: Pulse oximetry is a noninvasive device for continuous measurement of arterial oxygen saturation. It has become a defining standard of care, and is useful for the early detection of hypoxemia during sedation for GIE procedure, owing to the evidence that clinical observation alone is inaccurate in the detection of hypoxemia. Generally, hypoxemia occurs within 5 min of drug administration or intubation of the endoscope^[4]. Oxygen saturation levels under 90% must be treated as potentially serious. However, pulse oximetry and supplemental oxygen administration has not been shown to decrease the severity or incidence of cardiopulmonary complications. Oxygen desaturation is relatively late sign of suboptimal ventilation^[5].

Capnography: It is important to point out that pulse oximetry does not measure alveolar hypoventilation. Oxygen administration may prevent hypoxemia and its deleterious effects, but it will not detect the development of hypercapnea. Additionally, there was a poor correlation between clinical observation and objective measures of ventilation. Capnography is based on the principle that carbon dioxide absorbs light in the infrared region of the electromagnetic spectrum. In the literature, capnography was found to be more sensitive than pulse oximetry or visual assessment in the detection of apneic episodes^[6]. It has also been utilized to allow the safe titration of propofol by a qualified gastroenterologist during endoscopic retrograde cholangiopancreatography (ERCP) and endoscopic ultrasonography (EUS).

Cardiovascular monitoring

Noninvasive blood pressure: Blood pressure and heart rate are important parameters of cardiovascular monitoring. Mean arterial pressure can be an indirect parameter to estimate hypnotic effects. Changes in arterial blood pressure are mediated by cardiodepressive side effects of sedative agents. Baseline hemodynamic parameters also provide useful information of the effects of various medical conditions. Continuous pulse oximetry,

blood pressure, heart rate, respiratory rate and level of consciousness will be documented before the sedation, and at least 5 min for deep sedation and every 15 min for moderate sedation. Blood pressure was therefore far more likely to predict increasing and decreasing doses of sedative agents. Importantly, they provide important feedback throughout the GIE procedure. Additionally, these parameters may influence the selection of the sedative agents.

Electrocardiography: The use of electrocardiography (ECG) was initially intended to detect cardiac arrhythmias in high risk patients undergoing sedation/anesthesia. However, the role of continuous electrocardiography during GIE sedation remains uncertain^[7]. ASA and the American Society for Gastrointestinal Endoscopy (ASGE) practice guidelines indicate that patients with significant cardiovascular diseases or dysrhythmia should have electrocardiographic monitoring during GIE sedation. ECG is not required for low risk patients including patients with ASA physical status I or II^[1,8].

Other monitors

Generally, the invasive monitors such as arterial blood pressure, central venous pressure (CVP) and pulmonary arterial catheterization (PAC) are rarely used during sedation for GIE procedures. These monitors may be utilized in some patients. For example, arterial blood pressure is used in patients with severe hemodynamic instabilities or patients with shock, and CVP or PAC is used for fluid resuscitation in patients with severe gastrointestinal bleeding.

Sedation depth monitoring

Bispectral index monitoring: As depth of sedation cannot be reliably judged by clinical assessments alone, a reliable method is needed to measure the hypnotic component of sedation. Recently, processed electroencephalogram (EEG) variable such as the Bispectral (BIS) index is developed to ease EEG interpretation. This tool has been reported to be more precise in measurement of sedation level. BIS monitoring is a noninvasive method of assessing patient's level of consciousness. The BIS scale ranges from 0 to 100 (0, no cortical activity or coma; 40-60, unconscious; 70-90, varying levels of conscious sedation; 100, fully awake). BIS monitor is designed to measure patient consciousness during general anesthesia. To date, its use has subsequently expanded into the use of sedation technique for GIE procedures.

The usefulness of BIS monitoring for GIE procedures remains controversies. The study of Bower *et al*^[9] showed that BIS index correlated moderately well with the level of sedation determined by using the Observer Assessment of Alertness/Sedation scale. Al-Sammak *et al*^[10] performed a study to compare BIS with clinical assessment of sedation in patients undergoing ERCP. The results in terms of duration of sedation, recovery rate, patient satisfaction and total dose of sedative agent fa-

vored the group monitored with BIS^[10]. In contrast, many papers demonstrated that BIS index had low accuracy for detecting deep sedation and it was not useful for titrating propofol to an adequate level of sedation^[11,12].

Narcotrend™: Narcotrend™ (MonitorTechnik, Hannover Medical School) performs a computerized analysis of the raw electroencephalogram. It has two recording modes: the one channel mode as the standard for the assessment of the depth of hypnosis during anesthesia and sedation, and the two channel mode for comparison of signals from the two hemispheres of the brain. After accounting for artifact, a multivariate statistical algorithm is used for analysis which results in a six-stage classification from A (awake) to F (general anesthesia/coma) and 14 substages^[13].

My previous study showed that the Narcotrend™ system monitoring can be successfully used to provide deep sedation in patients undergoing ERCP procedure^[14]. Consequently, the use of Narcotrend™ system for monitoring significantly reduced sedation-related adverse events and hemodynamic alterations^[15].

SEDATIVE AND ANALGESIC AGENTS

Midazolam

Midazolam is the drug most commonly used for sedation during GIE procedures. It is a shorting, water soluble benzodiazepine with anxiolytic, amnestic, sedative, muscle relaxant, and anticonvulsant properties. These actions are considered to be the result of binding to gamma-amino butyric acid receptors in the central nervous system. It has a rapid onset (1-3 min), a rapid peak effect (3-5 min) and a short duration of action (20-60 min). Duration of midazolam is greater in the elderly patients. Factors that potentiate effects of midazolam include hypoalbuminemia, advanced age, diminished liver function and concomitant use of drugs that inhibit cytochrome P450. The usual adult dose is 1 to 5 mg (0.015-0.07 mg/kg)^[16]. Midazolam has few side effects. These effects are not serious. Respiratory depression is the most important adverse effect. Other side effects are nasal itching, dizziness, anxiety, rash, irritability, dreams, seizures and involuntary muscle movement. Respiratory depression is synergistic when used in combination with opioids.

Fentanyl

Fentanyl is a potent synthetic opioid with no intrinsic anxiolytic or amnestic properties. It has a rapid onset, short duration of action, lack of direct myocardial depressant effects, and absence of histamine release. The onset of action is 30 to 60 s, peak effect is 5 to 15 min, and duration of action is 30 to 45 min. Its dose for GIE procedure is 1 to 2 mcg/kg, with a maximum dose of 100 to 150 mcg in most adult patients. Intravenous fentanyl can be easily and rapidly titrated for painful procedures. The combination of fentanyl and midazolam is a popular regimen, with a safety profile when both drugs

are carefully titrated^[17-19]. Similar to all opioids, fentanyl can cause respiratory depression including apnea and nausea and vomiting. It can also produce the decrease of heart rate and skeletal muscle rigidity.

Meperidine (pethidine)

Meperidine is a synthetic opioid. It has an inferior safety profile and a long duration of action compared with fentanyl. Its onset of action is 1 to 3 min, peak effect is 5 to 20 min, and duration of action is 2 to 4 h. Intravenous dose of meperidine in adult patients is 0.5 to 2 mg/kg with a maximum dose of 100 mg. The metabolites of meperidine are toxic to the central nervous system at high doses and in patients with renal impairment. Fatal reactions have also occurred in patients taking monoamine oxidase inhibitors or in patients with hyperthyroidism^[20]. Meperidine 0.5-1.0 mg/kg *iv* combined with midazolam 0.05-0.1 mg/kg *iv* provides effective sedation for GIE procedure. However, meperidine is not recommended for sedation in the emergency department.

Ketamine

Ketamine is a dissociative agent which largely spares upper airway muscular tone and laryngeal reflexes, and may represent an alternative to narcotics and benzodiazepines for sedating children for GIE procedures. It can cause a wide range of effects including analgesia, amnesia, anesthesia and sedation. Routes of administration can be oral or rectal, but are usually intravenous or intramuscular. Ketamine is demethylated to form norketamine that is one fifth to one third as potent as ketamine. Intense analgesia can be achieved with subanesthetic dose of ketamine 0.2 to 0.5 mg/kg intravenously. Return of consciousness usually occurs in 10 to 15 min, but complete recovery is delayed.

An undesirable effect is the triggering of visual and auditive hallucinations, which can lead to the nightmares limits the clinical usefulness of ketamine in adults. Dreams and hallucinations can occur up to 24 h after administration of ketamine. Factors associated with an increased incidence of emergence delirium include the age greater 16 years, female sex, dose of ketamine intravenously greater than 2 mg/kg, and history of personality problems. These effects can be prevented by the prior administration of benzodiazepine. Ketamine also has been highly associated with a high potential for laryngospasm. The critically ill patients may response to ketamine with unexpected decreases in blood pressure and cardiac output. Previous studies have been reported with the combination of ketamine and midazolam for sedation in pediatric GIE procedures^[21]. The importance of ketamine for sedation in adult GIE procedures is still needed for further studies^[22].

Propofol

Propofol is a phenol derivative with sedative, hypnotic and anesthetic properties. It has antiemetic, anxiolytic, hypnotic, amnestic and anesthetic properties. However, it

does not have analgesic effects. Propofol rapidly crosses the blood-brain barrier, and causes a depression in consciousness. The onset of hypnosis is 30-60 s^[23]. The plasma half-life ranges from 1.30 to 4.13 min. Dose reduction is required in patients with cardiac dysfunction and in the elderly due to decreased clearance of the drug. It is not necessary to reduce the dose of propofol in patients with moderately severe liver disease or renal failure.

The advantage of propofol over midazolam and meperidine has been demonstrated for therapeutic GIE procedures and not for diagnostic GIE procedures^[24]. Propofol potentiates the effects of narcotic analgesics and sedatives such as benzodiazepines, barbiturates, and droperidol and therefore the dose requirements may be reduced. However, propofol associated with hypotension, respiratory depression and airway obstruction. The combination of propofol and opioid or benzodiazepine can cause significant cardiovascular depression. Unfortunately, propofol lacks a reverse agent. It also has a narrow therapeutic window which may result in a deeper than expected depth of sedation. Pain at the injection site is the most frequent local complication. To date, it is a controversial issue that personnel specifically trained in the administration of propofol with expertise in emergency airway management need to be present and constantly monitoring the patient's parameters. However, this issue varies among the countries.

Propofol administration techniques

Many methods for propofol delivery have been used for sedation for GIE procedures. Generally, propofol is administered intravenously as a repeated bolus injection, continuous infusion or a mixture of both. In the bolus technique, the initial bolus dose is adjusted according to the patient's weight, age, ASA physical status and comorbidities. Continuous propofol infusion is titrated to the desired sedation level and to the patient's characteristics.

Other administration techniques of propofol delivery such as target controlled infusion (TCI), patient controlled sedation (PCS) or computer assisted personalized sedation (CAPS) have been investigated. Propofol TCI rather than bolus method may be a better choice for the prevention of hemodynamic response during GIE procedure. However, propofol TCI does not confer any benefit over bolus propofol with respect to drug consumption and recovery profile for sedation in colonoscopy^[25]. PCS with propofol is effective and results in high patient satisfaction and faster discharge^[26]. PCS has been demonstrated to be the effective technique for pain control during GIE procedure^[27]. CAPS uses feedback from the real time measures of drug effect and patient reaction to tactile stimuli to control propofol infusion^[28].

Propofol for GIE procedures

Esophagogastroduodenoscopy: In a randomized study, 199 patients underwent esophagogastroduodenoscopy (EGD) procedures received fentanyl 0.5 mcg/kg or remifentanyl 0.5 mcg/kg, followed by a bolus injection of 1

mg/kg of propofol. The subsequent doses of propofol were 0.5 mg/kg when the patient was conscious or body movement appeared^[29]. Recovery time and total dosage of propofol given in the remifentanyl group was significantly less than it was in the fentanyl group. However, the frequency of apnea was significantly higher in the remifentanyl group. There were no significant differences in frequency of hypoxemia, bag ventilation, or body movement between the two groups. Sedation with propofol is also safe and effective for use in patients with upper gastrointestinal bleeding undergoing urgent therapeutic gastroscopy^[30]. The study from Canada demonstrates that sedation with propofol alone or propofol combined with fentanyl or midazolam in children is safe and effective. Propofol in combination with fentanyl or midazolam gives better sedation and ease of endoscopy than propofol alone^[31]. In addition, the reports from developing countries including Thailand are also showed that propofol-based sedation for GIE procedures in pediatric patients is safe and effective. Serious adverse events are rare^[17,32,33].

ERCP: A meta-analysis shows that propofol sedation during ERCP leads to shorter recovery time without an increase of cardiopulmonary side effects. Propofol sedation can provide adequate sedation during ERCP^[34]. Propofol deep sedation administered by an anesthesiologist with appropriate monitorings seems to be a safe procedure during colonoscopy or ERCP in cirrhotic patients^[35]. Our previous study demonstrated that propofol-based deep sedation for ERCP procedure in sick elderly patients by trained anesthetic personnel with appropriate monitoring was safe and effective. The clinical efficacy of this technique in sick elderly patients was not different or worse than in non-sick elderly patients. Serious adverse events were rare^[14]. In general knowledge, dose requirement and complications of propofol are lower when used in the diluted form than in the undiluted form. However, our previous study in ERCP patients did not show that. Propofol requirement and recovery time in the diluted and undiluted propofol groups were comparable. Sedation-related hypotension was significantly lower in the diluted group than the undiluted group^[36].

Colonoscopy: Patient-controlled sedation with propofol/remifentanyl yields superior facility in sedation and recovery time compared with midazolam/fentanyl when used in an appropriate care setting^[37]. Wang *et al*^[38] compared cardiorespiratory function and sedative and analgesic effects, using combinations of midazolam with either fentanyl or propofol in a non-randomized group of 480 patients undergoing colonoscopy procedures. The combination of midazolam with either fentanyl or propofol allowed patients to undergo colonoscopy under comparable sedative and analgesic conditions. The combination with fentanyl had a significantly lower effect on pulse rate and blood pressure. The combination with propofol produced superior amnesic effects.

The use of sedation for GIE procedures in very elderly patients has been established as a safe and effective technique when carried out by trained anesthetic personnel with appropriate monitoring and dose adjustment^[16]. In the past, there was controversy regarding the frequency of sedation-related complications of colonoscopies especially for colonoscopic perforation. Many physicians believed that propofol-based sedation usually tended to deepen the sedation level and mask the earlier signs and symptoms of colonoscopic perforation. To date, we know that colonoscopy under propofol-based sedation does not increase the perforation rate^[39].

Percutaneous endoscopic gastrostomy: Garcia-Suarez and colleague evaluated the efficacy and safety of propofol sedation administered by endoscopists, while performing percutaneous endoscopic gastrostomy (PEG). All PEG procedures were carried out successfully, at a median time of 8 min. All sedation-related complications were mild and quickly reversible^[40]. Similar to other GIE procedures, low-dose propofol sedation is safe and may be enough for very elderly patients (≥ 90 years of age) undergoing PEG procedures^[41]. Consequently, propofol-based sedation does not increase rate of complication during PEG procedure^[42,43].

EUS: The safety of balanced propofol sedation in 112 patients underwent EUS with fine needle aspiration (FDA) procedures was assessed by Pagano *et al*^[44]. The study showed that all patients completed the examination. Mean dose of midazolam and propofol was 2.1 mg (range 1-4 mg) and 350 mg (range 180-400 mg) respectively. The mean recovery time after procedure was 25 min (range 18-45 min). No major complications related to sedation were occurred during the procedures. The oxygen saturation never reduced to less than 85%. Furthermore, there does not appear to be a significant difference between complication rates for propofol deep sedation and meperidine/midazolam administered for moderate sedation^[45]. Propofol combined with fentanyl and midazolam is commonly used for GIE procedures including EUS^[16,18,46,47].

Nurse-administered propofol: ASA guideline on sedation by non-anesthesiologists characterizes propofol as an agent that is frequently associated with deep sedation. It does not preclude the administration of propofol by non-anesthesiologists^[1]. In contrast, ASGE guideline on deep sedation restates the opinions of the ASA guideline. The ASGE guideline does not recommend the use of propofol for routine procedures^[48]. To date, many studies have documented the safe administration of propofol by non-anesthesiologists. Administration by registered nurses is more cost-effective than administration by anesthesiologists. However, the administration of propofol by a registered nurse supervised only by the endoscopist is controversial because the drug has the potential to produce sudden and severe cardiorespiratory depression.

The safety and efficacy of propofol administered by registered nurses has been reported in a case series including 2000 patients undergoing elective EGD and/or colonoscopy^[49]. Five episodes of oxygen desaturation to < 85%, four of which required temporary mask ventilation, occurred. Four of these episodes occurred during upper endoscopy.

Another study is also showed that nurse-administered propofol sedation (NAPS) provided by properly trained nurses is safe and only associated with a minor risk. The study of 2527 patients undergoing 2656 GIE procedures was assessed. Patients were ASA group I, II and III in 34.7%, 56.0% and 9.3%, respectively. One hundred and nineteen of 2527 patients developed short lasting hypoxia (4.7%), 22 patients (0.9%) required bag-mask ventilation and 8 patients (0.3%) had to be discontinued. In 11 patients (0.4%), anesthetic assistance was called due to short lasting desaturation^[50]. However, the national or international structured training programs are at present few or none.

Gastroenterologist-administered propofol: Similar to qualified nurses, the gastroenterologist can administer propofol effectively. The qualified nurses and gastroenterologists must have a thorough knowledge of the pharmacology of the agents used for sedation and the training necessary to recognize and manage oversedation. However, the importance of preprocedural assessment and preparation as well as appropriate monitoring cannot be overlooked. Many guidelines recommend that gastroenterologist and nurse-administered propofol should be sedated the patients only in mild or moderate (conscious) sedation level. Additionally, the patients must have ASA physical status not more than III.

Vargo *et al*^[51] completed a randomized, controlled trial of gastroenterologist-administered propofol *vs* meperidine and midazolam for elective ERCP and EUS. Capnography was used to detect apnea or hypercapnia. This study shows that propofol leads to significantly improved recovery of baseline activity and food intake 24 h after the procedure. The authors suggest that propofol would be more cost-effective than meperidine and midazolam for ERCP and EUS procedures. Additionally, patients undergoing advanced upper endoscopic procedures and monitoring with graphic assessment of respiratory activity, received a propofol infusion under the control of a qualified gastroenterologist can detect early phases of respiratory depression, resulting in a timely decrease in the propofol infusion without significant hypoxemia, hypercapnia, hypotension, or arrhythmias, and the satisfaction scores are extremely high^[52].

Anesthesiologist-administered propofol: Generally, propofol is administered by anesthesiologists for sedation/anesthesia in various surgical procedures including GIE procedures. To date, there are controversial issues about propofol. For example, who, when and how should administer propofol? In Western countries, propofol can

be performed by well-trained registered nurses or physicians. So, anesthesiologist-administered propofol compared with nonanesthesiologist-administered propofol is less cost-effectiveness. However, in developing countries like Thailand, propofol-based sedation is performed by anesthesiologists or anesthetic nurses and is usually done in the operating room. In Siriraj GI Endoscopy Center, topical anesthesia is the most common anesthetic technique used for GIE procedure. General anesthesia for this procedure is performed about 2.7%^[47].

Berzin *et al*^[53] accomplished a prospective cohort study of sedation-related adverse events, patient and procedure-related risk factors associated with sedation, as well as endoscopist and patient satisfaction with anesthesiologist-administered sedation. The study confirmed that the anesthesiologist-administered sedation for ERCP patients is safe and effective. Cardiac and respiratory events are generally minor. Despite the frequency of minor sedation-related events, procedure interruption or premature termination is rare in the setting of anesthesiologist-administered sedation. However, no randomized, controlled studies comparing anesthesiologist-administered propofol with nonanesthesiologist-administered propofol for GIE procedure are done.

Fospropofol: Fospropofol is a water-soluble prodrug of propofol that currently approved for sedation and analgesia for diagnostic and therapeutic procedures^[54]. It is hydrolyzed rapidly to release propofol. Fospropofol is characterized by a smooth and predictable rise and decline rapidly observed following intravenous administration. It does not cause pain on intravenous injection, but it has been associated with paresthesias in the perineal and perianal area. However, the mechanism of this is still unknown. Similar to propofol, fospropofol causes dose dependent hypotension, respiratory depression and apnea^[55]. Additionally, the US FDA approval information and product label state that fospropofol should be administered only by persons trained in the administration of general anesthesia.

Dexmedetomidine: Dexmedetomidine is a centrally acting alpha 2-adrenoreceptor agonist with sedative and analgesic effects. It also has been considered for sedation for GIE procedure. Because of minimal effects on ventilation, dexmedetomidine may be beneficial in patients with respiratory depression or airway obstruction. One reported advantage is that patients can be sedated but are able to be aroused to full consciousness easily. However, dexmedetomidine can cause hypotension and bradycardia^[56]. The other disadvantages of dexmedetomidine include a slow onset and longer duration of action.

To date, the efficacy of dexmedetomidine for GIE procedures remains controversial issues. In the study of Demiraran *et al*^[57], dexmedetomidine performed as effectively and safely as midazolam when used as a sedative in upper gastroscopy and it was superior to midazolam with regard to retching, rate of side effects and endosco-

pist satisfaction. Another study showed that dexmedetomidine provided more efficient hemodynamic stability, higher sedation scores, higher satisfaction scores and lower pain scores in colonoscopies^[58]. However, dexmedetomidine alone is less effective than propofol/fentanyl for conscious sedation during endoscopic retrograde cholangiopancreatography^[59]. Consequently, the use of dexmedetomidine to provide analgesia/sedation for colonoscopy is limited by distressing side effects, pronounced hemodynamic instability, prolonged recovery, and a complicated administration regimen^[60].

REVERSAL DRUGS

Naloxone

Naloxone is a pure mu-opioid antagonist with a high affinity for the receptor. It can reverse both the analgesic and respiratory effects of opioids^[61]. Naloxone may be administered intravenous, intramuscular, subcutaneous and endotracheal tube. The dosage of intravenous naloxone is 1 to 2 mcg/kg every 2 to 3 min with a maximum dose of 0.1 mg/kg up to 2 mg. Because of its rapid removal from the brain, naloxone has a short duration of action and one dose typically only lasts for 30-45 min. The patients should be monitored for at least 2 h after administration of naloxone to ensure that resedation does not occur. Potential adverse reactions of naloxone include reversal of opioid withdrawal, nausea/vomiting, hypertension, tachycardia, pulmonary edema and cardiac dysrhythmias.

Flumazenil

Flumazenil is a benzodiazepine antagonist and can safely reverse the sedative and respiratory effects caused by benzodiazepines^[62]. It is a highly specific benzodiazepine receptor antagonist. The usual adult dose is 0.01 mg/kg up to 1 mg. Its clinical duration of action is approximately 1 h^[61]. However, its effects are reversible, so it is not recommended for routine use. Similar to naloxone, the patients should be monitored for at least 2 h after administration of flumazenil to ensure that resedation does not occur. Potential adverse reactions of flumazenil include sweating, flushing, nausea/vomiting, hiccups, agitation, abnormal vision, paresthesia and seizures.

POST-SEDATION CARE

Blood pressure, heart rate, respiratory rate, oxygen saturation and level of consciousness are monitored and documented at least every 15 min or less, for a minimum of thirty minutes after the last dose of sedation medication. A written record of these parameters should be maintained in the recovery phase. If the patient received a reversal agent, the patient must be in a recovery room for at least 2 h after the last administration of that reversal agent. The sedated patients are discharged from the recovery area when patients meet the discharge criteria. The discharge criteria include the requirement for

monitoring for at least 30 min after the last intravenous drug administration or at least 90 min after the last intramuscular drug administration^[63]. In ambulatory cases, prior to discharge from the hospital, patients' vital signs must remain stable and must be free from active bleeding or excessive pain. Additionally, patients must be able to tolerate fluids. The presence of a driver and an escort must be verified. Consequently, the patients should be reminded not to drive for at least 24 h.

CONCLUSION

Sedation for GIE procedure can be safely and effectively performed with a multi-drug IV regimen utilizing anesthesiologist or non-anesthetic personnel with appropriate monitoring. However, comprehensive pre-sedation assessment and proper patient selection and preparation as well as availability of skilled professionals for sedation administration are key components to provision of quality patient care. Additionally, the physician must always be prepared to rescue patients who move to a deeper level of sedation, and there should be an awareness of complications.

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Repeat colonoscopy's value in gastrointestinal bleeding

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Abstract

AIM: To assess the diagnostic yield and clinical value of early repeat colonoscopies for indications other than colorectal cancer (CRC) screening/surveillance.

METHODS: A retrospective review of patients who had more than one colonoscopy performed for the same indication within a three year time frame at our tertiary care referral hospital between January 1, 2000 and January 1, 2010 was conducted. Exclusion criteria included repeat colonoscopies performed for CRC screening/surveillance, poor bowel preparation, suspected complications from the index procedure, and incomplete initial procedure. Primary outcome was new endoscopic find-

ing that led to an endoscopic therapeutic intervention or any change in clinical management. Clinical parameters including age, sex, race, interval between procedures, indication of the procedure, presenting symptoms, severity of symptoms, hemodynamic instability, duration between onset of symptoms and when the procedure was performed, change in endoscopist, withdrawal time, location of colonic lesions and improvement of quality of bowel preparation were analyzed using bivariate analysis and logistic regression analysis to examine correlation with this primary outcome.

RESULTS: Among 19 772 colonoscopies performed during the above mentioned period, 947 colonoscopies (4.79%) were repeat colonoscopies performed within 3 years from the index procedure. Out of these repeat colonoscopies, 139 patient pairs met the inclusion criteria. The majority of repeat colonoscopies were for lower gastrointestinal bleeding (88.4%), change in bowel habits (6.4%) and abdominal pain (5%). Among 139 eligible patient pairs of colonoscopies, only repeat colonoscopies that were done for lower gastrointestinal bleeding and abdominal pain produced endoscopic findings that led to a change in management [25 out of 123 (20.33%) and 2 out of 7 (28.57%), respectively]. When looking at only recurrent lower gastrointestinal bleeding cases, new endoscopic findings included 8 previously undetected hemorrhoid lesions (6.5%), 7 actively bleeding lesions requiring endoscopic intervention, which included 3 bleeding arterio-venous malformations (2.43%), 2 bleeding radiation colitis (1.6%), and 2 bleeding internal hemorrhoids (1.6%), 5 previously undetected tubular adenomas [4 were smaller than 1 cm (4.9%) and 1 was larger than 1 cm (0.8%)], 3 radiation colitis (2.43%), 1 rectal ulcer (0.8%), and 1 previously undetected right sided colon cancer (0.8%). Of the 25 new endoscopic findings, 18 (72%) were found when repeat colonoscopy was done within the first year after the index procedure. These findings were 1 rectal ulcer, 3 radiation colitis, 4 new hemorrhoid lesions, 3 previously undetected tubular

adenomas, and 7 actively bleeding lesions requiring endoscopic intervention. Of all parameters analyzed, only the interval between procedures less than one year was associated with higher likelihood of finding a clinically significant change in repeat colonoscopy (odds ratios of interval between procedures of 1-2 year and 2-3 year compared to 0-1 year were 0.09; 95%CI 0.01-0.74, $P = 0.025$ and 0.26; 95%CI 0.09-0.72, $P = 0.010$ respectively). No complications were observed among all 139 colonoscopy pairs.

CONCLUSION: There is clinical value of repeating a colonoscopy for recurrent lower gastrointestinal bleeding, especially within the first year after the index procedure.

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Key words: Lower gastrointestinal hemorrhage; Recurrent hemorrhage; Colonoscopy; Colonic disease; Diagnostic yield

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INTRODUCTION

Colonoscopy has emerged as the procedure of choice for evaluation of lower gastrointestinal bleeding, colorectal cancer (CRC) screening, and polyp surveillance due to its high diagnostic yield as well as its ability for therapeutic intervention. However, even though colonoscopy is generally safe, it is an invasive procedure that can rarely be complicated by perforation, hemorrhage, infection, and even death^[1-3]. Repeating a colonoscopy unnecessarily is therefore, not only time consuming and resource wasting, but can lead to undue harm.

While the intervals for repeating colonoscopy for CRC screening or for polyp surveillance are well described, the evidence for repeating colonoscopy for other indications such as recurrent lower gastrointestinal bleeding or abdominal pain is sparse and less clear^[4-7]. Previous studies have suggested early colonoscopy for acute lower gastrointestinal bleeding but management in recurrent episodes is not well standardized^[8-13]. Therefore, when patients who recently had a colonoscopy performed present with the same symptoms, the dilemma remains-should we or should we not repeat another colonoscopy?

The objective of this study is to retrospectively assess the diagnostic yield of repeat colonoscopy performed for the same indication within a three year time frame from the original procedure. An additional goal is to identify factors that may help predict when a repeat colonoscopy will produce a clinically significant change. We hypothesized that early repeat colonoscopy for recurrent lower

gastrointestinal bleeding would yield little clinical information beyond the original procedure.

MATERIALS AND METHODS

A retrospective review of patients who had more than one colonoscopy performed within a three year time frame from the time period including January 1, 2001 through January 1, 2010 for the same indication was conducted at our tertiary care referral hospital.

The reason for this three year time frame is because it is the shortest interval recommended for a repeat colonoscopy in individuals without a personal history of CRC/adenomatous polyps, a personal history of inflammatory bowel disease, or a family history of rare genetic diseases such as familial adenomatous polyposis and hereditary non polyposis colon cancer. We believe that the majority of our study population is similar to individuals described, who are average-risk individuals and individuals with family history of CRC/adenomatous polyps.

Exclusion criteria included; patients, whose repeat colonoscopies were done for CRC surveillance, repeat colonoscopy performed due to suspected complications from the initial one such as postpolypectomy bleeding, poor bowel preparation or incomplete first colonoscopy, and patients with missing data.

For eligible patients, data on age, sex, race, intervals between procedures, settings of the procedures (inpatient *vs* outpatient), whether the same endoscopist performed both procedures, a fellow's involvement in the procedure, indication for the procedures presenting symptoms, severity of symptoms, hemodynamic instability, duration between onset of symptoms and when the procedure was performed, findings of the procedures, completion of the procedure (whether cecal intubation was performed), pre-procedure diagnosis, post-procedure diagnosis, complications from the procedures, withdrawal time, location of colonic lesions, quality of bowel preparation, endoscopic intervention performed, and clinical management of the patients after the colonoscopies were collected. After colonoscopies with poor bowel preparation were excluded, the quality of bowel preparation was categorized using arbitrary scale into fair, good and excellent as judged and documented by the endoscopist who performed the procedure. Improvement of the quality of bowel preparation in the repeat procedure was noted and analyzed as one of the clinical parameters. All data were collected by two independent data collectors using one simple data collection form to avoid any collection bias.

Each of these clinical parameters was analyzed to evaluate the possibility of correlation between these variables and clinically significant change. "Clinically significant change" was defined as any new endoscopic finding that altered diagnosis, prognosis, management, or any change that required endoscopic intervention; a change in physical finding only was not considered a "clinically significant change".

This study has been approved by an institutional re-

Table 1 Demographic characteristics of study population (*n* = 139) (%)

Characteristics	Value
Age (yr), mean \pm SD (range)	68.2 \pm 15.2 (20-92)
Sex	
Male	55
Female	45
Race	
African-American	76
Caucasian	14
Hispanic	7
Asian	3
Indication of the procedures	
Lower gastrointestinal bleeding	88.4
Changes in bowel habit	6.4
Abdominal pain	5
Abnormal imaging studies	0.2
Endoscopist performing the procedures	
Same endoscopist	37
Different endoscopist	63
Fellow involvement	
No fellow involvement	48.8
Same fellow involvement	7.9
Different fellow involvement	43.3
Duration between procedures in days, mean \pm SD (range)	171 \pm 31 (3-1085)
Within the first year after the index procedure	45.3
Between 1-2 yr after the index procedure	17.3
Between 2-3 yr after the index procedure	37.4
Setting of the procedures	
Inpatient procedures	50.4
Outpatient procedures	28.4
Outpatient then inpatient setting	9.1
Inpatient then outpatient setting	12.1

view board for human research conduct.

Statistical analysis

The statistical analysis was performed using Statistics and Data, version 11.0 (College Station, Texas, United States). Odds ratios (ORs) were calculated by performing bivariate logistic regression analysis in order to evaluate the association between colonoscopy-related variables and clinically significant change. Statistical significance was set at *P* value of less than 0.05.

RESULTS

Among 19 772 colonoscopies performed during the above mentioned period, 947 colonoscopies (4.79%) were repeat colonoscopies performed within 3 years from the index procedure. Out of these repeat colonoscopies, majority of exclusions were poor bowel preparation (32.52%), different indications (20.48%), and CRC surveillance (17.74%). A total of 139 patient pairs of colonoscopies (1.41%) met the inclusion criteria.

Demographic data of the eligible patients are shown in Table 1. Among 139 eligible pairs of colonoscopies, 27 cases (19.42%) produced a “clinically significant change” as defined above. Only repeat colonoscopies that were done for lower gastrointestinal bleeding and abdominal pain produced endoscopic findings that resulted in a

change in management (25 out of 123 and 2 out of 7, respectively).

However, the number of colonoscopies performed for indications other than lower gastrointestinal bleeding was too small for statistical analysis (9 pairs of colonoscopies for change in bowel habits and 7 pairs of colonoscopies for abdominal pain). Therefore, we analyzed only those performed for recurrent lower gastrointestinal bleeding.

After excluding index procedures with poor bowel preparation, majority of the colonoscopies’ bowel preparation quality were documented using arbitrary scale. 22.0% were excellent, 22.8% were good, 19.9% were fair, and 2.8% were poor. 22.3% were documented as “adequate” and there was no comment on bowel preparation in 10.2% of the procedures.

Out of 123 pairs of colonoscopies done for recurrent lower gastrointestinal bleeding, 25 cases (20.33%) had new endoscopic findings on the repeat procedure that led to a change in management as shown in Table 2.

Of 25 new endoscopic findings, 18 (72%) were found from repeat colonoscopy within the first year after index procedure. These findings were 1 rectal ulcer, 3 radiation colitis, 4 new hemorrhoid lesions, 3 previously undetected tubular adenoma (all were less than 1 cm in size), and 7 actively bleeding lesions requiring endoscopic interventions.

Of all parameters analyzed, Only the interval between procedures less than one year was associated with higher likelihood of finding a clinically significant change in repeat colonoscopy (ORs of interval between procedures of 1-2 year and 2-3 year compared to 0-1 year were 0.09; 95%CI 0.01-0.74; *P* = 0.025 and 0.26; 95%CI 0.09-0.72, *P* = 0.010 respectively), as shown in Table 3. Analysis of correlation between clinical parameters and clinically significant change using either bivariate analysis or logistic regression analysis has shown the same result.

No complications were observed among all 139 repeat colonoscopies studied.

DISCUSSION

The results of this study showed that the diagnostic yield of repeat colonoscopies for recurrent lower gastrointestinal bleeding was 20.33%. Majority of the endoscopic findings were new hemorrhoid lesions, actively bleeding lesions that required endoscopic intervention, previously undetected tubular adenomas, and one cancer. This suggests that repeating colonoscopy for recurrent lower gastrointestinal bleeding appears to have clinical value.

We opted to include new hemorrhoid lesions in “clinically significant change” as they were potential source of bleeding and bear some differential diagnostic value. However, new hemorrhoid in endoscopic findings may be subject to reporting bias. Since documentation of retroflexion maneuver at the rectum was not available in all cases and hemorrhoids are not always of key interest during colonoscopy, it is possible that presence of small

Table 2 New endoscopic findings on the repeat colonoscopy that led to a clinically significant change (*n* = 25)

Findings	Description	Location
8 previously undetected hemorrhoid lesions (6.5%)	2 small hemorrhoid lesions 2 large hemorrhoid lesions	Rectum Rectum
7 actively bleeding lesions requiring endoscopic interventions (5.7%)	4 hemorrhoid lesions with no comment on size 3 arterio-venous malformations	Rectum 2 in ascending colon 1 in descending colon
5 previously undetected tubular adenomas (4.1%)	2 bleeding radiation colitis 2 bleeding internal hemorrhoids 4 smaller-than-1-cm tubular adenomas	Descending colon Rectum 1 in sigmoid colon, 1 in descending colon 2 in ascending colon
3 radiation colitis (2.43%)	1 larger-than-1-cm tubular adenoma	Ascending colon 2 in descending colon 1 in rectum
1 rectal ulcer (0.8%)		Rectum
1 previously undetected cancer (0.8%)	1 large ulcerated mass	Ascending colon

Table 3 Logistic regression analysis of correlation between clinical parameters and clinical significant change

Clinical parameters	Odds ratio	95%CI	P value
Gender (male as reference)	1.83	0.72-4.65	0.205
Age > 60 yr	0.47	0.17-1.28	0.138
Race			
Caucasian (reference)	1.00		
African-American	3.48	0.43-28.4	0.245
Asian	3.48	0.43-28.4	0.245
Hispanic	9.60	0.85-108.7	0.068
Interval between procedure			
< 365 d (reference)	1.00		
365-630 d	0.09	0.01-0.74	0.025
630-1095 d	0.26	0.09-0.72	0.010
Hospital setting			
Inpatient procedures (reference)	1.00		
Outpatient procedures	1.08	0.36-3.23	0.887
Outpatient then inpatient setting	1.26	0.36-4.34	0.718
Inpatient then outpatient setting	1.25	0.34-4.53	0.738
Presenting signs/symptom			
Hematochezia	4.31	0.94-19.7	0.059
Occult heme positive stool	0.64	0.13-3.13	0.583
Anemic symptoms	0.86	0.32-2.30	0.771
Hemodynamic instability	1.40	0.44-8.9	0.599
Location of diverticulosis			
Right-sided (reference)	1.00		
Left-sided	1.78	0.29-11.13	0.535
Pandiverticulosis	0.29	0.36-2.29	0.238
Improved quality of bowel preparation	0.84	0.33-2.17	0.725
Change in endoscopist	0.98	0.39-2.4	0.961
Fellow involvement	2.19	0.87-5.59	0.098
Duration between onset of symptoms and procedure more than 2 d	0.91	0.25-3.25	0.882
Withdrawal time more than 7 min	0.59	0.31-1.14	0.578

hemorrhoids may not be reported at the index colonoscopy.

Even though it is unlikely that previously undetected tubular adenomas were the source of bleeding, but their detection have led to a change in the patients' surveillance protocol, thus they were included in "clinically significant change" as well^[4-7]. However, as previous studies have reported rates of missing adenomas and/or cancer within 3

years as high as 2%-12%^[14-19], missing small polyps during repeat colonoscopy for lower gastrointestinal bleeding is even more likely and expected.

One case of new cancerous lesion within 3 year interval despite good bowel preparation in the index procedure is concerning, but is also not unexpected, especially in the right side colon^[20,21]. As interval cancers and advance adenomas have been described after screening colonoscopy, missing such lesions at the time of urgent colonoscopy during a lower gastrointestinal bleeding episode is understandable. In this case, the interval between procedures was 498 d. Shorter interval cancer detection after screening colonoscopy has been reported^[14,15,22-24].

Logistic regression analysis of clinical parameters showed that the interval between procedures was the only predictive factor for a clinically significant change in repeat colonoscopies. An interval between procedures of less than one year was more likely to find any clinically significant change.

Actively bleeding lesions were of key interest as they can not only reveal the cause of lower gastrointestinal bleeding but also can be promptly treated by endoscopic interventions. Interestingly, all 7 actively bleeding lesions were found in repeat colonoscopy performed within the first year of the index procedure. The reasons for this are unclear. However, severity of bleeding on clinical presentation did not have any significant association with a clinically significant new endoscopic finding, as shown in Table 3.

The decision to repeat colonoscopy should be individualized by clinical judgment on a case-by-case basis. However, since the repeat colonoscopies within the first year after the index procedure have significantly higher yield than remote procedures, we propose that threshold to repeat colonoscopy when bleeding recurs within the first year should be lower than those who rebleed after the first year.

As previously undetected tubular adenomas and cancer were found in a small but potentially important number of patients (4.1% and 0.8%, respectively), we suggest that a colonoscopy performed for lower gastrointestinal

bleeding should not be a substitute for a screening colonoscopy.

Improvement in quality of bowel preparation did not have any statistically significant correlation with clinically significant change. However, this study is limited by small sample size and the grading of the bowel preparation quality was subjective using arbitrary scale, which could be endoscopist-dependent. Even though, index procedures with poor bowel preparation were excluded, it is possible that small lesions could have been missed in good or fair bowel preparation. We suggest that in cases when the bowel preparation was sub-optimal, the decision to repeat colonoscopy should be individualized.

Majority of population included in this study were African-American (76%), who have the highest incidence of sporadic colorectal cancer^[25-27]. This may contribute to the higher rate of previously undetected tubular adenoma and colon cancer than anticipated found in this study. Generalization of these results to other ethnic group should be made with caution.

The reasoning behind the increase in diagnostic yield in repeating colonoscopy within the first year after the index procedure is unclear. Our study was limited by a retrospective design, single-center study, and a small sample size. Also, the number of repeat colonoscopy performed for indications other than recurrent LGIB such as abdominal pain, change in bowel habit, or diarrhea were too small to do any statistical analysis. Clinical use of repeat colonoscopy for these indications remains unknown. Further prospective studies with larger sample size are warranted.

In summary, the diagnostic yield of 20.33% and a low complication rate among repeat colonoscopies performed for recurrent lower gastrointestinal bleeding in our study, the benefit clearly outweighs the risk. These results suggest that there is clinical value of repeating a colonoscopy for this indication. We conclude that the answer to our question, when bleeding recurs, should colonoscopy be repeated, is yes.

COMMENTS

Background

Colonoscopy is the procedure of choice for evaluation of lower gastrointestinal disorder. While the intervals for repeating colonoscopy for colorectal cancer screening are well described, it is not known if repeating colonoscopy for other indications such as lower gastrointestinal bleeding is clinically useful. Moreover, repeating the procedure unnecessarily not only time consuming and resource wasting, but can lead to undue harm.

Research frontiers

Lacking new evidence to support the use of repeat colonoscopy, when patients who recently had colonoscopy performed present with recurrent lower gastrointestinal bleeding, the dilemma remains-should people or should people not repeat another colonoscopy?

Innovations and breakthroughs

To date, there is no guideline to suggest the proper interval of repeat colonoscopy for the same indication other than for colorectal cancer screening and surveillance. With 20.33% of new endoscopic finding that led to a change in management, authors have validated clinical value of repeat colonoscopy for lower gastrointestinal bleeding. Interestingly, they also found the significant increase in diagnostic yield of early repeat colonoscopy within the first year of the

index procedure.

Applications

With high diagnostic yield of repeat colonoscopy for lower gastrointestinal bleeding, the authors proposed that when lower gastrointestinal bleeding recurs, colonoscopy should be repeated.

Terminology

Clinically significant change is defined as any new endoscopic finding that altered diagnosis, prognosis, management, or any change that required endoscopic intervention

Peer review

This is an interesting single-center retrospective study in which authors evaluate the diagnostic yield of repeat colonoscopy. The results suggest that there is clinical value in repeat colonoscopy for lower gastrointestinal bleeding. High diagnostic yield in the first year of index procedure is intriguing and should warrant further prospective studies.

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Comparison of Pentax HiLine and Olympus Lucera systems at screening colonoscopy

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Abstract

AIM: To compare the performance characteristics of Pentax HiLine (PHL) (with i-scan) and Olympus Lucera (OL) systems in a screening population.

METHODS: Screening colonoscopies in asymptomatic guaiac faecal occult blood test-positive patients with PHL ($n = 58$) and OL ($n = 425$) colonoscopes were analysed. All procedures were performed by a single colonoscopist. PHL used white-light endoscopy (WLE) on scope insertion and contrast/surface enhancement (i-scan 1) on withdrawal, and OL utilised WLE both on insertion and withdrawal. Patient age, sex, instrument insertion and withdrawal times, nurse assessed patient comfort scores, midazolam and fentanyl doses, procedure completion and rates of lesion detection were recorded separately for each group. Comparisons between the groups were made using either Fisher's exact test (for dichotomous variables) or Mann-Whitney U test (for ordinal and continuous variables).

RESULTS: Colonoscopy completion rates were similar

in both groups: 413/425 (97.2%) for OL and 55/58 (94.9%) for PHL ($P = 0.24$). For complete colonoscopies, the two groups were well matched for age, sex, colonoscopy insertion times (mean 11.1 min in OL vs 11.6 min in PHL, $P = 0.93$) and normal colonoscopy withdrawal times (mean 15.6 min in OL vs 14.7 min in PHL, $P = 0.2$). Patients in the PHL group experienced a small increase in discomfort (mean patient comfort scores were 0.49 in the OL and 0.95 in the PHL group, $P < 0.0001$). While Fentanyl doses required were similar between groups (mean 57.5 μg in OL vs 61.4 μg in PHL, $P = 0.13$), slightly more Midazolam was required in the PHL group (mean 2.1 mg in OL vs 2.4 mg in PHL, $P = 0.035$). There was no difference in polyp (58% in OL vs 67% in PHL) or adenoma (49% in OL vs 56% in PHL) detection rates between the groups. Neither the total number of polyps and adenomas, nor the characteristics of these (including size, location or presence of advanced features) were different between the two systems.

CONCLUSION: This study suggests that there is no advantage of either colonoscopy system in lesion detection.

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Key words: Pentax HiLine; i-scan; Polyp; Adenoma; Colonoscopy

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INTRODUCTION

Colonoscopy is the gold-standard test for the diagnosis of colorectal neoplasia. Aside from diagnosis of

colorectal carcinoma (CRC), detection and removal of pre-malignant precursor lesions is an essential part of colonoscopy and has been shown to significantly reduce mortality from CRC^[1].

Even with the most thorough colonoscopic examination, adenoma miss rates, as established by same-day tandem colonoscopies, remain significant and are higher in patients with at least 2 adenomas found on baseline colonoscopy with an inverse correlation with adenoma size (between 6% for large adenomas ≥ 1 cm and 27% for those ≤ 5 mm)^[2]. The expected incidence of CRC in one study, based on missed adenomas at screening colonoscopy, was 1.1 per 1000 persons within 5 years^[3].

The effect of a variety of technical manoeuvres and mucosal enhancement technologies on adenoma detection and miss rates has been studied, including prolongation of colonoscope withdrawal time^[4], systematic patient positioning^[5], pancolonic dye-spray chromoendoscopy^[6], cap-assisted colonoscopy^[7], narrow band imaging (NBI)^[8] and endoscopic trimodal imaging^[9], with variable degrees of success.

The i-scan technology was developed and introduced by Pentax (Japan) and is based on digital surface, contrast and tone enhancement, designed to reveal minute mucosal irregularities and subtle changes in colour that are not visible at conventional white light endoscopy (WLE)^[10]. This technology has been incorporated into the Pentax HiLine (PHL) system representing a latest generation of high definition (HD+) colonoscopes.

The efficacy of i-scan compared to standard white-light colonoscopy has been studied in prospective trials and the results are somewhat conflicting. One randomized study of the PHL system utilising surface enhancement on withdrawal demonstrated its superiority to standard Pentax video colonoscopes in neoplastic (adenomatous and cancerous) lesion detection (38% *vs* 13%)^[11]. Another prospective study, which randomised patients into 3 groups, each using a distinct modality on withdrawal (conventional high-definition WLE *vs* contrast/surface enhancement *vs* contrast/surface/tone enhancement), concluded there was no advantage in using i-scan for adenoma detection (31.9% *vs* 36.5% *vs* 33.1%, $P = 0.742$) and miss (22.9% *vs* 19.3% *vs* 15.9%, $P = 0.513$) rates^[12]. One more non-randomised study, however, suggests a superior polyp detection rate (PDR) with PHL compared to Olympus Lucera (OL) (66% *vs* 44%, $P = 0.01$) with no difference in median polyp size between the groups (3 mm *vs* 4 mm, $P = 0.98$)^[13]. This study enrolled 269 colonoscopies performed in the setting of the English National Bowel Cancer Screening Programme (BCSP) at a single centre. Neither surface nor tone enhancement was used systematically for lesion detection in this study.

We sought to determine whether there were advantages in terms of lesion detection with either OL WLE or PHL with routine use of i-scan surface enhancement on withdrawal.

MATERIALS AND METHODS

The BCSP in England offers biennial guaiac based faecal

occult blood testing (FOBT) between the ages of 60 and 74 and colonoscopy for those testing positive. As part of equipment familiarisation in preparation for a trial, we have intermittently utilised PHL since May 2010.

All patients undergoing baseline colonoscopy performed by a single endoscopist (EC) between receipt of the PHL system (18th May, 2010) and the beginning of the study (27th September, 2011) were identified from the Endoscopy Department reporting system. Cases were included if either PHL colonoscopes or OL Q-series colonoscopes were used. Colonoscopies utilising alternative systems, incomplete and those performed for post-polypectomy surveillance were excluded.

For OL, insertion and withdrawal was performed using WLE with NBI at the discretion of EC for lesion characterisation. For PHL, insertion was performed using WLE. On intubation of the caecal pole, the mode was switched to contrast/surface enhancement (i-scan 1) for withdrawal with utilisation of contrast/surface/tone enhancement (i-scan 2) for lesion characterisation at the discretion of the EC. Chromoendoscopy was not used in any case.

Data on patient age, sex, colonoscopy completion and limiting factors, Midazolam (mg) and Fentanyl (μ g) doses, nurse-assessed patient comfort score (0 = none, 1 = minimal, 2 = mild, 3 = moderate and 4 = severe), colonoscope insertion and withdrawal times (minutes), and the total number of polyps were collected for each colonoscopy. Each polyp detected was then characterized by its location in the colon, size (mm), morphology (stalked/sessile), histology (tubular/tubulo-villous or serrated adenoma, hyperplastic, or inflammatory), and presence of dysplasia (low- or high-grade) or cancer.

Intergroup comparisons were then made for each measure using either the Fisher's exact test or Mann-Whitney *U* test with the polyp data divided according to numbers of polyps and adenomas, adenomas proximal to the splenic flexure (proximal adenomas) and advanced adenomas (*i.e.*, > 1 cm in size, villous, or containing high-grade dysplasia or cancer). Polyp (PDR) and adenoma (ADR) detection rates were calculated for each group. For withdrawal times, only normal colonoscopies were included to remove any effect of polypectomy on duration. A power calculation was performed to determine whether these cohorts were of an appropriate size to detect the differences described by Banks *et al*^[13].

As a retrospective service evaluation, this study did not require ethics committee approval under NHS Research Governance arrangements^[14] and was registered with the local Risk and Patient Safety Department.

RESULTS

Colonoscopy completion rates were similar in both groups: 413/425 (97.2%) in the OL group and 55/58 (94.9%) in the PHL group ($P = 0.24$) with 3/12 (OL) and 2/3 (PHL) of the incomplete cases due to obstructing cancers. The two groups were matched for age and sex, and there was no difference in cancer detection rates (OL

Table 1 Colonoscopy completion rates, patient demographics, sedation doses, procedure times and comfort scores in the Olympus Lucera and Pentax HiLine groups

Indicator	Olympus Lucera	Pentax HiLine	P value
	<i>n</i> (% of total) ¹		
Complete colonoscopies	413/425 (97.2)	55/58 (94.9)	0.24
Male patients	239/413 (57.9)	35/55 (63.7)	0.5
	mean \pm SD ²		
Patient age (yr)	66.3 \pm 4.3	65.8 \pm 4.7	0.36
Fentanyl dose (μ g)	57.5 \pm 18.0	61.4 \pm 18.5	0.13
Midazolam dose (mg)	2.1 \pm 0.6	2.4 \pm 0.7	0.035
Comfort score	0.49 \pm 0.6	0.95 \pm 0.6	< 0.0001
Insertion time (min)	11.1 \pm 6.6	11.6 \pm 7.5	0.93
Normal colonoscopy withdrawal time (min)	15.6 \pm 8.2	14.7 \pm 8.0	0.20

Comparisons made using Fisher's exact test¹ or Mann-Whitney *U* test².

7.7% *vs* PHL 7.3%, *P* = 1.0).

The colonoscope insertion and normal colonoscopy withdrawal times were similar with OL and PHL (Table 1). There was a small but statistically significant increase in mean \pm SD, discomfort score in the PHL group. Although the average fentanyl dose was not different between the groups, there was also a small significant increase in midazolam requirements for the PHL patients.

There were no statistically significant differences in any of the polyp or adenoma detection measures between the two systems used. The comparison included the PDR, ADR (Table 2), mean numbers of polyps (MNP), adenomas (MNA), proximal and advanced adenomas, and polyps of large (> 1cm), small (\leq 1cm) and diminutive (\leq 5 mm) size (Table 3).

Our study had an 88% power to detect the differences found by Banks *et al*^[13].

DISCUSSION

One of the challenges of modern colonoscopy is to minimise the rate of missed pathology. It has been hoped that improvements in image quality might translate into increasing adenoma detection and there have been some suggestions from previous studies^[11,13] that this might be the case. In this study, however, we have not been able to identify any benefit even when subclassifying according to location and size of polyp.

Our data is discordant with the results of a previous similar study^[13]. There are several possible explanations for this, although it is noteworthy that our study has several advantages over the previous work, which would support the validity of our data. Firstly, our cohort was larger than that reported previously (*n* = 468 *vs* *n* = 269)^[13], and accordingly this study was well-powered to detect the described effect size. Secondly, we compare the performance of a single colonoscopist rather than pooling colonoscopies performed by 5 ECs using OL and comparing them to those performed by a single EC with PHL. It is therefore plausible that at least some of the difference previously identified might be explained by

Table 2 Polyp and adenoma detection rates in the Olympus Lucera and Pentax HiLine groups

	Olympus Lucera	Pentax HiLine	P value
With \geq 1 polyp	239/413 (58%)	37/55 (67%)	0.19
With \geq 1 adenoma	202/413 (49%)	31/55 (56%)	0.3

Comparisons made using Fisher's exact test.

Table 3 Polyps and adenomas of various characteristics in the Olympus Lucera and Pentax HiLine groups (mean \pm SD)

Size location	Olympus Lucera		Pentax HiLine		<i>P</i> value
	<i>n</i>	mean \pm SD	<i>n</i>	mean \pm SD	
Polyps					
All	586	1.42 \pm 1.96	87	1.58 \pm 1.73	0.19
> 1 cm	109	0.26 \pm 0.53	16	0.29 \pm 0.50	0.51
\leq 1 cm	477	1.15 \pm 1.78	70	1.27 \pm 1.58	0.27
\leq 0.5 cm	368	0.89 \pm 1.53	54	0.98 \pm 1.27	0.22
Adenomas					
All	414	1.00 \pm 1.54	59	1.07 \pm 1.27	0.27
Proximal	164	0.4 \pm 0.9	21	0.38 \pm 0.7	0.74
> 1 cm	97	0.23 \pm 0.50	14	0.25 \pm 0.48	0.6
\leq 1 cm	317	0.77 \pm 1.38	45	0.82 \pm 1.11	0.29
\leq 0.5 cm	229	0.55 \pm 1.13	31	0.56 \pm 0.96	0.63
Advanced adenomas					
All	145	0.35 \pm 0.7	16	0.29 \pm 0.5	0.64

Comparisons made using Mann-Whitney *U* test.

variation in performance between colonoscopists rather than systems. ADRs were markedly lower in this earlier study. Although not specifically reported, a PDR of 44% with OL will translate into an ADR much lower than the 49% with OL in our study. As adenoma detection increases, the potential for missed adenomas reduces and with it the potential for measurable differences between groups. It is theoretically possible that the use of i-scan 1 during colonoscopy withdrawal could have reduced lesion detection compared to PHL WLE without enhancements, although the high ADR in the PHL group in our study (56%) and the results of the study by Hoffman *et al*^[11] would argue against this. Thirdly, the earlier study by Hoffman *et al*^[11] suggested a marked advantage of high definition Pentax colonoscopes over standard WLE. Part of this advantage might be explained by the rather low ADR in the standard colonoscopy group (13% *vs* 38%). This study also included a heterogeneous patient population with patients undergoing screening colonoscopy, post-polypectomy surveillance or positive for faecal occult blood. The burden of pathology in these disparate patient groups is likely to be substantially different. Whilst no statistically significant difference was demonstrated in indications or sex of patients, there were some sizeable differences (more post-polypectomy surveillance and men with HD+) which in combination could have influenced the frequency of adenomas in each study arm. In addition, patients undergoing post-polypectomy surveillance represent a very heterogeneous group both by the size and numbers of previously detected adenomas^[15].

In contrast, our study comprises a homogenous group of patients (asymptomatic, FOBT-positive, aged between 60 and 74), which overcomes these limitations.

In addition to assessing the most widely used quality indicators for colonoscopy (ADR, PDR, MNA and MNP), we also analysed two further indicators. We considered the detection of proximal adenomas (*i.e.*, those proximal to the splenic flexure) as concerns have been raised about the performance of colonoscopy in the right colon^[16-18]. We also studied the detection of advanced adenomas since the detection of these lesions is most important, due to their increased likelihood to develop into CRC. One might expect that an effective image enhancement technology would significantly improve the discrimination of smaller polyps from the background mucosa to a greater degree than of larger polyps as the majority of the latter should be readily identifiable by WLE alone, unless they are hidden from view. We therefore also performed a detailed subgroup analysis of MNP/MNA of large (> 1 cm), small (\leq 1 cm) and diminutive (\leq 5 mm) size in each patient group. These sub-analyses did not detect any differences in the performance of the two endoscopy systems.

Our findings suggest that patients in the PHL group experienced small but statistically significant increases in discomfort and required slightly more Midazolam. A slight increase in discomfort with this system has been described previously^[13].

Although this data has several advantages over previous reports, there are some notable limitations. These include that our evaluation was not prospective or randomised and, as a single EC experience, it may not be generalisable.

In any cohort of patients, the number of detectable adenomas is finite. With increasingly thorough and systematic examination, the proportion of detected adenomas will approach a limit beyond which the contribution of any image enhancing technology will be negligible. Whilst studies tend to be carried out by high performing ECs, consideration should be given to evaluation in average performance settings.

In this detailed retrospective cohort study on a homogenous sample of FOBT-positive patients undergoing bowel cancer screening, we were unable to demonstrate any added benefit of either the HD+ PHL or the high-resolution OL system. All studied colonoscopy quality yield indicators were similar in the two studied patient groups. A randomised controlled study is required to fully evaluate the relative performance characteristics of these two systems.

COMMENTS

Background

Successful detection and removal of adenomas at colonoscopy is vital in reducing mortality from colorectal cancer. A number of optical image enhancement technologies have been developed and introduced into practical use with the aim of improving polyp detection from the background colonic mucosa. The i-scan technology is used in the Pentax HiLine (PHL) system of high-definition (HD+) colonoscopes and has been shown to produce better colonic polyp de-

tection in comparison with the same system's white light endoscopy (WLE).

Research frontiers

This study assessed and compared the performance of PHL with i-scan 1 (contrast/surface enhancement) mode and WLE with Olympus Lucera (OL), a high-resolution video-colonoscopy system also widely and successfully used in modern endoscopy units.

Innovations and breakthroughs

This study featured a high-quality methodology to evaluate for potential differences in polyp detection, patient comfort and sedation requirements at colonoscopies performed with the two equipment systems, PHL with i-scan 1 and OL WLE in a homogenous group of 468 faecal occult blood test positive patients enrolled in the National Bowel Cancer Screening Programme at a single tertiary care centre in England. As compared with the only other similar published study (Banks *et al*, *World J Gastroenterol* 2011), this investigation is based on a larger series of patients ($n = 468$ vs $n = 269$), represents a single- (rather than single-compared with multiple-) colonoscopist performance, thus minimizing operator-dependent differences in polyp detection, and includes a detailed sub-group analysis by polyp size, type, location and advanced pre-malignant features.

Applications

Based on the results of this study, neither PHL with i-scan 1, nor OL WLE offer an advantage for the detection of colonic polyps of various sizes, type, location and advanced pre-malignant features. OL instruments are associated with lower degrees of patient discomfort and lower requirements for Midazolam during colonoscopy.

Terminology

I-scan - optical imaging technology invented by Pentax, Japan, based on the application of digital colour filters to achieve tone, contrast and surface enhancement of gastrointestinal mucosa as an alternative to the standard (white-light) endoscopy. PHL - a latest-generation system of HD+ colonoscopes equipped with the i-scan technology in addition to the standard white-light endoscopy mode.

Peer review

Publication was recommended by the reviewers as the study had demonstrated conflicting results compared to another similar but much smaller study ($n = 269$) published earlier, and statistical calculations were found to have been very well performed in this study.

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Oral purgative and simethicone before small bowel capsule endoscopy

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Abstract

AIM: To evaluate small bowel cleansing quality, diagnostic yield and transit time, comparing three cleansing protocols prior to capsule endoscopy.

METHODS: Sixty patients were prospectively enrolled and randomized to one of the following cleansing protocols: patients in Group A underwent a 24 h liquid diet and overnight fasting; patients in Group B followed protocol A and subsequently were administered 2 L of polyethylene glycol (PEG) the evening before the procedure; patients in Group C followed protocol B and were additionally administered 100 mg of simethicone 30 min prior to capsule ingestion. Small bowel cleansing was independently assessed by two experienced endoscopists and classified as poor, fair, good or excellent according to the proportion of small bowel mucosa under perfect conditions for visualization. When there was no agreement between the two endoscopists, the

images were reviewed and discussed until a consensus was reached. The preparation was considered acceptable if > 50% or adequate if > 75% of the mucosa was in perfect cleansing condition. The amount of bubbles was assessed independently and it was considered significant if it prevented a correct interpretation of the images. Positive endoscopic findings, gastric emptying time (GET) and small bowel transit time (SBTT) were recorded for each examination.

RESULTS: There was a trend favoring Group B in achieving an acceptable (including fair, good or excellent) level of cleansing (Group A: 65%; Group B: 83.3%; Group C: 68.4%) [P = not significant (NS)] and favoring Group C in attaining an excellent level of cleansing (Group A: 10%; Group B: 16.7%; Group C: 21.1%) (P = NS). The number of patients with an adequate cleansing of the small bowel, corresponding to an excellent or good classification, was 5 (25%) in Group A, 5 (27.8%) in Group B and 4 (21.1%) in Group C (P = 0.892). Conversely, 7 patients (35%) in Group A, 3 patients (16.7%) in Group B and 6 patients (31.6%) in Group C were considered to have poor small bowel cleansing (P = 0.417), with significant fluid or debris such that the examination was unreliable. The proportion of patients with a significant amount of bubbles was 50% in Group A, 27.8% in Group B and 15.8% in Group C (P = 0.065). This was significantly lower in Group C when compared to Group A (P = 0.026). The mean GET was 27.8 min for Group A, 27.2 min for Group B and 40.7 min for Group C (P = 0.381). The mean SBTT was 256.4 min for Group A, 256.1 min for Group B and 258.1 min for Group C (P = 0.998). Regarding to the rate of complete examinations, the capsule reached the cecum in 20 patients (100%) in Group A, 16 patients (88.9%) in Group B and 17 patients (89.5%) in Group C (P = 0.312). A definite diagnosis based on relevant small bowel endoscopic lesions was established in 60% of the patients in Group A (12 patients), 44.4% in Group B (8 patients) and 57.8% in Group C (11 patients) (P = 0.587).

CONCLUSION: Preparation with 2 L of PEG before small bowel capsule endoscopy (SBCE) may improve small bowel cleansing and the quality of visualization. Simethicone may further reduce intraluminal bubbles. No significant differences were found regarding GET, SBTT and the proportion of complete exploration or diagnostic yield among the three different cleansing protocols.

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Key words: Small bowel capsule endoscopy; Bowel preparation; Polyethylene glycol; Simethicone

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INTRODUCTION

The usefulness of bowel preparation prior to small bowel capsule endoscopy (SBCE) remains a controversial issue. It is widely recognized that SBCE may have considerable limitations when the visualization is impaired by bubbles, bile, intraluminal fluid and debris, or when the capsule fails to visualize all of the small bowel due to delayed gastric or small bowel transit times. Since SBCE is a costly, time consuming and not usually a repeated procedure, it is critical to optimize the quality of visualization. The benefits of bowel preparation are, however, still a matter of debate and the best method remains to be determined. Furthermore, no standardized protocol has been widely accepted and overnight fasting remains the standard preparation for SBCE^[1].

The aim of this study was to compare the quality of mucosal visualization, as well as the diagnostic yield, gastric emptying time (GET), small bowel transit time (SBTT) and rate of complete small bowel exploration with cecum visualization within the capsule battery lifespan, using three different small bowel cleansing protocols.

MATERIALS AND METHODS

We conducted a prospective, randomized, single center study, which included 60 consecutive patients undergoing SBCE (PillCam[®] SB2, Given[®] Imaging Ltd. Yoqneam, Israel) for the evaluation of suspected small bowel disease, including overt or occult obscure gastrointestinal bleeding (OGB), suspected or established Crohn's disease (CD), chronic diarrhea or suspected small bowel neoplasia. All evaluations took place between August 2010 and March 2011. At the time SBCE was scheduled, patients were randomly assigned to Group A, B or C. Group A included 20 patients who followed the bowel prepara-

tion currently recommended by the capsule manufacturer, with a 24 h liquid diet and overnight fasting prior to SBCE. Group B included 20 patients who followed the same as protocol A plus 2 L of polyethylene glycol (PEG) solution (Endofalk[®], Dr. Falk Pharma GmbH, Freiburg, Germany), containing macrogol 3350 (105 g/L) + potassium chloride (0.370 g/L) + sodium bicarbonate (1430 g/L) + sodium chloride (2800 g/L), in the evening before the procedure; Group C included 20 patients who followed the same as patients in protocol B plus 100 mg simethicone liquid suspension (Aero-OM[®], OM Pharma SA, Geneva, Switzerland) 30 min prior to capsule ingestion. All patients were allowed to drink clear liquids at 2 h and to have a light snack 4 h after swallowing the capsule. Each examination was reviewed by two endoscopists with experience in SBCE who were unaware of the type of bowel preparation and independently evaluated the endoscopic findings and assessed the quality of mucosal visualization. When there was a disagreement, the images were reviewed and discussed until a consensus was achieved. The GET and the SBTT were automatically calculated by the RAPID Reader[®] software. GET was defined as the time from the first gastric image to the first duodenal image and the SBTT the time from the first duodenal image to the first cecal image. The primary outcome was to evaluate the effects of bowel preparation on the quality of images obtained by capsule endoscopy. The secondary outcome was to evaluate the effect of preparation on other parameters, such as diagnostic yield, GET, SBTT and rate of complete small bowel examination. In order to evaluate the effects of bowel preparation, obstacles such as intestinal contents, intraluminal gas, bile and food residues were evaluated. By using a timer, we recorded the exact time period during which the small intestinal mucosa was not clean. Following a methodology which was similar to that utilized in other publications^[2,3], the quality of small bowel cleansing was assessed according to the proportion of the small bowel mucosa with perfect conditions for visualization, without any liquid, bubbles or debris. We considered it to be excellent if an ideal visualization of the small bowel mucosa was achieved; good if > 75% of the mucosa was in perfect condition, with some fluid or debris which did not seem to interfere with the overall quality of the examination; fair if only 50%-75% of the mucosa was under perfect conditions for observation, with the presence of enough fluid, bubbles or debris to preclude a completely reliable examination; and poor if < 50% of the mucosa could be observed, with the presence of significant amounts of fluid, bubbles or debris such that the examination was unreliable (Figure 1). We considered that the cleansing was adequate if at least 75% of the small bowel mucosa was in perfect condition for visualization (*i.e.*, excellent or good preparation). For study analysis purposes, we further rated small bowel cleansing as acceptable if at least 50% of the mucosa was in perfect condition for visualization (*i.e.*, including excellent, good or fair cleansing).

On the evaluation of the endoscopic findings, those

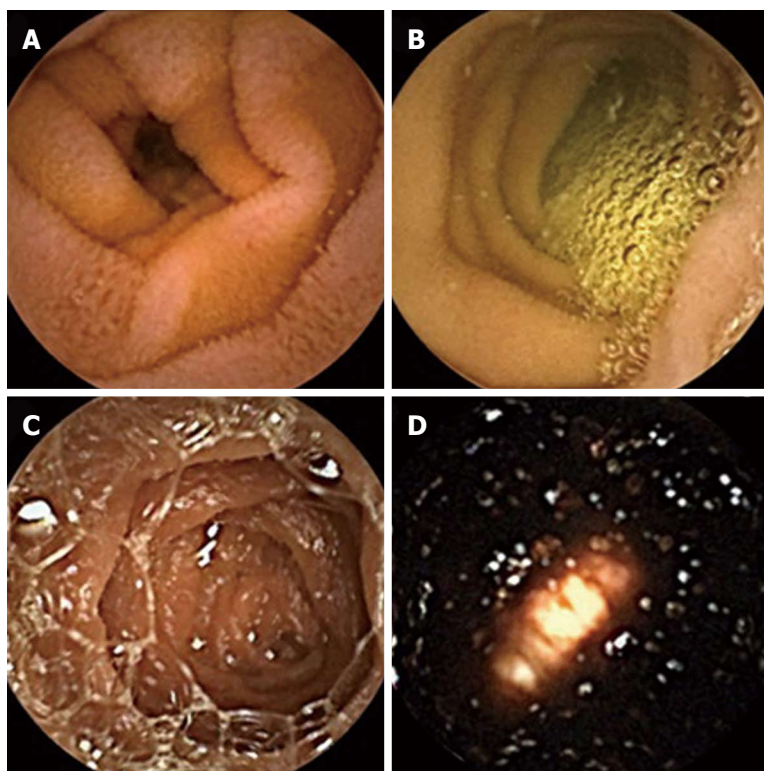


Figure 1 Small bowel cleansing classification. A: Excellent: perfect visualization in every small bowel segments; B: Good: > 75% of the mucosa in perfect condition, with some fluid or debris remaining; C: Fair: 50%-75% of clean mucosa, with the presence of enough fluid, bubbles or debris to preclude a completely reliable examination; D: Poor: < 50% of clean mucosa.

which were considered relevant were hemorrhagic lesions in patients with OGB and/or significant inflammatory activity (Lewis score, $LS \geq 135$) in patients with suspected or established CD.

Ethical considerations

All patients provided written consent to undergo capsule endoscopy and to be randomly assigned to one of the three protocols evaluated in the study. The study was approved by the Ethics Committee of the Alto Ave Hospital Center-Guimarães, Portugal.

Statistical analysis

Quantitative data were summarized as the mean \pm SD. Continuous measures were assessed using analysis of variance (ANOVA). Nonparametric data were analyzed with the Kruskal-Wallis test and categorical measures were compared using the χ^2 test or Fisher's exact test. $P < 0.05$ was considered statistically significant. All statistical analyses were performed using SPSS 16.0 (SPSS® Inc., Chicago, IL, United States).

RESULTS

Patients' characteristics

A total of 60 patients underwent SBCE for the evaluation of suspected small bowel disease, including OGB (occult: 23 patients; overt: 11 patients), CD (suspected CD: 12 patients; established CD: 9 patients), chronic diarrhea (2 patients) or suspected small bowel neoplasia (3 patients). Two patients from Group B were excluded due to technical issues that hampered the recording of several endoscopic images. One patient in Group C was

also excluded from the study because the capsule did not exit the stomach due to a pyloric benign stricture. Consequently, 57 patients (26 men and 31 women) were analyzed. Groups A, B and C included 20, 18 and 19 patients, respectively. Mean ages were 51.8 years for Group A, 50.4 years for Group B and 58.4 years for Group C. No significant differences were observed between the three groups in terms of age, sex or indication for SBCE (Table 1).

Transit time and quality of endoscopic images

The mean GET was 27.8 min for Group A, 27.2 min for Group B and 40.7 min for Group C ($P = 0.381$). The mean SBTT was 256.4 min for Group A, 256.1 min for Group B and 258.1 min for Group C ($P = 0.998$). The capsule reached the cecum in 20 patients (100%) in Group A, 16 patients (88.9%) in Group B and 17 patients (89.5%) in Group C ($P = 0.312$). In every patient with incomplete small bowel enteroscopy, capsule spontaneous exteriorization was confirmed with an abdominal plain radiography performed within two weeks after SBCE.

The number of patients with adequate cleansing of the small intestine, corresponding to excellent or good classification, was 5 (25%) in Group A, 5 (27.8%) in Group B and 4 (21.1%) in Group C ($P = 0.892$). In this subset, the cleansing was considered to be excellent in 2 patients (10%) from Group A, 3 (16.7%) from Group B and 4 (21.1%) from Group C ($P = 0.634$) and good in 3 (15%), 2 (11.1%) and 0 patients, respectively ($P = 0.522$). In a subanalysis also including those patients with fair cleansing, 8 (40%) in Group A, 10 (55.5%) in Group B and 9 (44.7%) in Group C ($P = 0.751$), the overall number of patients with acceptable small bowel cleansing,

Table 1 Patients' characteristics and indications for small bowel capsule endoscopy (%)

	Group A Overnight fast (n = 20)	Group B PEG (n = 18)	Group C PEG + simethicone (n = 19)	P value
Age (yr)	51.8 ± 21.6	50.4 ± 17.5	58.4 ± 18.8	0.437
Sex	11 (55)	11 (61.1)	9 (47.4)	0.702
N female (%)				
Indication				0.403
Occult OGIB	9	7	6	
Overt OGIB	5	0	5	
Suspected CD	3	6	3	
CD	3	2	3	
Chronic diarrhea	0	1	1	
Suspected SB neoplasia	0	2	1	

PEG: Polyethylene glycol; OGIB: Obscure gastrointestinal bleeding; CD: Crohn's Disease; SB: Small bowel.

corresponding to excellent, good or fair classification, was 13 (65%) in Group A, 15 (83.3%) in Group B and 13 (68.4%) in Group C ($P = 0.417$). Conversely, 7 patients (35%) in Group A, 3 patients (16.7%) in Group B and 6 patients (31.6%) in Group C were considered to have poor small bowel cleansing ($P = 0.417$), with significant fluid or debris so that the examination was unreliable (Figure 2). Focusing on the presence of a significant amount of bubbles, it occurred in 10 patients (50%) in Group A, 5 patients (27.8%) in Group B and 3 patients (15.8%) in Group C ($P = 0.065$). In the subanalysis between groups in a head to head comparison, in Group C where simethicone was used, the proportion of patients with a significant amount of bubbles (15.8%) was significantly lower than those in Group A (50%) ($P = 0.026$) (Table 2).

Diagnostic yield of capsule endoscopy

A definite diagnosis based on relevant small bowel endoscopic lesions was established in 60% of the patients in Group A (12 patients), 44.4% in Group B (8 patients) and 57.8% in Group C (11 patients) ($P = 0.587$).

DISCUSSION

Currently, there are no widely accepted guidelines for bowel preparation for SBCE, although inadequate cleansing, especially in the distal part of the small intestine, is considered a limitation^[4,5]. Moreover, only an average of 83.5% of the examinations are completed, with the capsule reaching the cecum during the recording time^[4,6]. The benefits of small bowel preparation prior to SBCE are still an issue of controversy^[7,8]. Currently, no uniform protocol is widely accepted and overnight fasting remains the standard preparation for SBCE. In a recently published prospective, multicenter randomized controlled study that included 291 patients, the authors concluded that a clear liquid diet and overnight fasting is sufficient to achieve an adequate level of cleanliness and is better

tolerated by patients than other forms of preparation^[9]. Another randomized study evaluated 150 patients, concluding that bowel purgatives and prokinetics did not improve completion rates or the quality of visualization and reduce patient acceptability^[10]. Conversely, accumulating evidence from other different studies seems to indicate that bowel preparation with purgative agents increases the diagnostic yield of the procedure by improving small bowel mucosal visualization compared with a clear liquid diet or overnight fast^[11-14]. The 2009 European Society of Gastrointestinal Endoscopy's updated information for SBCE stated that purgative bowel preparation enhances the quality of visualization and the diagnostic yield of SBCE^[1]. A meta-analysis has shown that small bowel purgative preparation, either with PEG solution or sodium phosphate (NaP), may improve the diagnostic yield of the examination^[15]. It also showed better quality of visualization of the mucosa in patients receiving purgatives, although it did not detect any difference between purgative preparation and a clear liquids diet regarding SBCE completion rate, GET and SBT^[15]. Those results are consistent with the conclusions from another meta-analysis that examined the effectiveness of bowel preparation for SBCE, which also included studies using prokinetics and simethicone^[16].

One of the reasons for the controversy surrounding this issue is that the cleansing grading systems have not been standardized, causing difficulties in comparing the results of numerous studies. Most of the reported grading systems are time consuming and difficult to apply routinely in clinical practice. In addition, the reliability and efficacy of these grading systems have rarely been evaluated^[17-19].

With respect to the type of purgative, there is also a lack of standardization in the methodology applied in the different studies, hampering the establishment of widely accepted recommendations. NaP and PEG were prospectively compared, resulting in a similar quality of small bowel preparation and completion rates^[20]. Nonetheless, most of the accumulated evidence in the literature supports the use of PEG. PEG solutions are non-absorbable and osmotically active and have been widely used in capsule endoscopy based on its ability to move through the bowel and potentially distend the lumen, wash out debris and bile, and possibly enhance small bowel transit time. The optimal dose of PEG that needs to be administered before SBCE is not entirely clear but 2 L appears to be sufficient^[21-23]. A recent study concluded that the ingestion of a small amount of PEG after the swallowing of an endoscopy capsule significantly improved CE image quality, but did not enhance the completion rate to the cecum^[24]. Another study has shown that bowel preparation with NaP also improved small bowel mucosal visualization when compared to 12 h overnight fasting^[3,25]. However, an important issue to be considered when using NaP is its potential ability to induce nonspecific aphthoid-like mucosal lesions, which may be endoscopically similar to those seen in CD; because of

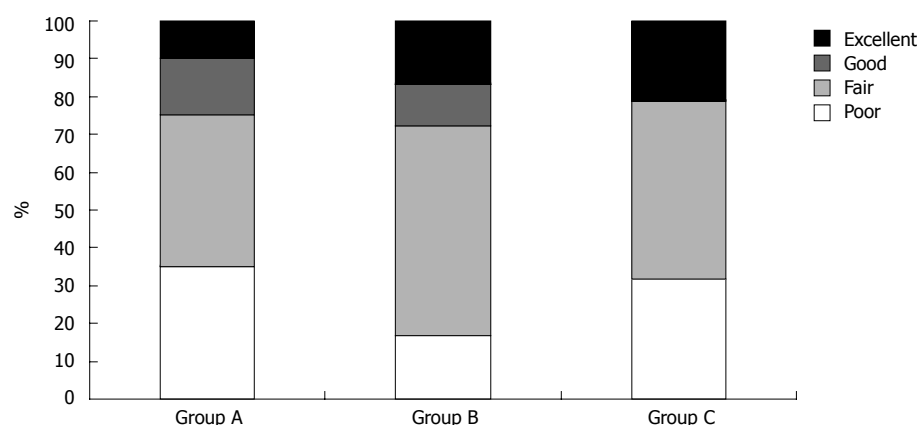


Figure 2 Small bowel cleansing among different groups. The number of patients with adequate cleansing of the small intestine, corresponding to excellent or good classification, was 5 (25%) in Group A, 5 (27.8%) in Group B and 4 (21.1%) in Group C ($P = 0.892$).

Table 2 Transit times, quality of image and relevant endoscopic findings (%)

	Group A overnight fast (<i>n</i> = 20)	Group B PEG (<i>n</i> = 18)	Group C PEG + simethicone (<i>n</i> = 19)	<i>P</i> value
GET (min)	27.8 ± 27.4	27.2 ± 35.2	40.7 ± 32.1	0.381
SBTT (min)	256.4 ± 91	256.1 ± 110	258.1 ± 113	0.998
ICV passing	20 (100)	16 (88.9)	17 (89.5)	0.312
Poor cleansing (< 50%)	7 (35)	3 (16.7)	6 (31.6)	0.417
Fair cleansing (50%-75%)	8 (40)	10 (55.6)	9 (47.4)	0.751
Good cleansing (> 75% although suboptimal)	3 (15)	2 (11.1)	0	0.522
Excellent cleansing	2 (10)	3 (16.7)	4 (21.1)	0.634
"Acceptable" cleansing (includes fair, good or excellent)	13 (65)	15 (83.3)	13 (68.4)	0.417
"Adequate" cleansing (includes good or excellent)	5 (25)	5 (27.8)	4 (21.1)	0.892
Bubbles	10 (50)	5 (27.8)	3 (15.8)	0.065 (A vs C), $P = 0.026$

PEG: Polyethylene glycol; GET: Gastric emptying time; SBTT: Small bowel transit time; ICV: Ileocecal valve.

the potential for misinterpretation of these lesions, some authors have contraindicated the use of NaP as a colonic cleansing preparation for patients with chronic diarrhea or in whom the diagnosis of inflammatory bowel disease is suspected^[26-28]. Moreover, as the oral NaP preparation may induce changes in serum levels of potassium and sodium, it is usually not recommended for patients with chronic renal failure, ischemic heart disease or cirrhosis, who frequently undergo SBCE for investigation of iron deficiency anemia^[25,29,30]. Another recent study evaluated magnesium citrate as preparation for SBCE and did not find differences regarding cleansing efficacy or rate of complete small bowel examinations^[31]. Simethicone is a detergent substance which can reduce the surface tension of air bubbles, thereby leading to their disruption. It is generally used to treat patients with symptoms caused by excess gas in the intestinal tract. Lately, it has also been shown to improve the quality of visualization of SBCE, although its effect on diagnostic yield remains controversial^[32-36]. Conversely, one other study did not support the use of 2 L of PEG and simethicone solution before SBCE^[37]. The recommended regimen for simethicone administration in this context has not been standardized.

In our study, we designed a control arm (Group A) corresponding to the current standard recommendations of liquid diet and overnight fast prior to SBCE and

aimed to compare the outcomes with those obtained when a purgative (PEG) was added to the preparation protocol (Group B). We also aimed to analyze if the addition of simethicone before swallowing the capsule (Group C) would carry any additional benefit. In this study, PEG or simethicone did not interfere with GET, SBTT, proportion of complete small bowel explorations or the diagnostic yield. We looked at the patients with acceptable small bowel cleansing, defining it as at least 50% of the mucosa with perfect condition for visualization, and there was a trend favoring Group B in this setting (Group A: 65%; Group B: 83.3%; Group C: 68.4%), although the differences were not statistically significant. However, if we look for those patients with an adequate small bowel cleansing, we could not find any significant difference between groups (Group A: 25%; Group B: 27.8%; Group C: 21.1%). Nonetheless, there was a trend favoring Group C in terms of attaining excellent cleansing (Group A: 10%; Group B: 16.7%; Group C: 21.1%), although not statistically significant. Our results for adequate cleansing were somewhat lower than those reported in other studies^[3,15,16], which may be due to different methodologies and a subjectivity in the assessment of endoscopic cleansing criteria. Our methodology included the use of a stopwatch to accurately determine the proportion of the mucosa under perfect cleansing conditions. Furthermore,

each exam was assessed by two experienced endoscopists and when there was no agreement, the images were reviewed until a consensus was achieved. Interestingly, when we focus specifically on patients with a significant amount of bubbles, felt by the reader to be sufficient to hamper a reliable interpretation of the endoscopic images, the subanalysis between groups in a head to head comparison showed that the proportion of those patients in Group C, where simethicone was used, was significantly lower than in Group A, where patients underwent standard preparation with liquid diet and overnight fast prior to SBCE (15.8% *vs* 50% ($P = 0.026$)).

In conclusion, this study shows that the use of simethicone before swallowing the capsule may reduce intraluminal bubbles in patients who were administered a purgative (PEG) the evening before the procedure when compared to standard preparation with clear diet and overnight fast before SBCE. Furthermore, there was a trend favoring the use of PEG to achieve a larger proportion of acceptable small bowel cleansing, and reduce the number of exams with poor cleansing, where the amount of fluid or debris may preclude a reliable interpretation. Moreover, there was also a trend towards obtaining excellent cleansing when protocol C was followed, although it was not statistically significant. This study has the limitation of not being designed to assess the outcomes of simethicone without the administration of concomitant purgative. To conclude, in our opinion, the preparation with 2 L of PEG the evening before SBCE, associated with the administration of 100 mL simethicone before capsule ingestion, seems to provide better conditions for the visualization of the small bowel mucosa when compared to the currently recommended preparation regimen and should be considered in patients who will undergo SBCE.

COMMENTS

Background

It has been over 10 years since small bowel capsule endoscopy (SBCE) was approved for clinical practice; however, the usefulness of routinely performing bowel preparation prior to SBCE still remains a matter of debate. To date, no standardized protocol has been widely accepted and overnight fasting remains the standard preparation for SBCE.

Research frontiers

It remains controversial whether the quality of mucosal visualization, diagnostic yield, gastric emptying time (GET), small bowel transit time (SBTT) and rate of complete small bowel explorations may be optimized with the use of a specific cleansing protocol prior to SBCE, with conflicting results being reported in the literature. This study aimed to evaluate whether the use of polyethylene glycol (PEG), with or without simethicone prior to capsule ingestion, may be useful in this context.

Innovations and breakthroughs

Bowel preparation with 2 L of PEG the evening before the procedure may improve small bowel cleansing and the quality of visualization, when compared to the currently recommended preparation regimen of overnight fasting. The additional use of 100 mg simethicone prior to capsule ingestion may further reduce intraluminal bubbles.

Applications

SBCE may have considerable limitations when the visualization is impaired by bubbles, bile, intraluminal fluid and debris. Since it is a costly and time consuming procedure, the adoption of a standardized regimen that may be able to opti-

mize the quality of visualization is needed. Though the results of these trial are encouraging, the role of PEG and simethicone in this setting should be further investigated in larger controlled studies.

Terminology

PEG (macrogol) is a polymer of ethylene oxide that works as an osmotically acting laxative. Simethicone is a mixture of polydimethylsiloxane and silicon dioxide that decreases the surface tension of gas bubbles and is used as an oral anti-foaming agent.

Peer review

The authors compared the quality of mucosal visualization, diagnostic yield, GET, SBTT and rate of complete explorations using three different cleansing protocols prior to SBCE, with the conclusion that preparation with 2 L of PEG before SBCE may improve small bowel cleansing and the quality of visualization and simethicone may further reduce intraluminal bubbles. This article elucidated the usefulness of bowel preparation prior to SBCE which can be used in clinical practice.

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Incidental finding of esophageal pneumatosis

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Abstract

Pneumatosis of the gastrointestinal tract is a rare condition characterized by the presence of air filled cavities in the gastrointestinal tract wall. Its occurrence has been described throughout the gastrointestinal tract from the esophagus to the rectum, however it is most commonly reported in the small intestine. Despite multiple case reports in literature, its pathogenesis still remains unclear. Pneumatosis may be idiopathic or associated with a variety of disorders namely peptic ulcer disease, jejunoileal bypass, intestinal obstruction and non-gastrointestinal disorders like asthma, chronic obstructive pulmonary disease, systemic lupus erythematosus, infectious enteritis, *etc.* We here present a rare case of pneumatosis of the esophagus diagnosed incidentally at an esophagogastroduodenoscopy (EGD). A 78-year-old asymptomatic woman underwent EGD and colonoscopy at our hospital for evaluation of anemia. Few months prior to EGD, she had undergone excision of laryngocele at our hospital. EGD revealed extensive submucosal blebs distributed throughout the esophagus, otherwise unremarkable stomach and duodenum. Colonoscopy showed a tubular adenomatous polyp. Since our patient was asymptomatic she did not require any surgical intervention. Management of pneumatosis depends on the underlying cause.

INTRODUCTION

Pneumatosis of the gastrointestinal tract is well known in medical literature. It is characterized by the presence of air filled spaces in the submucosa and subserosa.

It can appear in different locations in the gastrointestinal tract from the esophagus to the rectum, but more commonly the small bowel is involved^[1-4]. Pneumatosis of the gastrointestinal tract can be symptomatic or completely asymptomatic, where it is detected incidentally during endoscopy or autopsy. Clinical manifestations are variable and depend on the underlying clinical condition and the site of gastrointestinal tract involved. Commonly reported gastrointestinal symptoms include retrosternal chest pain, abdominal pain and gastrointestinal bleed. Initial evaluation of pneumatosis should be focussed on ruling out acute abdomen or sepsis and identification of the underlying pathology.

Pneumatosis involving the esophagus is a relatively rare condition. Ever since the first description of pneumatosis in medical literature about three centuries ago, only eight case reports of esophageal pneumatosis have been reported so far. We here report the ninth case of esophageal pneumatosis found incidentally on an esophagogastroduodenoscopy (EGD).

CASE REPORT

A 78-year-old African American woman was seen in our gastroenterology clinic for evaluation of anemia.

Table 1 Vital signs on initial examination

Vital signs	
Temperature	98.2°F
Blood pressure	208/103 mmHg
Pulse rate	108 beats per minute
Respiratory rate	20 breaths per minute
Oxygen saturation	95% (breathing ambient air)

Table 2 Laboratory findings

Laboratory values	
Hematocrit	38.90%
White blood cell count	7800/mm ³ (77% neutrophils and 13% lymphocytes)
Platelet count	229 000/μL
Prothrombin time	11.8 s
Activated partial thromboplastin time	26.4 s
Serum sodium	137 mEq/L
Serum potassium	3.6 mEq/L
Serum blood urea nitrogen	13 mg/dL
Serum creatinine	1.5 mg/dL
Serum total protein	6.9 g/dL
Serum albumin	3.3 g/dL
Serum alanine aminotransferase	13 U/L
Serum aspartate transaminase	25 U/L
Serum total bilirubin and direct bilirubin	1.2 mg/dL, 0.7 mg/dL
Serum creatine kinase	225 U/L
Hepatitis panel	Hepatitis C antibody positive Hepatitis B antigen negative

Five months before evaluation in the gastroenterology clinic, she was admitted to our hospital with symptoms of right-sided neck pain, dysphagia and sore throat of three days duration. She denied any shortness of breath, drooling of saliva, cough or chest pain. She reported no weight loss, fever or sick contacts.

Her medical history included diabetes mellitus, hypertension, sickle cell trait and chronic hepatitis C. She had no known allergies. She had smoked 1 pack per day for the past 50 years and had quit a year ago. She denied any alcohol or substance abuse.

She denied having any surgery in the past and her family history was unremarkable.

Initial vital signs and laboratory findings have been summarized in Tables 1 and 2 respectively. General physical examination showed a firm, nontender, non-mobile mass on the right side of the neck. Thyroid gland was normal on examination as was the remainder of the examination.

Chest radiograph was normal. Computed tomography (CT) of neck soft tissue was obtained after intravenous contrast which revealed uniformly hypodense, loculated collection with well demarcated thin enhancing margin measuring 3.8 cm × 2.5 cm × 4.2 cm bordering the right oropharynx and extended from the palatine tonsils to the tip of the esophagus (Figure 1). Displacement of the upper air passage towards the left side was also noted.

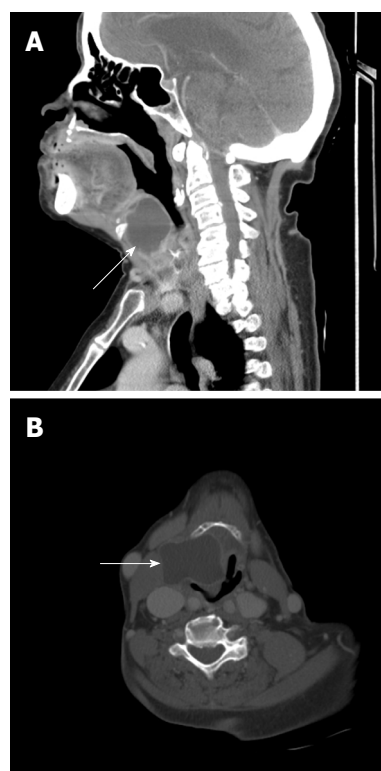


Figure 1 Computed tomography neck soft tissue. A: Sagittal view of neck soft tissue (arrow); B: Transverse view of neck soft tissue (arrow).

Patient was evaluated by ear nose and throat surgeon and was taken to operating room for excision of a possible infected laryngocele through a laryngotomy approach. Intraoperatively, approximately 5 cm × 7 cm cystic mass involving the larynx extending from the hyoid bone to the thyroid cartilage on the right side was noticed. The cyst extended through the thyrohyoid area into the larynx and communicated with the laryngeal vestibule. There was significant edema and fullness of the right aryepiglottic fold and supraglottic larynx, which obstructed view of the glottic airway. The patient required fiberoptic intubation for achieving general anesthesia.

After excision, a membranous saccular tissue measuring 4 cm × 2.8 cm × 0.3 cm was submitted for a pathological diagnosis, which later revealed respiratory epithelium-lined membranous fibrous tissue consistent with laryngocele (Figure 2). Pathological examination of the purulent fluid submitted with the laryngocele revealed acute inflammatory cell infiltrate comprising polymorphs, macrophages and cellular debris, and these features were suggestive of an abscess.

After the procedure, patient remained intubated with respiration supported on positive pressure mechanical ventilation for 11 d. Postoperative course was otherwise uneventful and patient was discharged home after a hospital stay of 2 wk.

Four months after discharge from the hospital, she was asymptomatic and seen in the clinic for evaluation of anemia. Upper gastrointestinal endoscopy was done which incidentally showed extensive submucosal blebs of

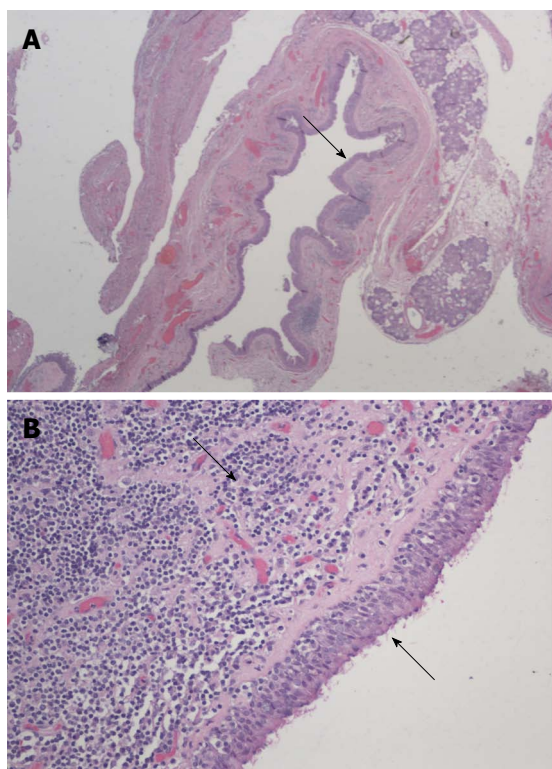


Figure 2 Hematoxylin and eosin stain. A: The respiratory epithelium lined membranous fibrous tissue (arrow) consistent with laryngocele (low power magnification); B: The laryngocele wall showing focal chronic inflammation and reactive lymphoid aggregates (arrows, high power magnification).

the esophagus without any involvement of the stomach (Figure 3). There was gastric erythema with biopsy showing *Helicobacter pylori* gastritis. Colonoscopy was also performed at the same time, which revealed a tubular adenomatous polyp but otherwise unremarkable.

DISCUSSION

Pneumatosis of the gastrointestinal tract was first reported in a cadaver in the year 1730 by Thorpe^[5] and Duvernoi^[6]. Later in the year 1876, pneumatosis intestinalis was reported in humans by Bang^[7]. Since then numerous cases of pneumatosis of the gastrointestinal tract have been described. In 1979, Jamart reported a review of 919 cases of pneumatosis intestinalis and found that pneumatosis of small bowel was predominantly subserous and that of colon was submucosal in location^[8]. Pneumatosis can involve any part of the gastrointestinal tract from the esophagus to the rectum, but has been reported more commonly in small bowel than large bowel. Cases of gastric pneumatosis have also been published but esophageal pneumatosis has been a rare occurrence.

On review of the available medical literature, we found eight cases (Table 3) of esophageal pneumatosis reported till date. Interestingly, most of these cases including our case as well were reported in females except for two cases. Vanasin *et al.*^[9], described the first case of esophageal pneumatosis in a 62 year old woman related

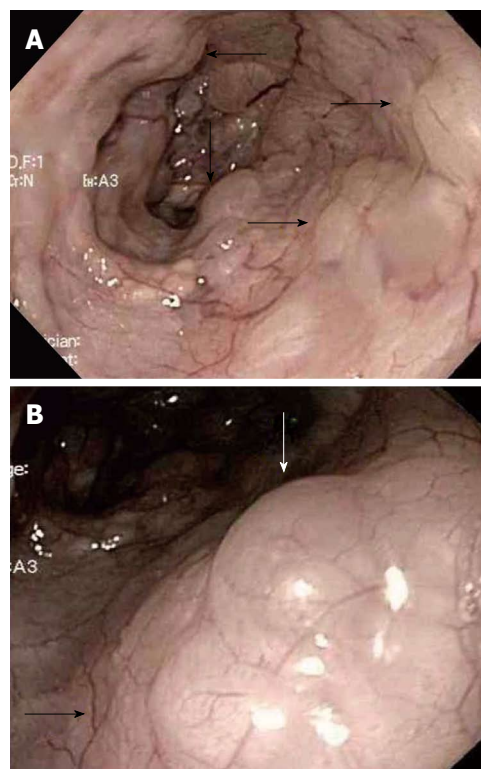


Figure 3 Endoscopic view of the esophagus. A: Endoscopic view of the esophagus showing the submucosal air blebs (arrows) throughout the esophagus; B: Magnified view of the pneumatosis of the esophagus on endoscopy. These air blebs (arrows) were seen throughout the esophagus.

to esophageal stricture. Katz *et al.*^[10] reported three cases of esophageal pneumatosis related to fiberoesophagocopy. Fifth case was described by McKelvie *et al.*^[11] in a 76-year-old man with infectious gastritis. Sixth case in a 74-year-old woman post duodeno-pancreatectomy was published in 1998 by Tixedor *et al.*^[12]. McLaughlin *et al.*^[13] reported the seventh case of esophageal pneumatosis in a 77-year-old man who had underwent resection of cholangiocarcinoma. Yahng *et al.*^[14] reported the eighth case in a 62-year-old woman who developed esophageal pneumatosis post chemotherapy with neutropenia.

Pneumatosis may be idiopathic or may occur secondary to underlying pathological process. These secondary forms of pneumatosis account for about 85% of total cases^[15,16]. Pneumatosis intestinalis has been described in various medical conditions including necrotizing enterocolitis, pyloric stenosis, peptic ulcer disease, jejunoileal bypass, and intestinal obstruction. Besides being described in gastrointestinal disorders, it has also been reported in non-gastrointestinal disorders like asthma, chronic obstructive pulmonary disease, celiac disease, systemic lupus erythematosus, infectious enteritis, acquired immunodeficiency syndrome, primary immunodeficiency, leukemia, organ transplantation and bone marrow transplantation^[3,17].

Despite several cases reported in literature, pathogenesis of pneumatosis remains unclear. Two important theories proposed among several other proposed are mechanical and bacterial theory. According to mechanical

Table 3 Esophageal pneumatosis case reports

Ref.	Age	Sex	Etiology	Treatment	Follow up
Vanasin <i>et al</i> ^[9]	62	F	Esophageal stricture	None	Post mortem diagnosis. Died of aspiration pneumonia
Katz <i>et al</i> ^[10]	85	F	Post esophagoscopy	Surgery	Died in 6 wk
Katz <i>et al</i> ^[10]	46	F	Post esophagoscopy	Surgery	Survived
Katz <i>et al</i> ^[10]	39	F	Post esophagoscopy	Antibiotics	Survived
McKelvie <i>et al</i> ^[11]	76	M	Infection	None	Post mortem diagnosis
Tixedor <i>et al</i> ^[12]	74	F	Post pancreato-duodenectomy	Nasogastric aspiration	Survived
McLaughlin <i>et al</i> ^[13]	77	M	Gastric dilatation	100% oxygen	Survived
Yahng <i>et al</i> ^[14]	62	F	Chemotherapy and neutropenia	Observation	Died in 5 wk due to ARDS

F: Female; M: Male; ARDS: Acute respiratory distress syndrome.

theory, air present in the gastrointestinal tract lumen dissects into the walls of the gastrointestinal tract through a mucosal tear. Bacterial theory proposes that the air entering the walls of bowel is produced by gas forming bacteria in the bowel.

In our patient, we hypothesize that resection of the laryngocele followed by positive pressure ventilation may have predisposed to the formation of the pneumatosis, and hence supporting mechanical theory. Other possible etiology in our patient could be the underlying chronic bronchitis secondary to long standing smoking.

Typically it is an asymptomatic condition as in our patient. However may have a broad spectrum of presentation from an incidental finding to retrosternal chest pain, abdominal pain or septic shock. Symptoms may vary depending upon site of gastrointestinal tract involved.

Work up includes radiographs of the chest and the abdomen. CT, magnetic resonance imaging and barium studies^[3] can also be used, but CT has better sensitivity to detect intramural air^[18,19].

Management largely depends on the underlying etiology. Various treatment modalities have been utilized in the past including oxygen therapy and antibiotic use. Normobaric oxygen therapy, after its first experimental use in 1935, was used successfully for treatment of pneumatosis by Forgacs *et al*^[20]. Later in 1978, the use of hyperbaric oxygen was also shown to be beneficial by Masterson *et al*^[21]. Antibiotic therapy with Metronidazole has also been reported to be efficacious in literature supporting the bacterial theory of genesis^[22].

Algorithm for surgical management of pneumatosis has been suggested by Greenstein *et al*^[23] in cases of obstruction, elevated white cell count, advanced age and portal venous gas. Endoscopic modalities of therapy with cyst puncture and sclerotherapy have also been described^[24]. But with numerous case reports of success with conservative therapy, treatment of pneumatosis essentially remains non-surgical unless acute abdomen is suspected.

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Food impaction in older age: Think about an eosinophilic esophagitis

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Abstract

Eosinophilic esophagitis is an inflammatory condition of esophagus. It is generally seen in childhood and young population. Men are more commonly affected than women. However, it is not common in an advanced age. Eosinophilic esophagitis decreases the ability of the esophagus to stretch and accommodation against foods. Therefore, the major symptom in adults with eosinophilic esophagitis is difficulty in swallowing solid food (dysphagia). Specifically, the food gets stuck in the esophagus after it is swallowed. Less common symptoms include heartburn and chest pain. Because of this, it may be incorrectly diagnosed as a gastroesophageal reflux disease. Here, we reported a case presented with food impaction at advanced age. As a conclusion, eosinophilic esophagitis is a rare entity that must be

remembered in advance aged patients presenting with food impaction.

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Key words: Dysphagia; Eosinophilia; Esophagitis; Food impaction; Allergy

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TO THE EDITOR

Eosinophilic esophagitis is generally seen in childhood and less often in advanced ages. It may be incorrectly diagnosed as gastroesophageal reflux disease. Dysphagia is the most common symptom. In a new report from Western society, eosinophilic esophagitis was reported in 9% of cases presented with food impaction^[1-4]. Eosinophilic esophagitis presented in young adults was rarely reported in our country^[5]. In this report, we reported a case presented with food impaction at advanced age.

A 52-year-old male patient was admitted to the emergency service with complaining of dysphagia and retrosternal pain started after eating. Endoscopy showed impacted food approximately 5-6 cm in diameter in proximal esophagus and was extracted with snare. Because of attended rings in esophagus (Figure 1), histologic samples were taken from mucosa of esophagus for pathologic examination. Eosinophilic infiltration (> 20 eosinophils per high power field) (Figure 2) was revealed in samples taken from esophagus and fluticasone 125 mcg inhaler therapy (3 × 4 puff) was recommended for 6 wk.

Eosinophilic esophagitis is rare entity that must be remembered in advance aged patients presenting with food impaction.

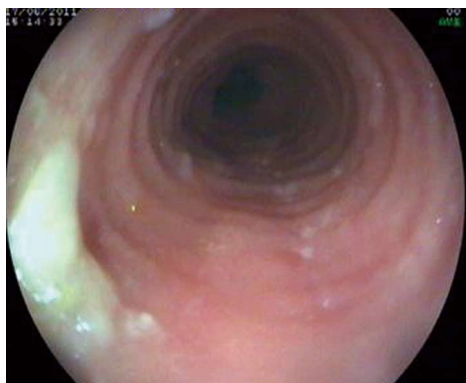


Figure 1 Concentric rings of esophagus in endoscopic examination.

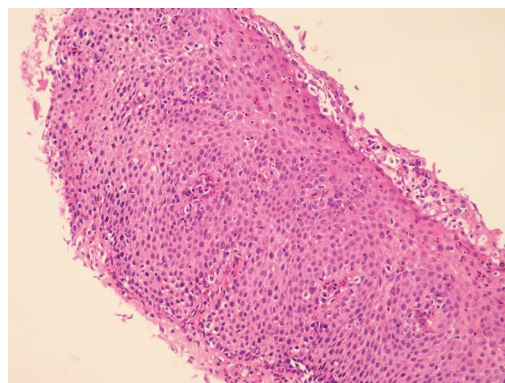


Figure 2 Eosinophilic infiltration with hematoxylin and eosin stain.

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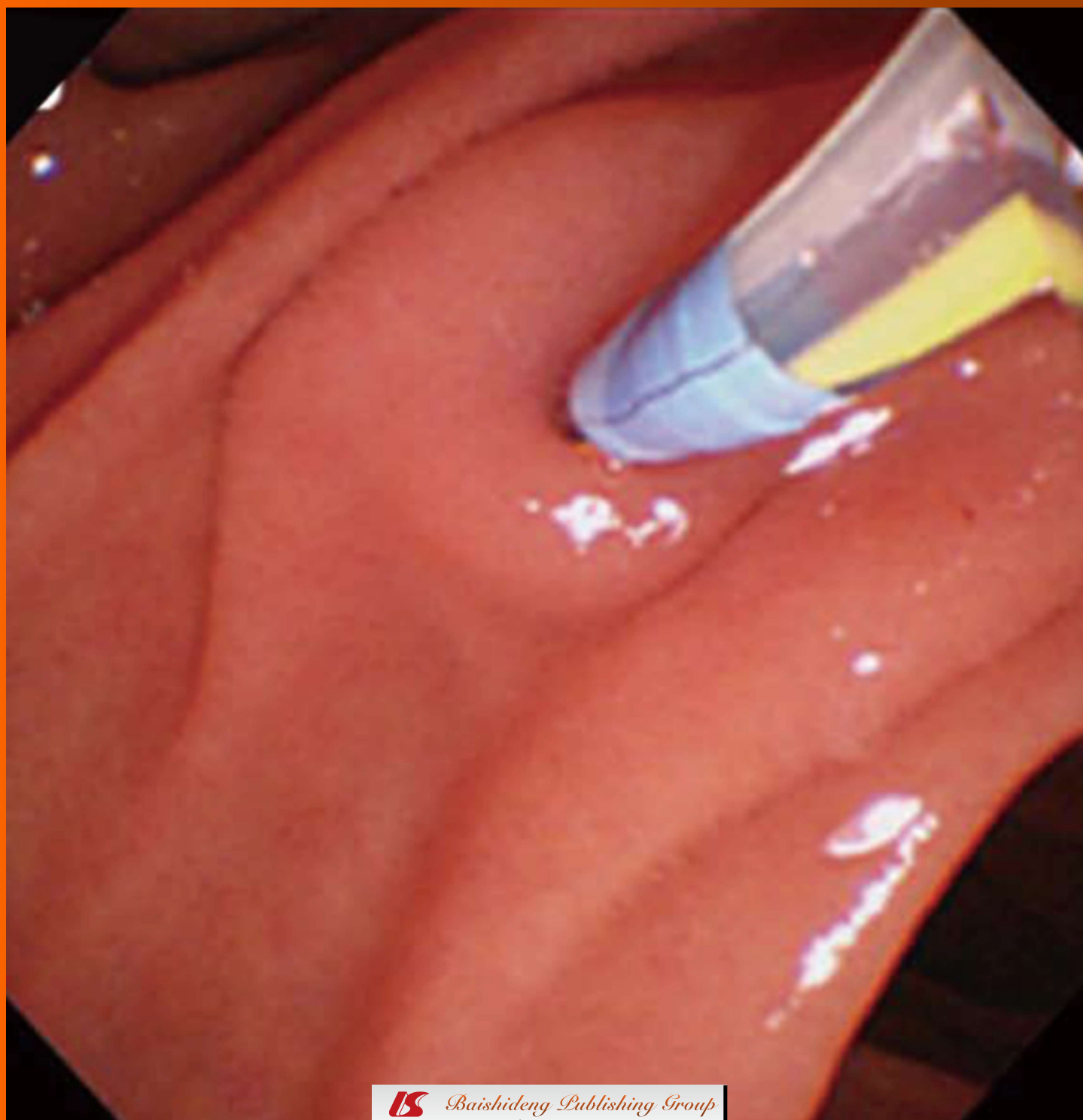
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Fujimori N, Igarashi H, Asou A, Kawabe K, Lee L, Oono T, Nakamura T, Niina Y, Hijioka M, Uchida M, Kotoh K, Nakamura K, Ito T, Takayanagi R. Endoscopic approach through the minor papilla for the management of pancreatic diseases. *World Journal of Gastrointestinal Endoscopy* 2013; 5(3): 81-88
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Endoscopic approach through the minor papilla for the management of pancreatic diseases

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spectively evaluated the clinical profiles of the patients, the endoscopic interventions, short-term outcomes, and complications.

RESULTS: Of 44 ERCPs, 26 were diagnostic ERCP, and 18 were therapeutic ERCP. The most common cause of difficult access to the main pancreatic duct through the major papilla was pancreas divisum followed by distortion of Wirsung's duct. The overall success rate of minor papilla cannulation was 80% (35/44), which was significantly improved by wire-guided cannulation ($P = 0.04$). Endoscopic minor papillotomy (EMP) was performed in 17 of 34 patients (50%) using a needle-knife (13/17) or a pull-type papillotome (4/17). EMP with pancreatic stent placement, which was the main therapeutic option for patients with chronic pancreatitis, recurrent acute pancreatitis, and pancreatic pseudocyst, resulted in short-term clinical improvement in 83% of patients. Mild post-ERCP pancreatitis occurred as an early complication in 2 cases (4.5%).

CONCLUSION: The endoscopic minor papilla approach is technically feasible, safe, and effective when the procedure is performed in a high-volume referral center by experienced endoscopists.

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Key words: Endoscopic papillotomy; Endoscopic retrograde cholangiopancreatography; Minor papilla; Pancreas divisum; Pancreatitis

Abstract

AIM: To clarify the efficacy and safety of an endoscopic approach through the minor papilla for the management of pancreatic diseases.

METHODS: This study included 44 endoscopic retrograde cholangiopancreatography (ERCP) procedures performed in 34 patients using a minor papilla approach between April 2007 and March 2012. We retro-

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INTRODUCTION

The endoscopic approach through the major papilla is generally considered the most common and effective method for the management of pancreatic diseases. However, access to the main pancreatic duct (MPD) through the major papilla is sometimes impossible due to pancreas divisum, distortion of Wirsung's duct, or other causes. When it is difficult to use a major papilla approach in diagnostic or therapeutic endoscopic retrograde cholangiopancreatography (ERCP), cannulation of the minor papilla is attempted as an alternative method^[1]. Endoscopic treatment through the minor papilla, including endoscopic minor papillotomy (EMP) and endoscopic pancreatic stent (EPS) placement, have been developed in previous studies for patients with pancreas divisum^[2-6]. For patients with pancreas divisum and recurrent acute pancreatitis (RAP), endoscopic treatment through the minor papilla is considered an effective therapeutic option^[1]. However, a number of problems associated with these techniques are still unresolved, including the indications for using this approach, the procedures, and the therapeutic efficacy and safety. Therefore, in this study, we reviewed patients who underwent ERCP with a minor papilla approach and evaluated whether this procedure is useful for the management of pancreatic diseases. Herein, we describe a single center experience and review the literature on the endoscopic minor papilla approach.

MATERIALS AND METHODS

Patients

We retrospectively reviewed our ERCP database to find patients who underwent an endoscopic minor papilla approach at Kyushu University Hospital from April 2007 to March 2012. A total of 1418 ERCPs were performed during the study period, and 44 ERCPs using a minor papilla approach in 34 patients were included in the analysis. There were 19 men and 15 women, and the mean age was 55 (range, 13-79) years. The clinical profiles, endoscopic interventions through the minor papilla, short-term outcome, and complications associated with the endoscopic procedures were evaluated for all patients. Post-ERCP pancreatitis (PEP), one of the major complications, was diagnosed on the basis of the criteria proposed by Cotton *et al.*^[7]. PEP was defined as pancreatic pain and hyperamylasemia occurring within 24 h of the procedure. Pancreatic pain was defined as persistent pain in the epigastric or periumbilical region. Hyperamylasemia was defined as an increase in serum amylase level to more than 3 times the upper normal limit^[7,8]. All patients provided written informed consent for ERCP, including endoscopic treatment.

ERCP, minor papilla cannulation and EMP

To achieve sedation and duodenal aperistalsis, patients usually received intravenous midazolam (5 mg), pentazocine (7.5 mg), and glucagon (1 mg). A side-viewing duodenoscope (JF-260V; Olympus Medical Systems, Tokyo,

Japan) was used, and the major papilla was first cannulated with a standard catheter (Tandem XL; Boston Scientific, Boston, MA). When endoscopists judged its access to the MPD through the major papilla difficult due to pancreas divisum, distortion of Wirsung's duct, or other causes, minor papilla cannulation was attempted. For 1 patient without pancreas divisum, in whom a guidewire was passed retrograde into Wirsung's duct *via* the major papilla and antegrade out of the minor papilla, a rendezvous technique was employed^[9,10].

The minor papilla was usually cannulated using a tapered catheter (PR-9Q-1; Olympus Medical Systems) loaded with or without a guidewire (Jagwire; 0.025 inch in diameter, 450 cm in length; Boston Scientific). Since April 2009, we have employed wire-guided cannulation (WGC) to the minor papilla approach. For WGC, a guidewire was advanced into the orifice of the minor papilla, and then the wire was carefully advanced 10-20 mm into Santorini's duct or until any resistance was encountered (Figure 1A and B)^[11]. Subsequently, the cannula was lightly impacted on the minor papilla to obtain a dorsal pancreatogram. After we confirmed the course of Santorini's duct and the distal MPD, we advanced the guidewire and catheter deeply into the tail of the pancreas.

EMP was performed using a needle-knife (RX Needle-knife XL; Boston Scientific) or a pull-type sphincterotome (CleverCut; Olympus Medical Systems, or Autotome; Boston Scientific). A precut papillotomy with the needle-knife over a guidewire was typically performed because the orifice of the minor papilla was usually too small to deeply advance a pull-type sphincterotome (Figure 1C and D). However, when the orifice permitted passage of a pull-type sphincterotome, a standard sphincterotomy was performed (Figure 1E). The extent of the cut was determined by the size of the minor papilla, and generally ranged from 3 to 6 mm.

EPS, endoscopic nasopancreatic drainage and peroral pancreatoscopy through the minor papilla

Following minor papillotomy, a 5 Fr to 7 Fr EPS (Geenen pancreatic stent, 5 to 9 cm in length; Cook Medical, Winston-Salem, NC) was inserted through the minor papilla as a therapeutic option. An endoscopic nasopancreatic drainage (ENPD) tube (5 Fr; Cook Medical) was inserted through the minor papilla for repeated cytology in diagnostic ERCP, or for pancreatic pseudocyst drainage in therapeutic ERCP. Peroral pancreatoscopy (POPS) (Spy-Glass; Boston Scientific) through the minor papilla was performed for the diagnosis of a patient with main-duct type intraductal papillary mucinous neoplasm (IPMN).

Statistical analysis

Fisher's exact test was used for statistical analysis. A *P* value of less than 0.05 was considered statistically significant.

RESULTS

Clinical profiles of the patients

From April 2007 to March 2012, 44 ERCPs through the

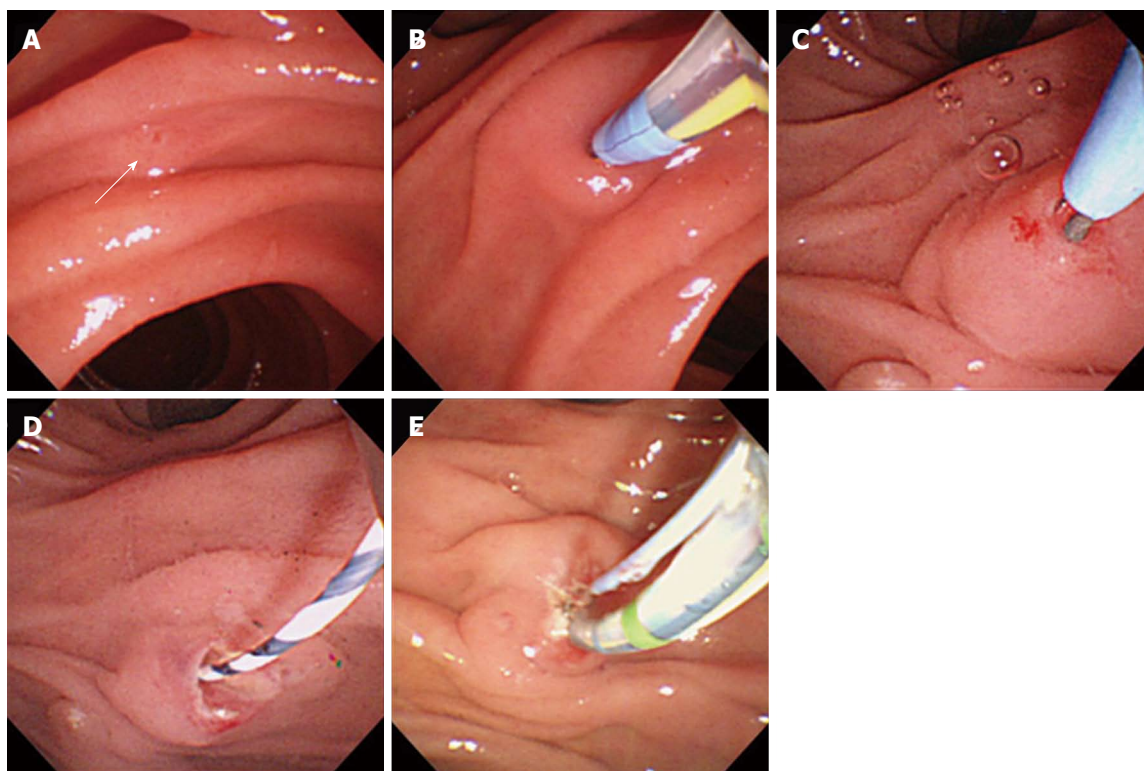


Figure 1 Minor papilla cannulation and endoscopic minor papillotomy. A: Endoscopic features of the minor papilla (arrow); B: Minor papilla cannulation using wire-guided cannulation; C: Endoscopic minor papillotomy with a needle-knife; D: Endoscopic view after minor papillotomy with a needle-knife; E: Endoscopic minor papillotomy with a pull-type sphincterotome.

minor papilla were attempted in 34 patients at our institution. Patient characteristics and procedure indications are summarized in Table 1. A total of 1418 ERCPs were performed in our department during the study period; therefore, the rate of approach through the minor papilla was 3.1%. Pancreas divisum was the most common cause of difficult access to the MPD through the major papilla (45%) (Figure 2). Of the 20 cases with pancreas divisum, 17 were complete pancreas divisum and 3 were incomplete pancreas divisum. Other causes of difficult access besides pancreas divisum were, in descending order, distortion (Figure 3), stenosis, and compression of Wirsung's duct (Table 1). In these cases, a guidewire could not be advanced through the major papilla to the MPD in the tail of the pancreas (Figure 3B and D). Of the 44 ERCPs, 26 were diagnostic (59%) and 18 were therapeutic (41%). The most common indication for diagnostic ERCP was pancreatic cystic neoplasm, such as IPMN. Other indications were autoimmune pancreatitis (AIP), pancreas divisum, RAP, and pancreatic mass, *etc.* In 3 cases with pancreatic masses, including pancreatic cancer, pancreatic neuroendocrine tumor, and metastatic pancreatic tumor, it was difficult to make a definite diagnosis by endoscopic ultrasound (EUS) or EUS-guided fine-needle aspiration, and we consequently performed diagnostic ERCP in these patients. Of the 19 diagnostic ERCP cases with successful cannulation of the minor papilla, 8 included a diagnostic pancreatogram only, 11 underwent aspiration of pure pancreatic juice for cytologic examination,

including 4 cases with placement of an ENPD tube for repeated cytology, and 2 cases underwent POPS through the minor papilla and pancreatic juice cytology for the evaluation of main-duct type IPMN. In addition, therapeutic ERCP was performed in patients with chronic pancreatitis (CP), RAP, pancreatic pseudocysts, or MPD injury due to pancreatic trauma. EMP was performed in 17 of 34 patients (50%) with naive minor papilla by using a needle-knife (13 cases) or pull-type papillotome (4 cases).

Minor papilla cannulation

Minor papilla cannulation was successful in 35 of 44 ERCPs (80%). After we included WGC in the minor papilla approach in April 2009, the success rate of cannulation showed significant improvement (conventional contrast cannulation *vs* WGC = 50% *vs* 86%, $P = 0.04$) (Table 2). Application of WGC to the minor papilla may be useful as well as biliary cannulation.

Intervention through the minor papilla and short-term outcomes of therapeutic ERCP

The clinical profiles of the 13 patients who underwent 18 sessions of therapeutic ERCP are summarized in Table 3. Therapeutic procedures were completed in 16 of 18 cases (89%). Of the 16 therapeutic ERCP cases with completed treatment procedures, 11 underwent minor papillotomy with placement of an EPS or ENPD tube. One case received balloon dilation of the minor papilla

Table 1 Patient demographics and procedure indications

Number of patients	34
Mean age (range)	55 (13–79)
Male/female	19/15
Patients with pancreas divisum	16
ERCP sessions through the minor papilla	44
Total ERCPs during the study period	1418
Rate of minor papilla approach	3.10%
Causes of difficult access through the major papilla	44
Pancreas divisum (complete/incomplete)	20 (17/3)
Distortion of Wirsung's duct	16
Stenosis or compression of Wirsung's duct	6
Other	2
Diagnostic ERCP	26
Indications	
Cystic neoplasm (IPMN/ MCN/ SCN)	7 (5/1/1)
AIP	5
Pancreas divisum	4
RAP	5
Pancreatic mass	3
Others	2
Pancreatic juice cytology (with ENPD/ with POPS)	11 (4/ 2)
Therapeutic ERCP	18
CP	8
RAP	5
Pancreatic pseudocyst	4
Pancreatic trauma	1
Minor papillotomy	17
Needle-knife	13
Pull-type papillotome	4

ERCP: Endoscopic retrograde cholangiopancreatography; IPMN: Intraductal papillary mucinous neoplasm; MCN: Mucinous cystic neoplasm; SCN: Serous cystic neoplasm; AIP: Autoimmune pancreatitis; CP: Chronic pancreatitis; RAP: Recurrent acute pancreatitis; ENPD: Endoscopic nasopancreatic drainage; POPS: Peroral pancreatoscopy.

following a minor papillotomy, and 4 cases underwent exchange or removal of an EPS. In 1 case, it was difficult to perform the endoscopic treatment due to a MPD injury resulting from pancreatic trauma because a guidewire could not be advanced to the pancreatic tail.

Of the 16 cases in which therapeutic procedures were completed, 15 (94%) achieved short-term improvement, *i.e.*, pain relief in patients with CP, no recurrence in patients with RAP, or effective drainage in patients with pseudocyst. In 1 case of pancreatic pseudocyst, although an ENPD tube was successfully inserted into the pseudocyst through the minor papilla, the infection was not controlled. He underwent a surgical procedure (pseudocyst-jejunostomy), which resulted in immediate improvement. As a result, clinical improvement was achieved in 83% (15/18) of all therapeutic ERCP sessions.

Complications

There were no complications, such as bleeding or perforation, related to minor papillotomy or balloon dilation. However, 2 cases (4.5%) developed mild PEP. One case was a diagnostic ERCP for AIP and only a diagnostic pancreatogram was performed. The other was a therapeutic ERCP for a patient with RAP who underwent a minor papillotomy plus pancreatic stent placement through the minor papilla. In both cases, cannulation

Table 2 Success rate of minor papilla cannulation

	Success	Failure	Total	Success rate	P value
Before April 2009 (CC)	4	4	8	50%	0.04
After April 2009 (WGC)	31	5	36	86%	0.04
Total	35	9	44	80%	

CC: Conventional contrast cannulation; WGC: Wire-guided cannulation.

and contrast injection were attempted through the major papilla prior to the minor papilla approach. Conservative treatment promptly resolved PEP in both cases. No other complications, including problems in stent placement (migration or occlusion), occurred in the present study.

DISCUSSION

Endoscopic diagnosis or treatment of pancreatic diseases is usually performed through the major papilla. However, the major papilla approach is sometimes difficult for patients with pancreas divisum or distortion of the MPD. In those patients, an approach through the minor papilla is attempted as the only alternative for the management of pancreatic diseases, although minor papilla cannulation remains challenging even for experienced endoscopists. Inui *et al.*^[12] reported that an endoscopic approach through the minor papilla requires superior endoscopic skills, and the number of patients who require these procedures is relatively small, which should limit the use of this approach to select institutions with appropriate expertise. In this study, we reviewed patients who underwent procedures using an endoscopic minor papilla approach at our institution, evaluated the content, safety and outcome of this procedure.

In this study, minor papilla cannulation was successful in 35 of 44 ERCPs (80%). This result is lower than previously reported, as shown in Table 4.

However, the cannulation success rate improved after we employed a WGC technique (50% to 86%). Wire-guided biliary cannulation has recently attracted attention, and meta-analyses of randomized controlled trials (RCT) have demonstrated a higher cannulation success and lower PEP when a wire-guided technique is used, than with conventional contrast methods^[13,14]. However, the number of studies on the application of WGC to the minor papilla is very limited. Maple *et al.*^[11] reported that physician-controlled WGC in the minor papilla approach is an effective and safe technique. In agreement with the previous study, WGC or wire-assisted cannulation in the minor papilla approach improved the success rate. Although skill development due to the high number of patients may be another reason for the cannulation success rate improvement, application of WGC to the minor papilla approach may be useful as well as biliary cannulation. Maple *et al.*^[11] also stated that a highly experienced assistant was required for wire management. At our institution, 2 experienced endoscopists usually perform this procedure; 1 handles the endoscope while the other assists with the guidewire. We believe that insertion of the

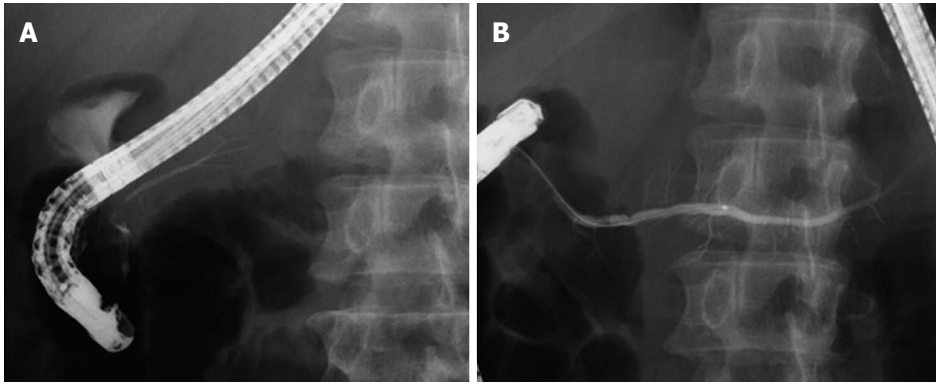


Figure 2 Endoscopic retrograde pancreatography in a patient with pancreas divisum. A: Pancreatogram via the major papilla showing a short ventral pancreatic duct tapering into small side branches; B: Pancreatogram via the minor papilla showing a dorsal pancreatic duct without a connection to the ventral pancreatic duct, indicating complete pancreas divisum.

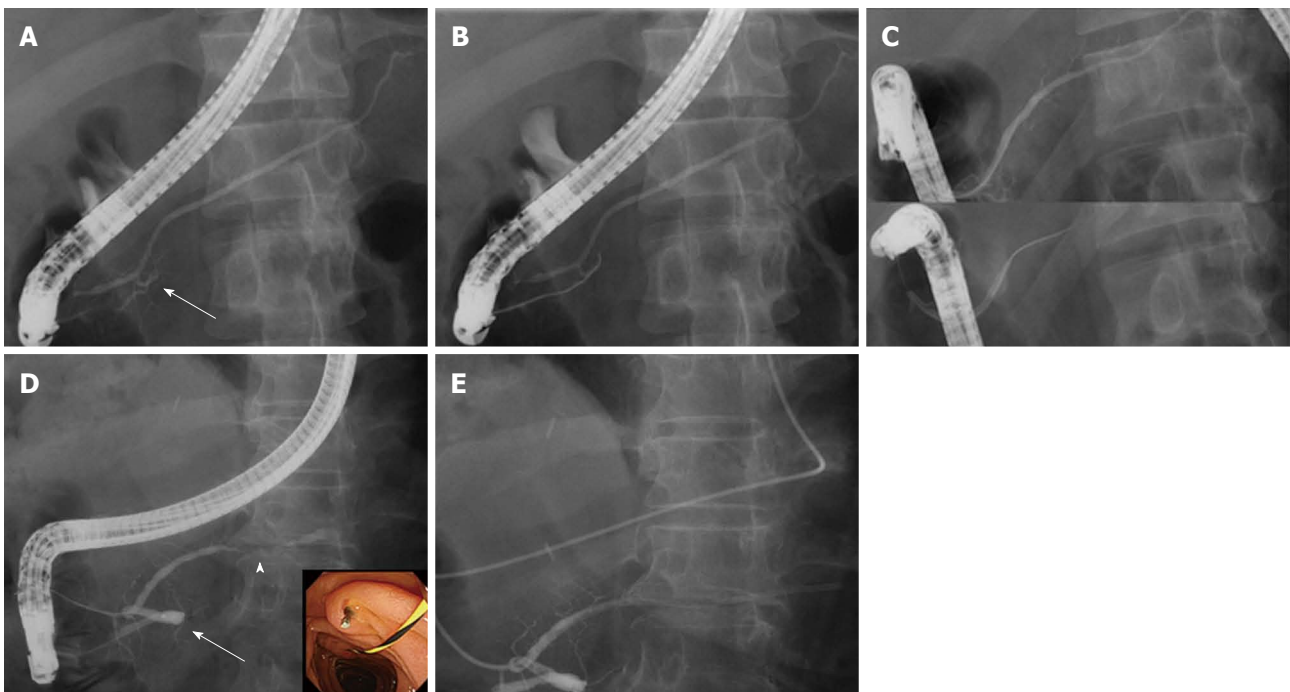


Figure 3 Endoscopic retrograde pancreatography in a patient with a distortion of Wirsung's duct. A-C: A patient with recurrent acute pancreatitis; A: Pancreatogram via the major papilla showing a distorted Wirsung's duct (arrow); B: A guidewire could not be advanced along the main pancreatic duct (MPD) from the body to tail of the pancreas through the major papilla; C: Pancreatogram via the minor papilla. A guidewire could be advanced to Santorini's duct and the distal MPD through the minor papilla (upper row). An endoscopic pancreatic stent was inserted through the minor papilla after minor papillotomy (lower row); D, E: A patient with a metastatic pancreatic tumor; D: Pancreatogram via the major papilla showing stenosis of the MPD in the body of the pancreas (arrowhead). However, a guidewire could not be advanced to the distal MPD due to distortion of Wirsung's duct (arrow). The guidewire inserted through the major papilla entered duodenum via the minor papilla, and was confirmed by an endoscopic view; E: An endoscopic nasopancreatic drainage tube was inserted through the minor papilla after minor papilla cannulation using a rendezvous technique.

guidewire into Santorini's duct is the most important step during the procedure, and it requires close corporation between the endoscopist manipulating the catheter and the assistant advancing the guidewire^[12].

A summary of this study and recently published data on the minor papilla approach is shown in Table 4^[2-6,9,11,15-17]. Most patients had pancreas divisum, which is the most common anatomical variation affecting the pancreatic ductal system^[1]. Although most patients with pancreas divisum demonstrate no symptoms, relative

outflow obstruction of the minor papilla and increased ductal pressure may result in pancreatitis, such as CP and RAP, which require surgical or endoscopic treatment^[2]. Many studies have demonstrated the benefit of minor papillotomy for patients with pancreas divisum and RAP, with response rates as high as 90%^[6,18,19]. In this study, 4 patients with pancreas divisum underwent minor papillotomy as a therapeutic option (Table 3) and all of them clinically responded, that is, they experienced pain relief or no recurrence of AP. Although we only obtained

Table 3 Patient characteristics and short-term outcomes of therapeutic interventions through the minor papilla

Patients	Age/sex	Session	Disease	Causes of difficult access through the major papilla	Intervention	Technical success/failure	Short-term outcome	Complication
1	13/F	1	Trauma	MPD injury		Failure	NA	None
2	62/M	2	Pseudocyst	Compression of WD	EMP + ENPD	Success	Appropriate drainage	None
		3	Pseudocyst	Compression of WD	Exchange of EPS	Success	Appropriate drainage	None
		4	Pseudocyst	Compression of WD	Removal of EPS	Success	Collapse of pseudocyst	None
3	69/M	5	CP	Distortion of WD	EMP + EPS	Success	Pain relief	None
4	36/M	6	CP	Distortion of WD	EMP + EPS	Success	Pain relief	None
5	69/M	7	CP	Divisum	EMP + EPS	Success	Pain relief	None
		8	CP	Divisum	Balloon dilation	Success	Pain relief	None
6	64/M	9	Pseudocyst	Compression of WD	EMP + ENPD	Success	Ineffective ¹	None
7	40/M	10	RAP	Stenosis of WD	EMP + EPS	Success	Appropriate drainage	PEP
		11	RAP	Stenosis of WD	Exchange of EPS	Success	No recurrence	None
8	36/M	12	RAP	Divisum	EMP + ENPD	Success	Appropriate drainage	None
		13	RAP	Divisum	Exchange of EPS	Success	No recurrence	None
9	62/M	14	CP	Divisum	EMP + EPS	Success	Pain relief	None
10	74/M	15	CP	Divisum	EMP + EPS	Success	Pain relief	None
11	42/M	16	CP	Distortion of WD		Failure	NA	None
12	68/F	17	CP	Distortion of WD	EMP + EPS	Success	Pain relief	None
13	68/M	18	RAP	Distortion of WD	EMP + EPS	Success	No recurrence	None

¹Required a surgical procedure. F: Female; M: Male; CP: Chronic pancreatitis; RAP: Recurrent acute pancreatitis; MPD: Main pancreatic duct; WD: Wirsung's duct; EMP: Endoscopic minor papillotomy; EPS: Endoscopic pancreatic stent; ENPD: Endoscopic nasopancreatic drainage; PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; NA: Not available.

Table 4 Review of recently published data on an endoscopic approach through the minor papilla

Ref.	No. of patients	Disease	Divisum	Cannulation method	Cannulation success	Intervention	Improvement	PEP
Borak <i>et al</i> ^[2]	113	RAP	100%	NA	NA	EMP + EPS	62%	10.60%
Maple <i>et al</i> ^[3]	64	RAP	100%	Endoscopists' preference	85	EMP + EPS	NA	14%
Chacko <i>et al</i> ^[4]	57	RAP/CP	100%	Tapered catheter and guidewire	86	EMP + EPS	58%	10.70%
Attwell <i>et al</i> ^[5]	184	CP	100%	Tapered catheter	NA	EMP + EPS	72%	6.50%
Song <i>et al</i> ^[6]	11	CP	0%	Rendezvous technique or CC	91	EMP + ENPD, ESWL	91%	0%
Heyries <i>et al</i> ^[6]	24	RAP	100%	Tapered catheter and guidewire	NA	EMP 8, EMP + EPS 16	92%	12.50%
Maple <i>et al</i> ^[11]	25	RAP	88%	Physician-controlled WGC	96	EMP + EPS	NA	12%
Gerke <i>et al</i> ^[13]	53	RAP	100%	NA	NA	EMP	60.40%	11.20%
Ertan <i>et al</i> ^[16]	25	RAP	100%	Tapered catheter and guidewire	74	Dilation	76%	0%
Boerma <i>et al</i> ^[17]	16	CP	100%	NA	NA	EPS with/without EMP	69%	6.30%
This study	34	RAP/CP	45%	WGC or CC	80	EMP + EPS	83%	4.50%

PEP: Post-endoscopic retrograde cholangiopancreatography pancreatitis; RAP: Recurrent acute pancreatitis; CP: Chronic pancreatitis; WGC: Wire-guided cannulation; CC: Conventional contrast cannulation; EMP: Endoscopic minor papillotomy; EPS: Endoscopic pancreatic stent; ENPD: Endoscopic nasopancreatic drainage; ESWL: Extracorporeal shock wave lithotripsy; NA: Not available.

short-term outcomes, clinical improvement was achieved in 83% of all therapeutic procedures, which is nearly equal to that in previous studies, as shown in Table 4. Endoscopic intervention through the minor papilla can be an effective therapeutic option when it is difficult to access the MPD through the major papilla.

Several previous studies of endoscopic intervention through the minor papilla have reported an early complication rate with PEP of 10% to 14%^[2-4,6,11,15]. Another report by Moffatt revealed that patients with pancreas divisum undergoing minor papilla cannulation with or without minor papillotomy should be considered at high risk for PEP (10.2% with papillotomy and 8.2% without)^[20]. Therefore, endoscopic minor papilla intervention is regarded as somewhat more hazardous than typical ERCP techniques^[5]. Minor papillotomy is usually performed using either a needle-knife or pull-type sphincterotome,

however, which of these techniques is better remains uncertain. Attwell *et al*^[5] reported that both techniques are equally safe and effective. At our institution, the needle-knife technique is used more often because the orifice of the minor papilla is usually too small to allow a pull-type sphincterotome to advance too deeply. We performed minor papillotomy with both techniques being careful not to cut too much, and the incision range was usually determined within the orifice of the minor papilla. Therefore, no major complications directly related to the incision such as bleeding and perforation were encountered. On the other hand, early complications with PEP occurred in 4.5% (2/44) of procedures in the present study. Both cases with PEP underwent major papilla cannulation and contrast injection prior to the minor papilla approach. In 1 case, a diagnostic ERCP was performed for AIP, and an EPS was not inserted through the minor

papilla after ERCP. In the other case, a therapeutic ERCP was performed for RAP with minor papillotomy and EPS placement through the minor papilla. His pancreatogram revealed stenosis of Wirsung's duct; therefore, the PEP may be related to the major papilla cannulation and contrast injection. Major papilla cannulation in these cases is inevitable because unanticipated findings of pancreas divisum or distortion of Wirsung's duct may be revealed during ERCP; however, the procedure should be performed with greater caution. We should also consider prophylactic pancreatic stent placement through the minor papilla, even in diagnostic ERCP, for the prevention of PEP^[8,21]. No other complications, such as bleeding or perforation, were observed in this study. Although this study was small compared to previous studies, the results were favorable. We believe that the endoscopic minor papilla approach is technically feasible and safe when performed in a high-volume referral center by experienced endoscopists.

This study confirmed the feasibility, benefit of WGC, and safety of endoscopic intervention through the minor papilla for the management of pancreatic diseases. However, a number of limitations must be considered while evaluating the results of this study. For example, these data were obtained in a retrospective study, not a comparative study. We only described a single-center experience; therefore, the number of patients was small, and may be inadequate to compare the therapeutic effects with different procedures for various pancreatic diseases. However, it is difficult to design a large-scale RCT due to the relatively small number of patients requiring a minor papilla approach. Nonetheless, further large-scale studies are required to definitively assess the efficacy of endoscopic interventions through the minor papilla in the management of pancreatic diseases.

COMMENTS

Background

When an endoscopic approach through the major papilla is difficult because of pancreas divisum, distortion of Wirsung's duct, or other causes, the minor papilla approach is attempted as the alternative for the management of pancreatic diseases. However, the efficacy and safety of this procedure is not fully understood.

Research frontiers

Minor papilla cannulation is challenging even for experienced endoscopists. Several previous studies revealed the success rate of minor papilla cannulation as approximately 70%-90%. Although the usefulness of wire-guided cannulation (WGC) for biliary tract has been reported, the number of studies on the application of WGC to the minor papilla is very limited. From the point of view of the endoscopic treatment through the minor papilla, several studies have demonstrated the benefit of minor papillotomy or endoscopic pancreatic stent placement in patients with pancreas divisum. However, endoscopic minor papilla intervention is regarded as somewhat more hazardous than typical endoscopic retrograde cholangiopancreatography (ERCP) techniques because of the high rates of post-ERCP pancreatitis (PEP).

Innovations and breakthroughs

In this study, the most common cause for difficult access to the main pancreatic duct through the major papilla was pancreas divisum followed by distortion of Wirsung's duct. The overall success rate of minor papilla cannulation was 80%, which showed significant improvement with WGC. Endoscopic minor papillotomy with pancreatic stent placement, which was the main therapeutic option for

patients with chronic pancreatitis, recurrent acute pancreatitis, and pancreatic pseudocyst, resulted in short-term clinical improvement in 83% of patients. Mild PEP occurred as an early complication in 2 cases (4.5%). The authors could obtain the feasible results of clinical improvement and complications compared to previous studies.

Applications

Application of WGC to the minor papilla approach may be as useful in biliary cannulation as well. The best candidates for endoscopic interventions through the minor papilla are patients with symptomatic pancreas divisum. The endoscopic minor papilla approach is technically feasible, safe and effective when the procedure is performed in a high-volume referral center by experienced endoscopists.

Peer review

This is a nicely written paper on an old subject; the discussion underlines old controversies on pancreas divisum source of chronic pancreatitis or pancreatic pain. WGC is a promising method for minor papilla cannulation.

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Changes in efficiency and resource utilization after increasing experience with double balloon enteroscopy

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Abstract

AIM: To investigate changes in efficiency and resource utilization as a single endoscopist's experience increased with each subsequent 100 double balloon enteroscopy (DBE) procedures.

METHODS: We reviewed consecutive DBE procedures performed by a single endoscopist at our center over 4 years. DBE was employed when the clinician deemed the procedure was needed for disease management. The approach (oral, anal or both) was chosen based on suspected location of the target lesion. All DBE was performed in a standard endoscopy room with a portable fluoroscopy unit. Fluoroscopy was used to aid in shortening the small intestine and reducing bowel loops. For oral DBE, measurements were taken from the incisors. For anal DBE, measurements were taken from the anal

verge. Enteroscopy continued until the target lesion was reached, until the entire small intestine was examined, or until no further progress was deemed possible. The length of small intestine examined (cm), procedure duration (min), and fluoroscopy time (s) were analyzed for sequential groups of 100 DBE. Sub-groups of diagnostic and therapeutic procedures were analyzed using multivariable linear regression.

RESULTS: 802 consecutive DBE procedures were analyzed. For oral DBE, median [interquartile range (IQR)] length of small bowel examined was 230.8 cm (range: 210-248 cm) and for anal DBE was 143.5 cm (range: 100-180 cm). No significant increase in length examined was noted for either the oral or anal approach with advancing position in series. In terms of duration of procedure, the median (IQR) for oral DBE was 86 min (range: 71-105 min) and for anal DBE was 81.3 min (range: 67-105 min). When comparing by the position in series, there was a significant (P value < 0.001) decrease in procedure duration for both upper and lower procedures with increasing experience. Median (IQR) time of exposure to fluoroscopy for oral DBE was 190 s (114-275) compared to anal DBE which was 196.4 s (312-128). This represented a significant (P value < 0.001) decrease in the amount of fluoroscopy used with increasing position in series. For both oral and anal DBE, fluoroscopy time was reduced by greater than 50% over the course of 802 total procedures performed. Sub-group analysis was conducted on therapeutic and diagnostic groups. Out of 802 procedures, a total of 434 were considered therapeutic. Argon plasma coagulation was by far the most common therapeutic intervention performed. There was no evidence of a difference in length examined or fluoroscopy exposure among oral DBE for diagnostic and therapeutic procedures, $P = 0.91$ and $P = 0.32$ respectively. The median (IQR) for length was 235 cm (range: 178-280 cm) for diagnostic vs 230 cm (range: 180-275 cm) for therapeutic procedures; additionally, fluoroscopy time median (IQR) was 180 s (range: 110-295 s) and 162 s (range: 102-263 s) for no intervention and interven-

tion. However, there was a significant difference in procedure duration among oral DBE ($P < 0.001$). The median (IQR) was 80 min (range: 60-97 min) and 94 min (range: 77-110 min) for diagnostic and therapeutic interventions respectively.

CONCLUSION: For a single endoscopist, increased DBE experience with number of performed procedures is associated with increased efficiency and decreased resource utilization.

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Key words: Double balloon enteroscopy; Obscure gastrointestinal bleed

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INTRODUCTION

Direct, intra-luminal imaging of the entire small bowel through non-surgical means was first made possible with the introduction of capsule endoscopy (CE) to clinical practice in 2001. However, CE is inherently limited by its inability to sample tissue or to perform therapeutic interventions. Double-balloon enteroscopy (DBE), first developed and reported by Yamamoto *et al*^[1,2], subsequently allowed for therapeutic endoscopic interventions of the small bowel, such as hemostasis, tissue biopsy, and polypectomy. The procedure relies on a combination of “push-pull” maneuvers with alternating inflation and deflation of balloons attached at the tip of the endoscope and overtube, allowing for deep intubation of the small intestine. This procedure can be carried out *via* an oral approach or anal approach. DBE, therefore, allows for non-surgical management of certain small intestine disorders previously requiring intra-operative endoscopy or surgical intervention. It was introduced in the United States in 2004, and is now performed at a limited number of United States centers.

As DBE is still a relatively new procedure performed at a small number of centers, it is not currently implemented as a standard in endoscopic training. The majority of reported experience with DBE has come out of Europe, Japan and the United States^[3-6], and has demonstrated effective clinical impact. However, the long length of procedure time and need for specific training have both been well documented, highlighting significant challenges for gastroenterologists who wish to perform DBE procedures.

A past study performed at our institution analyzed the initial experience of a single endoscopist using DBE over

the course of 200 procedures^[7]. Efficiency was analyzed with respect to procedure duration, estimated length of small intestine examined, and fluoroscopy time, for both oral and anal DBE. The only significant change demonstrated was increase in the estimated length of small bowel visualized after 100 anal DBE procedures^[7]. Therefore, we suggested that the development of expertise in performing DBE may require greater than 200 procedures’ worth of experience. In our current study, we examined the increase in efficiency associated with DBE by the same endoscopist with significantly more experience.

MATERIALS AND METHODS

Patients and data

We reviewed consecutive DBE procedures performed at our center between September 2005 and February 2009, under IRB review and approval. DBE was employed when the clinician deemed the procedure was needed for disease management. Eight hundred and two consecutive DBE procedures were included in our study. The length of small intestine examined (cm), procedure duration (min), and fluoroscopy time (s) were analyzed for sequential groups of 100 DBE. The length of small intestine examined, procedure duration, and fluoroscopy time were reported as median [interquartile range (IQR)] and were compared among 8 sequential groups of 100 patients each, with the last group containing 102 procedures. Trends were observed regarding different parameters of interest among these groups of patients.

Technical information

All DBE procedures were performed by a single endoscopist using the Double-Balloon Enteroscopy System (Fujinon Inc, Wayne, NJ), with the Fujinon EN-450T5 enteroscope and TS-13140 overtube (Fujinon), or the EN-450P5 enteroscope and TS-12140 overtube, respectively. The PB-10 Balloon Pump Controller (Fujinon) controlled balloon inflation. The approach (oral, anal or both) was chosen based on suspected location of the target lesion. All DBE was performed in a standard endoscopy room with a portable fluoroscopy unit. The endoscopist was assisted in all cases by a technician and a nurse, all of whom wore lead aprons and cumulative radiation exposure badge monitors. Fluoroscopy was used to aid in shortening the small intestine and reducing bowel loops.

Oral DBE was performed with endotracheal intubation and general anesthesia, in the supine position with right shoulder raised. Measurements were taken from the incisors. Anal DBE was employed under conscious sedation (meperidine and midazolam) with the patient in the left-lateral decubitus or supine position. Measurements were taken from the anal verge. All measurements were documented using the May method^[8]. Enteroscopy continued until the target lesion was reached, until the entire small intestine was seen, or until no further progress was deemed possible.

Table 1 Oral and anal double balloon enteroscopy intubation length, duration, and fluoroscopy time by position in series

Position in series (<i>n</i>)	Length, cm, median (IQR)	<i>P</i> value	Duration, min, median (IQR)	<i>P</i> value	Fluoroscopy time, s, median (IQR)	<i>P</i> value
Oral DBE						
1-100 (51)	220 (180-275)	< 0.97	100 (85-110)	< 0.001	275 (180-356)	< 0.001
101-200 (62)	210 (150-260)		83 (80-110)		278 (211-336)	
201-300 (58)	248 (200-285)		105 (80-12)		282 (188-339)	
301-400 (54)	230 (195-300)		92 (75-105)		193 (132-295)	
401-500 (55)	238 (175-295)		82 (60-100)		134 (80-159)	
501-600 (56)	240 (185-275)		80 (62-97)		114 (73-146)	
601-700 (54)	235 (180-275)		75 (62-97)		117 (85-164)	
701-802 (54)	225 (155-270)		71 (54-91)		129 (85-192)	
Anal DBE						
1-100 (49)	100 (70-150)	0.058	105 (75-125)	< 0.001	312 (191-469)	< 0.001
101-200 (38)	140 (100-170)		85 (75-105)		294 (206-360)	
201-300 (42)	130 (60-198)		80 (58-105)		253 (122-331)	
301-400 (46)	180 (100-250)		75 (56-102)		161 (85-223)	
401-500 (45)	145 (40-170)		67 (55-88)		128 (67-174)	
501-600 (44)	168 (100-213)		92 (74-110)		143 (90-202)	
601-700 (46)	140 (80-180)		76 (52-96)		138 (80-174)	
701-802 (48)	145 (100-190)		70 (56-87)		142 (83-204)	

DBE: Double balloon enteroscopy; IQR: Interquartile range.

Endoscopist training and experience

All DBEs were performed by a single endoscopist (Stark ME) with 15 years of endoscopic practice, including over 10 000 colonoscopies, 5000 upper endoscopies, and 200 push enteroscopies. The endoscopist learned the DBE technique through one day of instructions that included hands-on training with animal intestine models and observation of human cases performed by an expert. The endoscopist also reviewed the available literature and discussed the technique with endoscopists already experienced in DBE.

Statistical analysis

Comparative analyses of oral and anal DBE approaches were conducted by stratifying sequential series of 100 DBE procedures, with *P* values obtained using the non-parametric Jonckheere-Terpstra test for unidirectional trend. All DBE procedures were categorized into diagnostic or therapeutic procedures and subgroups were analyzed for these same three variables (time of procedure, length of bowel examined, fluoroscopy time used) using multivariable linear regression.

RESULTS

A total of 802 consecutive DBE procedures were analyzed. For oral DBE, median (IQR) length of small bowel examined was 230.8 cm (range: 210-248 cm). Consequently, for anal DBE, median (IQR) length of small bowel was 143.5 cm (range: 100-180 cm) (Table 1). No significant increase in length examined was noted for either the oral or anal approach with advancing position in series. In terms of duration of procedure, the median (IQR) for oral DBE was 86 min (range: 71-105 min) and for anal DBE was 81.3 min (range: 67-105 min). When comparing by the position in series, there was a significant (*P* value < 0.001) decrease in procedure duration for

both upper and lower procedures with increasing experience (Table 1). The final efficiency parameter analyzed was fluoroscopy time. Median (IQR) time of exposure to fluoroscopy for oral DBE was 190 s (range: 114-275 s) compared to anal DBE which was 196.4 s (range: 312-128 s). This represented a significant (*P* value < 0.001) decrease in the amount of fluoroscopy used with increasing position in series (Table 1). For both oral and anal DBE, fluoroscopy time was reduced by greater than 50% over the course of 802 total procedures performed.

After all 802 DBE procedures were analyzed, subgroup analysis was conducted on therapeutic and diagnostic groups. Out of 802 procedures, a total of 434 were considered therapeutic (Figure 1A). Argon plasma coagulation (APC) was by far the most common therapeutic intervention performed (Figure 1B). There was no evidence of a difference in length examined or fluoroscopy exposure among oral DBE for diagnostic and therapeutic procedures, *P* = 0.91 and *P* = 0.32 respectively. The median (IQR) for length was 235 cm (range: 178-280 cm) for diagnostic versus 230 cm (range: 180-275 cm) for therapeutic procedures. Additionally, fluoroscopy time median (IQR) was 180 s (range: 110-295 s) and 162 s (range: 102-263 s) for no intervention and intervention. However, there was a significant difference in time among oral DBE (Figure 2A) compared to anal DBE (Figure 2B). The median (IQR) was 80 min (range: 60-97 min) and 94 min (range: 77-110 min) for diagnostic and therapeutic interventions respectively.

DISCUSSION

To our knowledge, there are no published reports which quantify how increasing experience with DBE affects efficiency. An early study by Mehdizadeh *et al*^[4], set out to describe the learning curve associated with DBE by analyzing data from DBE procedures performed in six

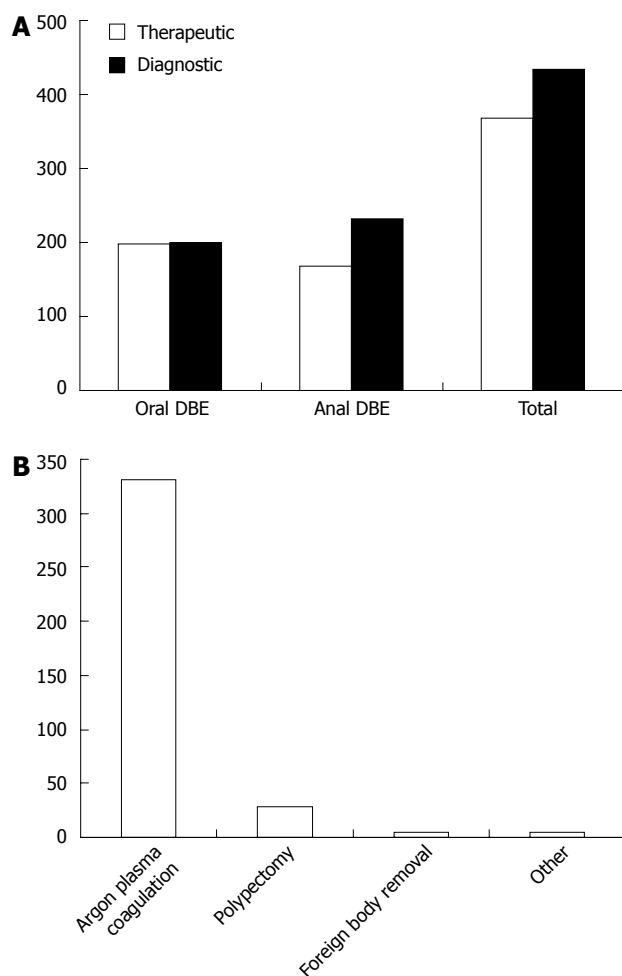


Figure 1 Double balloon enteroscopy procedures. A: Total double balloon enteroscopy (DBE) procedures; B: Double balloon enteroscopy therapeutic procedures.

tertiary United States centers over the course of one year. They subsequently found a clinically significant decline in the overall procedure time for oral DBE after the first 10 cases, but no change in anal DBE procedure time. In addition, this study reported a significant decline in mean fluoroscopy usage after 7 cases but no change in the mean depth of insertion *via* the oral or anal route with experience^[4]. Yamamoto *et al*^[2] initially demonstrated that examination of the entire small bowel was possible in up to 86% of patients, with a source of bleeding identified in 76% of patients with gastrointestinal bleeding. Our data corroborate this decrease in procedure time and decrease in fluoroscopy time with further experience by a single endoscopist. Further, our data show no evidence that increasing experience positively affects the length of bowel examined. The authors recognize, however, that in many cases the procedural goal is not to evaluate as much of the bowel as possible, but to reach a specific target lesion.

A recent meta-analysis of short-term data from nineteen different published series worldwide of DBE, including original data from Yamamoto *et al*^[2], revealed mean diagnostic yield of 67% \pm 14% (range: 41%-81%), and

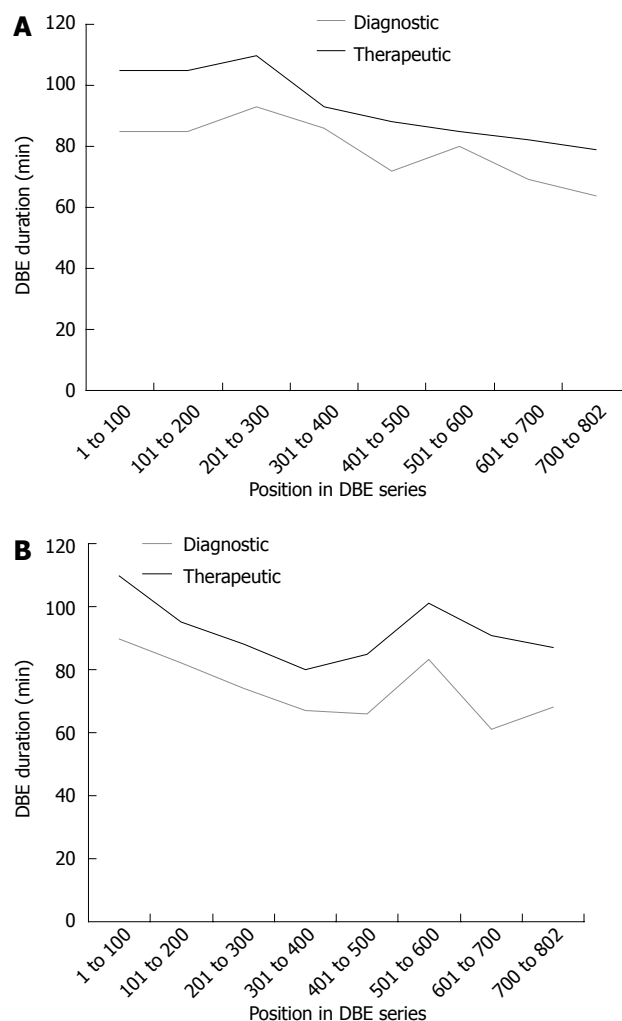


Figure 2 Double balloon enteroscopy duration by position in series. A: Oral double balloon enteroscopy (DBE) duration by position in series; B: Anal double balloon enteroscopy duration by position in series.

a mean treatment success rate of 64% \pm 13% (range: 42%-84%)^[9]. Total enteroscopy was performed on average, in 34% of patients (range: 0%-86%), though the author speculated that the low rate of total enteroscopy could be attributed to pathology being identified on initial approach of the endoscope, or from limiting anatomic factors encountered during the procedure.

By increasing DBE efficiency and thereby reducing fluoroscopy time needed during the procedure, unnecessary radiological exposure and cost of procedure is reduced. While DBE is largely considered a safe procedure for both the staff and the patient, safety monitoring did not show unsafe levels of exposure to our personnel. We did not directly measure radiation exposure to our patients, however, our radiation safety office estimated the exposure to be similar to that of a computed tomography (CT) or an endoscopic retrograde cholangiopancreatography. An increase in DBE efficiency thereby reducing procedural time would theoretically positively impact complication rates as well. This has been shown in a previously published ten year meta-analysis to include a minor complication rate of 9.1%, and major complication rate

of 0.72%, and included perforation, pancreatitis, bleeding, and aspiration pneumonia^[4]. Previously, the largest-ever study published from the German DBE register demonstrated a major complication rate of 1.2%^[10]. By decreasing procedural times through improved technique and efficiency, the endoscopist may limit patient risk for such events.

The overall cost of endoscopy and fluoroscopy are factors in justifying DBE in high volumes. As we show, a more efficient DBE endoscopist will continue to decrease even further the estimated resource utilization of DBE, including total procedure time and amount of fluoroscopy used. Our data demonstrate a significant decrease in procedure duration for both upper and lower procedures with increasing experience, as well as a reduction of fluoroscopy time of greater than 50% over the course of 802 total procedures performed, for both oral and anal DBE.

Our sub-group analysis demonstrates that length of bowel examined and fluoroscopy time were not different in the therapeutic compared to the diagnostic procedures, making therapeutic DBE a practical intervention. At our institution, APC was by far the most common of these DBE interventions as it is often selected as a treatment for obscure gastrointestinal bleeding (OGIB). Generally, the primary indication for DBE is OGIB, in which patients have persistent or recurrent bleeding from the gastrointestinal tract, with no source of bleeding identified after conventional upper endoscopy and colonoscopy. A recent systemic review of studies related to diagnostic DBE published over the past decade revealed that suspected mid-GI bleeding was by far the most common indication for DBE, accounting for 60.2% of the 12 267 procedures reviewed^[11].

Cost and resource utilization of DBE have been concerns raised by several recent studies, including Gerson *et al.*^[12]. Through cost-effective analysis, the authors determined that initial DBE was more cost effective than push enteroscopy, intraoperative enteroscopy, angiography, small bowel capsule endoscopy (CE), or guided DBE after initial CE in the management of obscure gastrointestinal. The model did not account for indirect costs such as days lost from work, but the combination of diagnostic and intervention provided by initial DBE did prove a statistically significant advantage in bleeding cessation rates compared to other modalities. Also, this study did not account for increasing efficiency as the endoscopist gains experience, which we see in our study as our endoscopist increased his total number of procedures. In a recent study, Benson *et al.*^[13] examined predicted and actual cost/profit analysis for an academic tertiary referral center. Although predicted percent margins were lower than expected, the authors found actual margins at 37 cm approaching 5% for double balloon procedures, with even greater margins seen in specific payer subsets. This data further support the financial benefit of double balloon procedures.

This study has many strengths associated with it. It was designed specifically as a follow up to our previous

study stating our initial experience with DBE. Being a tertiary referral center, we receive a large volume of patients from which to properly select ideal candidates for the DBE procedure. Most importantly, this study is well powered as there are a large number of consecutive DBE procedures. Additionally, these procedures were all performed by a single endoscopist, controlling for variations in experience and technical ability.

However, this study was not without weaknesses. Primarily, this was a retrospective review of a single endoscopist, and was not randomized or blinded. Our endoscopist had rapid access to advanced imaging such as CT enterography and capsule endoscopy, which allow for better estimation of the target lesion location and approach. This could have introduced selection bias into our statistics. Third, the lack of multiple DBE endoscopists at our center does limit the ability to compare intra-institutional data.

In conclusion, these results show that for a single endoscopist, increased DBE experience is associated with increased efficiency and decreased resource utilization, in terms of total time of procedure and fluoroscopy used. However, there is essentially no significant decrease in resource utilization or increase in efficiency with experience when comparing diagnostic *vs* therapeutic DBE.

DBE is a useful technique for directly visualizing the small intestine, and is generally accepted as a safe and effective procedure, particularly with regard to obscure gastrointestinal bleed management. In our initial experience of 200 total DBE procedures^[7], we did validate that safety and efficacy can be achieved after relatively limited DBE training. As DBE is still a relatively new procedure, and is currently not learned with standard endoscopic training, expectations concerning acquired efficiency over time are not universally established. Our data demonstrate that decreases in both procedural time and resource utilization are made possible by increases in the experience and efficiency of a single DBE endoscopist.

The rising cost of healthcare in the United States require that institutions explore cost-saving measures, and investigate the efficacy of any test or procedure that limits overall expenses of disease treatment. As Gerson *et al.*^[12] demonstrated in the case of OGIB management, DBE used in an efficient manner can contribute to reducing medical costs by providing a non-surgical diagnostic and therapeutic intervention.

COMMENTS

Background

Double balloon enteroscopy (DBE) relies on a combination of "push-pull" maneuvers with alternating inflation and deflation of balloons attached at the tip of the endoscope and overtube, allowing for deep intubation of the small intestine. As DBE is still a relatively new procedure performed at a small number of centers, it is not currently implemented as a standard in endoscopic training.

Research frontiers

DBE's long length of procedure time and the need for specific training have both been well documented, highlighting significant challenges for gastroenterologists who wish to perform the procedure. A past study performed at the institution analyzed the initial experience of a single endoscopist using DBE over the course of 200 procedures. The authors now present data on subsequent

procedures.

Innovations and breakthroughs

For a single endoscopist, increased DBE experience with number of performed procedures is associated with increased efficiency and decreased resource utilization.

Applications

The data demonstrate that decreases in both procedure time and resource utilization are made possible by increases in the experience and efficiency of a single DBE endoscopist. In an era of rising health care costs, DBE used in an efficient manner can contribute to reducing medical costs by providing a non-surgical diagnostic and therapeutic intervention.

Terminology

DBE: Performed with combination of "push-pull" maneuvers with alternating inflation and deflation of balloons attached at the tip of the endoscope and over-tube, allowing for deep intubation of the small intestine

Peer review

The article reports a large, retrospective, single operator series of DBEs over a period of four years. The study strengths and limitations are well highlighted in the discussion section. The article is well written and statistics are well done.

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Esophagogastroduodenoscopy-assisted bowel preparation for colonoscopy

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Abstract

AIM: To compare the quality and tolerance of esophagogastroduodenoscopy (EGD)-assisted and conventional split-dose polyethylene glycol electrolyte solution for inpatient colonoscopy.

METHODS: The study was a randomized controlled trial in hospitalized patients. Hospitalized patients undergoing colonoscopy the day following EGD for evaluation of gastrointestinal (GI) bleeding or other symptoms. Patients randomized to either EGD-assisted bowel prep [2 L polyethylene glycol (PEG) administered endoscopically into distal duodenum at time of EGD, plus 1 L PEG orally the following day] or conventional-PEG (2 L PEG orally the evening prior and 1 L PEG orally the following day). The main outcome measurements are bowel preparation quality and patient tolerance of bowel prep.

RESULTS: Forty-two patients randomized to EGD-assisted bowel prep and 40 patients to conventional-PEG. Overall mean \pm SD preparation quality was superior for EGD-PEG (4.1 ± 2.8) vs conventional-PEG (6.5 ± 3.1 ; $P = 0.0005$). Seventy-four percent of patients rated EGD-PEG as easy or slightly difficult to tolerate compared to 46% for standard-PEG ($P = 0.0133$). Mean EGD-procedural time was greater for EGD-assisted subject (24 ± 10 min) compared to conventional-PEG prep subjects

(15 ± 7 min; $P < 0.0001$). Conscious sedation requirements did not differ between groups. There were no significant prep-related adverse events in either group.

CONCLUSION: In selected hospitalized patients, compared to a conventional split-dose regimen, use of EGD to administer the majority of PEG solution improves patient tolerance and quality of bowel preparation for colonoscopy.

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Key words: Colonoscopy; Bowel preparation; Tolerability; Esophagogastroduodenoscopy-assisted

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INTRODUCTION

Adequate bowel preparation is of critical importance for colonoscopy. Insufficient colon cleansing may compromise the safety, accuracy and therapeutic potential of the procedure^[1]. Particularly among hospitalized patients, inadequate bowel preparation for colonoscopy may arise due to patient intolerance to the prescribed laxative regimen. In contrast to the ambulatory population, hospitalized patients are more often elderly and more likely to have co-existing conditions that impair their ability to ingest a large-volume laxative regimen^[2,3]. Suboptimal bowel preparation may in turn lead to repeat endoscopic procedures, invasive interventions such as nasogastric tube insertion for administration of purgative agents, and additional days of hospitalization^[4]. Thus, improvements in bowel preparation for colonoscopy in hospitalized patients would likely improve patient care and reduce

hospital costs. The purpose of this study was to determine if administering a portion of the bowel purgative *via* esophagogastroduodenoscopy (EGD) could improve colonoscopy preparation in hospitalized patients.

Bowel preparation for colonoscopy can be challenging under certain circumstances. For example, advanced age, hospital setting and comorbid illnesses have been demonstrated as factors that reduce the quality of bowel preparation^[2,3]. Suggestions to improve patient tolerance of bowel preparation include reducing the volume of purgative ingested, splitting the amount of purgative into two separate doses, and administering adjuvant agents to improve gastric emptying and reduce nausea and vomiting associated with ingestion of purgatives^[5]. Patients who are unable to tolerate oral ingestion of a sufficient quantity of purgative pose a particular challenge to adequate colon cleansing. In this situation, one approach is to place a nasogastric tube for administration of the purgative solution. However, in addition to the inherent drawbacks of nasogastric (NG) tube placement, NG-assisted bowel preparation carries the potential for pulmonary aspiration if large volumes of solution accumulate in the stomach^[6].

On the other hand, experience in other clinical situations has demonstrated the utility and an acceptable safety profile with rapid administration of large-volume PEG solution. Rapid whole gut lavage with large volumes of polyethylene glycol (PEG) electrolyte solution has been used for decades in the acute management of drug overdoses^[7]. Others have employed rapid PEG lavage *via* nasogastric tube for bowel preparation in the setting of acute lower gastrointestinal (GI) bleeding^[8]. One purported advantage of this approach is the resultant high quality of colonic mucosal visualization, which may improve the diagnostic or therapeutic yield of colonoscopy. The current study sought to extend this experience by evaluating a novel method of bowel preparation for colonoscopy: Rapid luminal infusion of PEG solution into the duodenum during EGD.

MATERIALS AND METHODS

Patients

This study was conducted at OSF St. Anthony's Medical Center and SwedishAmerican Hospital, community-based hospitals in Rockford, Illinois. Patients were enrolled from August, 2009 to July, 2011. The study was approved by the institutional review boards of the participating institutions. Adult inpatients were offered to participate in the study at the time of EGD if, depending on the EGD results, there was a possibility that colonoscopy would be performed the following day and during the hospital stay. Patients were excluded if there was evidence of bowel obstruction, suspicion of a diffuse GI motility disorder (patients with suspected gastroparesis were not excluded), inability to ingest oral bowel preparation, or if outpatient rather than inpatient colonoscopy was anticipated following EGD.

Study design

The study was a randomized controlled trial in hospitalized patients. In order to test the concept of EGD-assisted prep administration in routine clinical practice, patients in whom colonoscopy was anticipated the day following EGD comprised the study population. In this scenario the most common indication for EGD was GI bleeding but other indications were permitted. The non-bleeding indications included abdominal pain, positive fecal occult blood test with associated upper GI symptoms, and metastatic cancer of unclear origin. Patients provided written informed consent for the study at the time of EGD. They were informed that, if the upper endoscopy proved non-diagnostic or inconclusive (*e.g.*, no convincing source of bleeding identified), colonoscopy would be recommended and would be scheduled the following morning. Participating patients were randomized (in a 1:1 ratio) at the time of EGD to either the control arm or the intervention arm (see details below). Randomization was performed using a set of random numbers, which corresponded to assignments of conventional prep (control) or EGD-assisted subjects. Eligible subjects were randomized at the time of (negative) EGD, while the scope was still in the stomach. Sealed envelopes concealed the prep assignment until the time of randomization. Endoscopic procedures were performed by 15 experienced, board-certified GI physicians during day-to-day hospital rotations. Patients received conscious sedation with IV midazolam and IV fentanyl to achieve a moderate level of sedation. Left-lateral position was used for EGD. Monitoring included continuous measurement of heart rate, respiratory rate and SaO₂, and intermittent BP monitoring. When possible, the endoscopist was blinded to the subject's prep assignment. However, physician blinding was not possible in situations in which the endoscopist performing the colonoscopy had also performed the EGD the day before. The study's author performed 24/42 (57%) of EGD-assisted procedures; the remainder was distributed evenly among other physicians. In 19/42 (45%) cases, the endoscopist who performed the EGD-assisted procedure also performed the subsequent colonoscopy. There was no significant difference in the distributions of physicians scoring the bowel preps of EGD-assisted and conventional-PEG groups (data not shown).

Control group (conventional split-dose PEG)

Following (non-diagnostic) EGD, control subjects received routine instructions and management for split-dose PEG bowel preparation for colonoscopy the following day. They were prescribed a clear liquid diet over the day prior to colonoscopy, oral ingestion of two liters of PEG solution (Nulytely, Braintree Laboratories Inc, Braintree, MA) at 5 PM the evening prior to colonoscopy, and an additional 1 L of Nulytely 4 h prior to colonoscopy the next day. A 10 mg IV dose of metoclopramide was given 30 min prior to administration of PEG solution. Tap water enemas were administered 1 h prior to colonoscopy. The total volume of PEG prescribed was 3 L because

of our clinical experience that hospitalized patients rarely tolerate greater volumes of PEG solution. Recognizing that a 4-L PEG regimen may be used more commonly in clinical practice, the 2 plus 1 L split-dose PEG regimen falls within recent guidelines elaborated by a multi-society task force document on bowel preparation for colonoscopy^[5].

Intervention group (EGD-assisted preparation for colonoscopy)

At the completion of non-diagnostic upper endoscopy, subjects randomized to the intervention group received a 10 mg IV dose of metoclopramide. With the endoscope tip advanced as distally as possible in the post-bulbar duodenum, a 2-L volume of Nulytely solution was instilled through the channel of the endoscope, either with repeated injections of a 60 cc syringe or with a foot-pedal activated pump (Endogator, Byrne Medical Inc., Conroe, TX) attached directly to the container of PEG solution. The PEG solution was instilled slowly, typically over 10 to 15 min, depending on the individual patient's ability to accommodate the fluid load. The total duration of the EGD procedure was recorded but time to instill the prep solution was not recorded separately. Patients were positioned in the left-lateral position with the head elevated 30 degrees. As a further safety precaution, PEG infusion was continued only if there was sufficient bowel motility to propel the fluid distally from the duodenum. Based on early experience with this method, endoscopists were given instruction to observe the presence of duodenal contractions and the effect that this had on the ability to instill more fluid. For example, if there was adequate motility to clear the lumen of fluid to such a degree as to appreciate an air-fluid interface, as opposed to a lumen completely full of fluid, then additional PEG solution could be instilled. Fluid that refluxed back into the stomach was suctioned out through the endoscope. However, small volumes (*i.e.*, < 50 cc) of fluid that pooled in the fundus were not suctioned out. Care was taken to keep the stomach decompressed by suctioning out air. Other than instructions to administer fluid slowly over 10 to 15 min, there was no written protocol to direct physicians. If fluid was obviously being propelled distally, the rate of administration was more rapid than if fluid pooled in the duodenum. The endoscope was retracted into the stomach every 3 to 5 min to check for proximal fluid accumulation. The most practical observation that informed the appropriate rate of fluid instillation was observing peristaltic contractions followed by air in the lumen after fluid was propelled distally. Following EGD, patients were prescribed a clear liquid diet over the remainder of the day. The following morning, 4 h prior to colonoscopy, they were prescribed one liter of Nulytely to be ingested orally. Tap water enemas were administered 1 h prior to colonoscopy. Subjects who "failed" EGD-assisted prep administration, *i.e.*, were unable to tolerate endoscopic administration of the full 2-L fluid volume were not crossed over into an orally-ingested PEG first dose.

Statistical analysis

The mean \pm SD or median and corresponding range and inter-quartile range (IQR) were used to summarize data for continuous variables and percentages for categorical variables. Continuous variables with normal distributions were compared using student's *t*-test; variables with non-normal distributions were analyzed using the Mann-Whitney test. Differences in categorical variables were analyzed using the Fisher exact test and χ^2 test. A *P* value < 0.05 was considered statistically significant. Reported *P* values are two-tailed. Statistical tests were performed with the use of Analyse-it software (version 1.73, Leeds, United Kingdom). The sample size was calculated based on prior studies of bowel preparation^[9] in which approximately 50% of patients who received PEG solution for colonoscopy had a fair or poor quality preparation. For the current study, to detect a 33% difference in this rate of suboptimal bowel preparation, with 80% power and $\alpha = 0.05$, it was estimated that approximately 40 subjects would be required in each treatment arm.

Outcome measurements

The primary outcome measure was the quality of bowel preparation as assessed by the Ottawa bowel preparation scale^[10]. The secondary outcome was patient tolerance of bowel preparation, which was assessed *via* a questionnaire administered just prior to sedation for colonoscopy, used in previous studies at our center^[11,12]. Other variables measured included duration of procedures, amounts of sedative medications administered for EGD, and adverse events.

RESULTS

Study population

During the 23-mo study period a total of 6406 EGDs were performed in 4058 hospitalized patients. Of these procedures, 4212 were considered diagnostic and/or therapeutic such that follow-up colonoscopy was not indicated. Of the remaining patients, 1582 underwent inpatient colonoscopy more than one day following the EGD and 508 patients underwent outpatient colonoscopy, generally within 4 wk. The predominant reason for deferring inpatient colonoscopy following EGD related to managing concomitant medical conditions to achieve clinical stability to permit colonoscopy. The decision to enroll or not to enroll patients for EGD-assisted prep study was based on the clinical assessment of the physician at the time of EGD. Twenty-two patients either refused participation or were considered ineligible for the study. Of the remaining 82 subjects who comprised the study population, 42 were randomized to EGD-PEG and 40 to conventional-PEG. Thus, only 82/6406 (1.2%) of inpatient EGDs qualified for inclusion (Figure 1). Table 1 shows the baseline characteristics of these study subjects. There were no statistically-significant differences in the baseline characteristics of control and intervention subjects. The median age of subjects was 73 ± 13 years. Congestive heart failure, renal

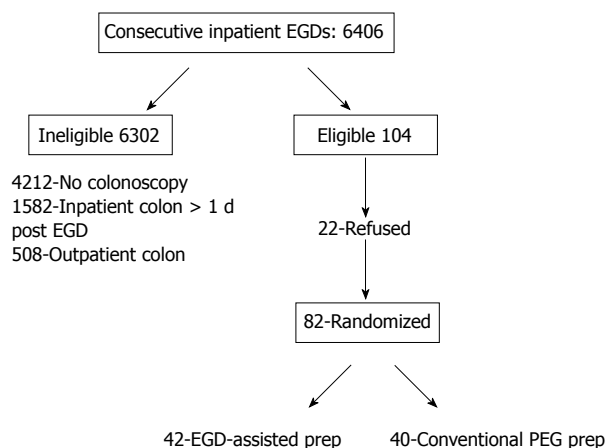


Figure 1 Enrollment of subjects. EGD: Esophagogastroduodenoscopy; PEG: Polyethylene glycol.

failure and diabetes mellitus were common, with roughly one-third of study subjects having at least one of these major comorbid disorders. The predominant indication for EGD was overt GI bleeding (74% of subjects). Other indications included abdominal pain, iron deficiency anemia and abnormal results of imaging studies (detailed data not shown).

Quality of bowel preparation

Figure 2A shows frequency distributions of Ottawa preparation scale scores for EGD-assisted and conventional split-dose PEG groups. With this scale, the numerical value is inversely related to the overall quality of the preparation. Overall mean preparation quality was superior for EGD-assisted bowel prep (4.1 ± 2.8) *vs* conventional-PEG (6.5 ± 3.1 ; $P = 0.0005$). Bowel preparation quality in EGD-assisted bowel prep subjects was also superior to conventional-PEG subjects when analyzed by specific colonic segment (Figure 2B). Four subjects (10%) in the conventional-PEG group required repeat colonoscopy due to inadequate preparation compared with zero patients in the EGD-assisted bowel prep group ($P = 0.0523$). Two of these subjects who required repeat colonoscopy because of inadequate prep had their procedures scored by the study author. Within each group, there appeared to be a trend toward poorer preparation of the right colon compared to distal segments, but these differences were not statistically significant. For example, the most pronounced differences were between the right- and mid-colon segments ($P = 0.0614$ for EGD-assisted and $P = 0.0629$ for conventional-PEG subjects).

When the analysis was confined to cases in which the endoscopist who performed the colonoscopy had not performed the prior EGD, there were 23 subjects who received EGD-assisted bowel preparation and 24 subjects who received conventional split-dose PEG preparation. Among these subjects, bowel prep was superior in EGD-assisted subjects (mean overall Ottawa prep score 4.2 ± 2.9) compared to conventional-PEG subjects (6.0 ± 2.8 ; $P = 0.0361$).

Table 1 Baseline characteristics of subjects (%)

	EGD-assisted (<i>n</i> = 42)	Conventional-PEG (<i>n</i> = 40)
Age [median (range (IQR))]	73 [42-99 (19.25)]	73.5 [45-97 (17.5)]
Males/females	15/27	20/20
Bleeding as indication for EGD	28 (67)	33 (83)
Diabetes mellitus	12 (29)	13 (33)
Congestive heart failure	11 (26)	10 (25)
Stroke	10 (24)	4 (10)
Azotemia	16 (38)	10 (25)
Opiate/anticholinergic medications	16 (38)	13 (33)

EGD: Esophagogastroduodenoscopy; IQR: Inter-quartile range.

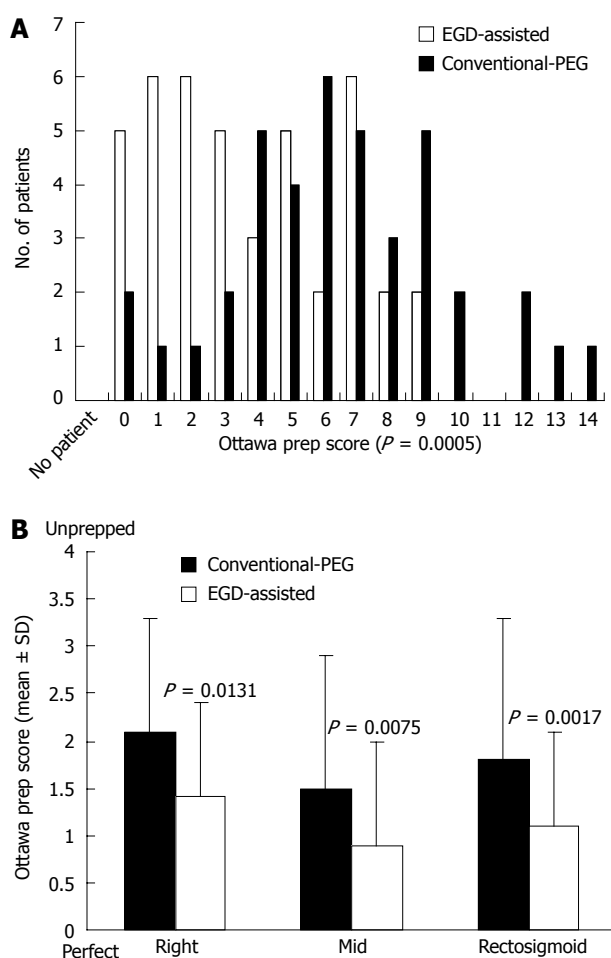


Figure 2 Quality of bowel preparation. A: Overall bowel prep quality; B: Prep quality according to colon segment. EGD: Esophagogastroduodenoscopy; PEG: Polyethylene glycol.

Patient tolerance of bowel preparation

Figure 3 shows the overall level of patient tolerance of EGD-assisted *vs* standard split-dose PEG. The overall trend for tolerance of prep was significantly in favor of EGD-assisted prep *vs* the conventional-PEG protocol ($P = 0.0044$). 74% of patients rated EGD-assisted prep as easy or slightly difficult to tolerate compared to 46% for standard-PEG ($P = 0.0133$). Three patients in the

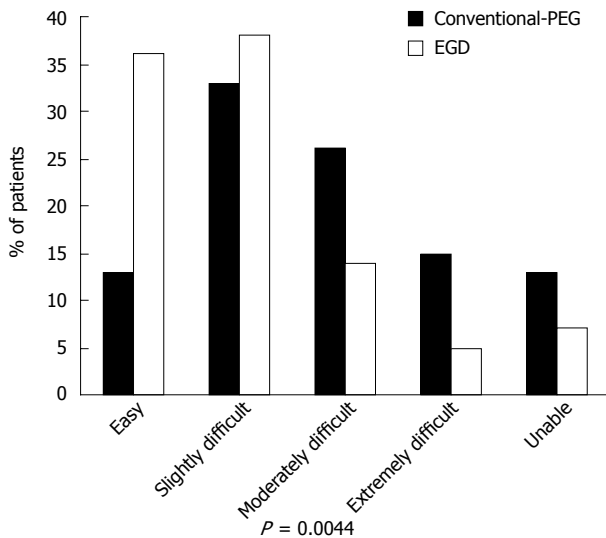


Figure 3 Overall patient acceptance of prep. EGD: Esophagogastroduodenoscopy; PEG: Polyethylene glycol.

EGD-assisted PEG group were unable to complete the orally-ingested portion of the prep compared to 6 conventional-PEG patients ($P = 0.02963$), with failure defined as inability to consume the prescribed fluid volume. Table 2 shows individual symptom profiles among EGD-assisted *vs* conventional-PEG subjects. In comparison to EGD-assisted subjects, conventional-PEG subjects had significantly greater rates of nausea, taste intolerance and a greater inclination to try an alternative prep for future procedures.

Procedure times, medications and adverse events

Median EGD-procedural time was greater for EGD-assisted subjects [20 min; range 6-45 min (IQR 15)] than for conventional-PEG subjects [15 min; 3-25 min (10); $P = 0.0036$]. Six subjects in the EGD-assisted prep group had EGD procedural times of 10 min or less: Two did not tolerate the endoscopic infusion of prep solution and 4 in whom the entire volume of prep solution was able to be instilled in less than 10 min. After eliminating these outliers from the analysis of EGD procedure times, the mean EGD-time in EGD-assisted prep subjects was 24 ± 10 min, compared to 15 ± 7 min in conventional-PEG prep subjects ($P < 0.0001$). There was no significant difference in conscious sedation requirements between the two study groups: Median [range (IQR)] doses of midazolam and fentanyl in EGD-assisted subjects were, respectively, 3 [1-8 (3)] mg and 50 [25-150 (50)] mg; corresponding values for conventional-PEG subjects were 3 [1-6 (3)] mg and 100 [25-150 (50)] mg ($P = 0.9805$ and 0.2932 , respectively). Two subjects in the EGD-assisted bowel prep group were administered a minimal volume of PEG solution during EGD due to poor gastric emptying and a tendency of the prep to reflux back into the stomach. One of these subjects had a history of chronic use of opiate analgesics but no established history of GI dysmotility. In all other EGD-assisted prep subjects, only a small amount of prep solution was suctioned

Table 2 Symptom profiles of esophagogastroduodenoscopy-assisted/conventional-polyethylene glycol subjects¹

Symptom	None	Mild	Moderate	Severe	Intolerable	P value
Bloating	26/21	8/9	3/1	1/2	0/0	0.8325 ²
Dizzy	37/30	1/4	0/0	0/0	0/0	0.1280 ²
Nausea	30/18	7/10	0/6	0/1	1/0	0.0050 ²
Vomiting	35/30	2/2	0/1	0/1	0/0	0.3359 ²
Pain	28/21	8/12	1/1	1/0	0/0	0.2788 ²
Poor sleep	22/13	9/8	11/9	0/3	0/1	0.1915 ²
Taste	8/4	27/20	2/9	1/2	0/0	0.0176 ²
Complete	Yes	No	-	-	-	0.2963 ³
	35/29	3/6				
Other prep	Yes	No	-	-	-	0.0047 ³
	10/21	28/14				
Refuse	Yes	No	-	-	-	0.0982 ³
	1/5	37/30				

¹Values in each cell denote number of esophagogastroduodenoscopy-assisted/conventional-polyethylene glycol subjects; small numbers of subjects in certain categories were pooled as necessary to satisfy criteria for statistical analysis; ² χ^2 test for trend; ³Fisher's exact test; bolded P values denote statistical significance.

from the stomach, so that nearly all subjects received a standardized 2-L infusion of prep solution. One elderly woman in the EGD-assisted group developed hypoxemia immediately following EGD. This corrected quickly following administration of reversal agents (flumazenil and naloxone) and noninvasive (bipap-assisted) ventilation. Chest radiographs showed no evidence of pulmonary aspiration. There were no additional significant prep-related adverse events in either group. The majority of EGD-assisted subjects began passing liquid stools within 2 h, after they had been transferred from the GI endoscopy unit to the hospital floor. However, two subjects (5%) began passing watery stools during EGD-assisted administration of the PEG solution.

The median colonoscopy procedure time was significantly longer for conventional-PEG subjects [33.0 min; range 14-65 min (IQR 12)] compared to EGD-assisted subjects [28 min; 8-56 min (15); $P = 0.0324$].

DISCUSSION

Hospital-based colonoscopy typically is performed in older, acutely ill patients, in contrast to ambulatory colonoscopy, which is weighted towards a younger and generally healthy population undergoing screening procedures^[13,14]. Advanced age, comorbid illness and other factors contribute to a decreased ability of hospitalized patients to comply with oral preparation for colonoscopy^[2,3]. In particular, a substantial number of patients are unable to consume the most commonly-prescribed regimen, large-volume PEG electrolyte solution, for colonoscopy preparation. In an attempt to address the issue of inadequate preparation due to intolerance of a large-volume prep among hospital patients undergoing colonoscopy, this study tested a novel and unconventional approach to bowel preparation: Direct administration of the majority of the purgative solution into the small bowel lumen

through the endoscope at the time of EGD. Judging by superior patient tolerance (*e.g.*, significantly better nausea and taste profiles) and improved bowel preparation quality when compared to conventional split-dose PEG solution prep, EGD-assisted bowel preparation appears to be a promising approach in selected hospitalized patients. Using a careful technique emphasizing precautions to minimize risks of aspiration, there were no significant adverse events directly attributable to the prep administration. Though EGD-assisted preparation added a small amount of time to standard EGD, conscious sedation medication needs were similar for EGD-assisted and standard EGD examinations. The mean incremental increase in EGD-procedure time for EGD-assisted patients was only nine minutes, but this may not be an accurate reflection of the actual time required for prep infusion, which was not measured separately. There was a reciprocal decrease in the observed colonoscopy procedure times among EGD-assisted bowel prep subjects compared to conventional-PEG subjects, which would be consistent with less time required for washing and suctioning to improve visualization in the superiorly prepped EGD-assisted subjects. Furthermore, the use of EGD-assisted bowel preparation in this study obviated repeat colonoscopy due to inadequate preparation, which was required in 10% of patients who received conventional-PEG preparation.

Although EGD-assisted bowel preparation would be impractical and unnecessary for all hospitalized patients, such an approach could be considered in selected patients who were unable to ingest any (or especially a large) volume of oral purgative solution. Given that this study excluded patients unable to ingest an oral prep and included younger healthier patients better able to tolerate a conventional oral prep, the results likely under-estimate the true benefit of EGD-assisted bowel preparation. In patients unable to ingest an oral prep, the alternative of nasogastric tube placement to facilitate bowel preparation has drawbacks of significant patient discomfort and the potential for serious risks, including nasopharyngeal trauma, inadvertent tube misplacement and pulmonary aspiration^[6]. Indeed, based on the results of the current study, one could speculate that the aspiration risk of an NG-administered prep might exceed that of EGD-assisted prep given the ability of the latter approach to directly visualize the stomach during fluid administration, thereby ensuring that a large volume of fluid does not accumulate in the stomach. However, further prospective study is needed to clarify the balance of risks and benefits of methods such as NG-assisted or EGD-assisted administration of bowel preparation in patients with extreme difficulty ingesting sufficient prep volumes. Although American Society of Anesthesia guidelines^[15] prohibit oral fluid intake within two hours prior to sedated upper endoscopy, there are particular clinical situations in which administration of fluid into the upper GI tract may be required during sedated endoscopy. For example, during endosonography for gastroduodenal lesions, (tem-

porary) water instillation into the stomach or duodenum is often necessary for accurate characterization of mural-based pathology^[16]. This technique is considered standard practice for upper endosonography, a procedure with an excellent safety record spanning approximately three decades. EGD-assisted administration of a purgative solution for bowel preparation involves administration of a greater fluid volume, which is delivered distal to the pylorus. However, in contrast to EUS, the endoscopist actively intervenes to prevent gastric retention of fluid during the procedure to reduce the risk of pulmonary aspiration.

This study had certain limitations. As it was performed at a single center in a relatively small number of subjects, it would be premature to assume the results apply to a wider population of patients and practice settings. In particular, given that this study tested a highly unconventional approach to bowel preparation, which could pose significant risks if it were widely adopted without additional evidence of its safety, the findings should be considered provocative rather than definitive. Since pulmonary aspiration can be a life-threatening adverse event, one would want to confirm in a larger patient population a low - ideally, zero - risk of aspiration with this approach. The fact that most of the EGD-assisted procedures were performed by a single endoscopist limits its generalizability regarding safety of the procedure. In terms of study design, it was impractical for this study to be double-blinded, since the scheduling of hospital-based physicians precluded blinding endoscopists to patients' prep assignments. However, the risk of physician bias in grading the prep was mitigated by adherence to a validated prep scoring system and by the fact that the majority of colonoscopies that followed EGD-assisted preparation were performed by endoscopists who had not conducted the prior EGD. Finally, it is conceivable that a split-dose small-volume bowel prep may have achieved superior colon cleansing and patient tolerance compared to large-volume PEG solution. However, currently in the United States, options for small-volume prep solutions are limited. In addition, as observed in the current study, many hospitalized patients have co-existing conditions such as cardiac or renal failure, which may make the safety profile of a small-volume hyperosmotic prep less than ideal.

In conclusion, among selected hospitalized patients, when compared to a conventional split-dose regimen, use of EGD to administer the majority of PEG solution for bowel cleansing improves patient tolerance and quality of bowel preparation for colonoscopy.

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COMMENTS

Background

Adequate bowel preparation is required for colonoscopy. Poor patient tolerance to large-volume purgatives contributes to suboptimal bowel preparation.

Research frontiers

Adequate bowel preparation is of critical importance for colonoscopy. Insufficient colon cleansing may compromise the safety, accuracy and therapeutic potential of the procedure. Particularly among hospitalized patients, inadequate bowel preparation for colonoscopy may arise due to patient intolerance to the prescribed laxative regimen. Bowel preparation for colonoscopy can be challenging under certain circumstances. Experience in other clinical situations has demonstrated the utility and an acceptable safety profile with rapid administration of large-volume polyethylene glycol (PEG) solution.

Applications

One purported advantage of this approach is the resultant high quality of colonic mucosal visualization, which may improve the diagnostic or therapeutic yield of colonoscopy. The current study sought to extend this experience by evaluating a novel method of bowel preparation for colonoscopy: Rapid luminal infusion of PEG solution into the duodenum during esophagogastroduodenoscopy.

Peer review

This is an interesting and methodologically well made paper. Their findings may be applicable to certain patients requiring both a diagnostic colonoscopy and upper gastrointestinal endoscopy.

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Novel serine/threonine kinase 11 gene mutations in Peutz-Jeghers syndrome patients and endoscopic management

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Abstract

AIM: To explore mutations in serine/threonine kinase 11 (*STK11*) gene in Peutz-Jeghers syndrome (PJS) with gastrointestinal (GI) hamartomatous polyps.

METHODS: Six Japanese PJS patients in 3 families were enrolled in this study. Each of the cases had hamartomatous polyposis in the gastrointestinal tract, including the small intestine, along with mucocutaneous

hyperpigmentation. Narrow-band imaging (NBI)-magnification endoscopy was employed to detect microvascular and microsurface irregularities in the GI lesions. NBI magnification findings could be classified into three groups (type A, type B, or type C). Endoscopic polypectomy was performed using double-balloon enteroscopy or colonoscopy. Genomic DNA was extracted from a whole blood sample from each subject. All of the coding exons of *STK11* gene, its boundary regions, and the promoter region containing the polymorphic regions were amplified by polymerase chain reaction, and direct sequencing was performed to assess the germline mutations.

RESULTS: NBI-magnification endoscopic observation could detect the abnormalities in microvessels and microsurface structures of GI polyps. Overall, we found 5 cases of type A and one case without the examination for the gastric polyps, while there were 4 cases of type B and 2 case of type A for the colorectal polyps. Seventy-nine small-bowel and 115 colorectal polyps over 27 sessions for each were resected endoscopically without significant complications. The only delayed complication included the occurrence of bleeding in a case, and this was successfully managed with hemoclips. Resected polyps contained no malignant components. Based on mutation analysis, all 3 cases in Family I exhibited the +658C>T nonsense mutation in exon 5, which resulted in the production of a truncated protein (Q220X). In Family II, a case had -252C>A and -193C>A in the promoter region. In Family III, a case was found to have the +1062C>G (F342L) mutation in exon 8.

CONCLUSION: We found two novel mutations of *STK11* in association with PJS. Endoscopic polypectomy of GI polyps in PJS patients appears to be useful to prevent emergency laparotomies and reduce the cancer risk.

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Key words: Peutz-Jeghers syndrome; Serine/threonine kinase 11; Gastrointestinal hamartomatous polyps; Double-balloon enteroscopy; Narrow-band imaging

Yajima H, Isomoto H, Nishioka H, Yamaguchi N, Ohnita K, Ichikawa T, Takeshima F, Shikuwa S, Ito M, Nakao K, Tsukamoto K, Kohno S. Novel serine/threonine kinase 11 gene mutations in Peutz-Jeghers syndrome patients and endoscopic management. *World J Gastrointest Endosc* 2013; 5(3): 102-110 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i3/102.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i3.102>

INTRODUCTION

Peutz-Jeghers syndrome (PJS) is a rare autosomal-dominant hereditary condition with incomplete penetrance that is characterized by hamartomatous polyps of the gastrointestinal (GI) tract and pigmented lesions of the buccal mucosa, perioral region and other sites^[1,2]. Variable penetrance and clinical heterogeneity make it difficult to determine the exact frequency of PJS^[2]. Most PJS patients develop significant hamartomatous polyps of the small bowel, with these polyps commonly arising in the stomach and colorectum. PJS patients also have an increased risk of cancer at multiple locations, although it is predominantly found in the colon, small intestine, stomach, esophagus, pancreas, breast, ovary and uterine cervix^[3,4].

PJS occurrence is primarily associated with germline mutations in the serine/threonine kinase 11 (*STK11/LKB1*) gene, which are localized on the chromosomal segment 19p13.3^[5,6]. The gene spans 23 kb, and consists of nine coding exons and a final noncoding exon^[3,6]. The coded protein plays a role in cellular energy metabolism, cell polarization, p53-dependent apoptosis, and Wnt signal transduction^[3,7-9]. The germline mutation detection rates in PJS patients vary among reports^[1], but recent studies which have searched for germline mutations using state-of-art techniques demonstrate between 80% and 94%^[10-12]. Most mutations are single base substitutions/insertions or small deletions that result in an abnormal truncated protein^[1,3,10-12].

Narrow-band imaging (NBI) is a recent innovative optical technique that modifies the center wavelength and bandwidth of an endoscope's light in order to produce narrow-band illuminations of 415 and 540 nm^[13,14]. When combined with magnifying endoscopic observation, NBI can markedly improve the capillary pattern contrast. Use of this *in vivo* method makes it possible to visualize microvascular morphological changes that take place in the superficial neoplastic lesions^[14-16]. Several studies have reported on the advantages of using magnification endoscopy NBI for diagnosis of gastrointestinal neoplasia^[17]. Additionally, studies have also shown that when magnification chromoendoscopy is used in combination with crystal violet staining, the information obtained can be used to diagnose gastrointestinal tumors^[18].

However, PJS patients are subject to serious complications such as intussusception and bleeding from the GI, in particular from small intestinal polyps^[19]. Therefore, many of these patients often need to undergo multiple laparotomies with intestinal resection, which can ultimately result in short-bowel syndrome and/or severe adhesions^[20,21]. In order to control these small-bowel polyps, a combined endoscopic and surgical treatment procedure has been designed for use in these patients^[22,23]. Even with the new treatment regimen, however, many of these patients still end up undergoing multiple surgical treatments because of the appearance of new lesions or the growth of existing polyps. Double-balloon endoscopy (DBE) was developed as a new technique for visualization of, and intervention in the lesions that occur throughout the entire small intestine^[24]. DBE has been reported worldwide to be useful for both diagnosis and treatment of small intestinal polyps^[25]. As such, the use of DBE could potentially be a means of providing prophylactic polypectomy in PJS patients, thereby helping to prevent the intussusception and bleeding complications^[26,27].

In the current study, we performed a mutation analysis of STK11 in three PJS families. This study also presents data on the magnified endoscopy findings and the endoscopic treatments for the polyps.

MATERIALS AND METHODS

Subjects

PJS patients in 3 families were enrolled in this study (Figure 1). The PJS diagnosis was based upon clinical criteria proposed in 1987^[28].

To definitively diagnose PJS in individuals with histopathologically confirmed hamartoma, two of the following three findings are required: (1) family history consistent with autosomal dominant inheritance; (2) mucocutaneous hyperpigmentation; and (3) small-bowel polyposis. In the current study, each of the cases had hamartomatous polyposis in the gastrointestinal tract, including the small intestine, along with mucocutaneous hyperpigmentation on the hands, feet or lips.

Magnifying endoscopy

We performed NBI magnification gastroscopy and colonoscopy in each PJS case. The endoscopic system included a light source (CLV-260SL; Olympus, Tokyo, Japan), a processor (CV-260SL; Olympus), and a high-resolution magnifying endoscope (GIF-H260Z for the stomach and CF-H260AZI for the colorectum; Olympus). The unique features of PJS polyp are best appreciated in the larger PJS small intestine polyps, but the other polyps do not have specific gastrointestinal endoscopic findings. They can be similar to hyperplastic polyps^[29]. Recently, Lam-Himlin *et al*^[30] investigated the histologic features of gastric polyps in patients with established PJS to develop improved histologic criteria to distinguish these from gastric hyperplastic polyps. Histologic features to distinguish gas-

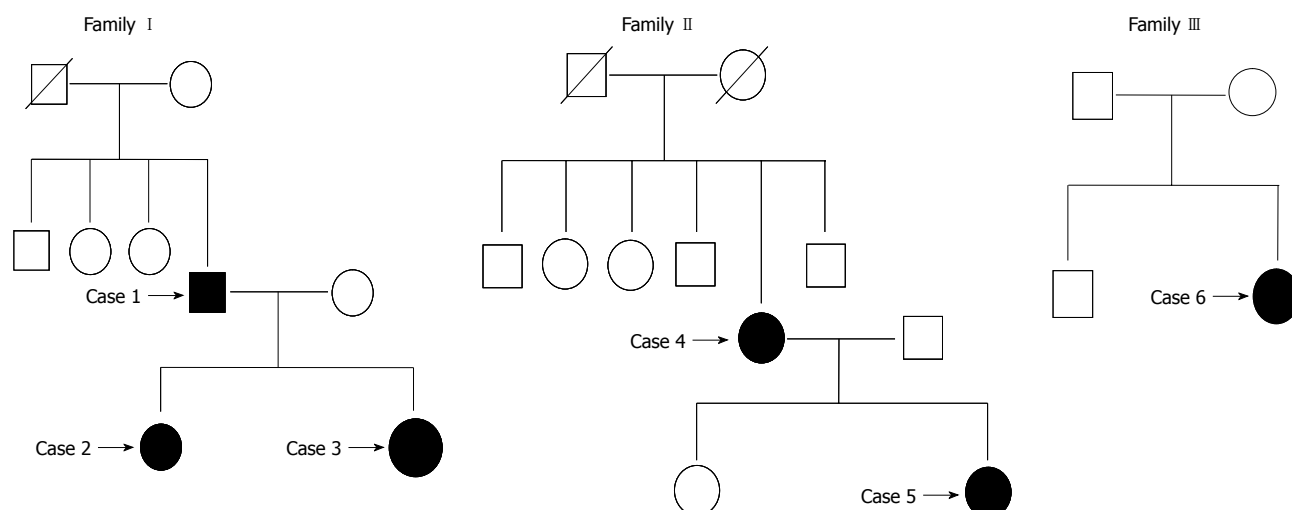


Figure 1 Each pedigree of the three families with Peutz-Jeghers syndrome.

tric PJS from gastric hyperplastic polyps were unreliable. There has been no available NBI classification for gastric non-neoplastic polyps including hamartomatous and hyperplastic polyps. Kanao *et al.*^[17] reported that NBI magnification findings could be classified into three groups (type A, type B, or type C) based on their microvessel architecture and pit appearance. In type A lesions, microvessels are not observed or are extremely opaque. Type B lesions exhibit fine microvessels around the pits, with clear pits observed *via* a nest of microvessels. Type C lesions exhibit irregular microvessels in which the vessel diameters or distributions are heterogeneous. Type C can be further divided into 3 subtypes (C1, C2, and C3) based on the detailed NBI magnification findings for the pit visibility, vessel diameter, irregularity, and distribution. Lesions are considered to be subtype C1 when the microvessels comprise an irregular network, the pits are slightly non distinct when observed *via* the microvessels, and the vessel diameters or distributions are homogeneous. For the C2 subtype, microvessels comprise an irregular network, the pits are irregular when observed *via* the microvessels, and the vessel diameters or distributions are heterogeneous. For the type C3 subtype, the pits *via* the microvessels are invisible, the irregular vessel diameters are thick or there is a heterogeneous vessel distribution, along with the observation of avascular areas.

Procedures of polypectomy *via* DBE and colonoscopy

For the small intestinal polyps, we used an EN-450T5/W double-balloon endoscope (Fujifilm, Tokyo, Japan), which has an accessory channel that is 2.8 mm in diameter. This scope made it possible to use a variety of therapeutic devices, including an endoscopic hemoclip. For polypectomy of the colorectal polyps, we used a CF-Q260AI colonoscope (Olympus). All of the procedures were performed by specialists (Yajima H, Isomoto H, Ohnita K, Shikuwa S). While moderate sedation with a combination of intravenous pethidine and diazepam

and/or midazolam was administered to most patients, general anesthesia was used in symptomatic intussusception cases. A combined oral and anal approach was performed during the first session. If polyps were recognized, careful observation was performed in order to determine their size, shape, and location. Resected polyp sizes were estimated by visual measurement. To avoid post-polypectomy bleeding and thermal injury of the deeper tissue layers, a saline-epinephrine solution (0.9% sodium chloride, 0.001% epinephrine, 0.002% indigo carmine) was injected, as needed, into the submucosal layer of the stalk and the base of the polyp prior to the polypectomy. Snare cautery polypectomy was performed using commercially available snares up to 33 mm in diameter.

Polymerase chain reaction and direct sequencing

After obtaining written informed consent, a whole blood sample was collected from all the patients for the analysis of the *STK11* gene mutation. Genomic DNA was extracted from a whole blood sample from each subject using a DNA Extractor WB-Rapid Kit (Wako, Osaka, Japan) in accordance with the manufacturer's protocol. All of the coding exons of the *STK11* gene, its boundary regions, and the promoter region containing the polymorphic regions were amplified by polymerase chain reaction (PCR) (Figure 2). Amplification was performed with a GeneAmp PCR System 9700 thermal cycler (Life Technologies, Carlsbad, CA) using 20 ng genomic DNA in a 25- μ L reaction mixture containing 1X GoTaq Green Master Mix (Promega, Madison, WI) and 15 pmol each of forward and reverse primers (Table 1). The amplification protocol consisted of initial denaturation at 95 °C for 2 min, followed by 35 cycles of denaturation at 95 °C for 30 s, annealing at 64 °C for 30 s, extension at 72 °C for 30 s, and a final extension at 72 °C for 5 min.

The PCR products were treated with ExoSAP-IT (Amersham Pharmacia Biotech, Piscataway, NJ) and then cycle sequenced using a BigDye Terminator v3.1 Cycle

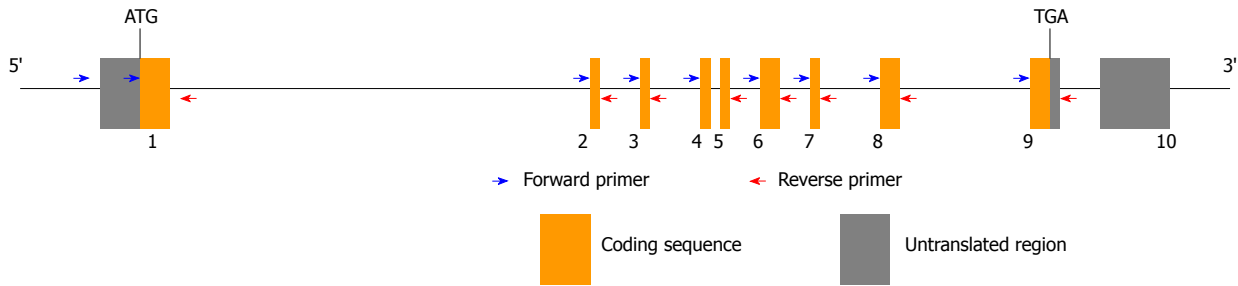


Figure 2 Sites of primers which are employed for polymerase chain reaction and direct sequencing to assess germline mutations of serine/threonine kinase 11 gene.

Table 1 Sequences of forward and reverse primers which are employed for analysis of germline mutations of serine/threonine kinase 11 gene

Primer	Sequence
STK11-5UTR-F	GGCCGTGTTTCATACTTGTC
STK11-Ex1-F	GTCGGAACACAAGGAAGGAC
STK11-Ex1-R	GACCCAGCAAGCCATACT
STK11-Ex2-F	TCCCACAGCACTGTGAATC
STK11-Ex2-R	ATTGCCACAATGGCTGACTT
STK11-Ex3-F	TTTCAGAGGGGTGGCTGAG
STK11-Ex3-R	CTGGCGACAGAGTGAGACT
STK11-Ex3-R-2	CAGAAGAATGGCGTGAACCT
STK11-Ex4-5-F	GCTGGACCTAGCCTTTCCTC
STK11-Ex4-5-R	ACCACCATCTGCCGTATGAG
STK11-Ex6-F	TGGTGAAGACAGAGGTGTCC
STK11-Ex6-R	AGTTCGGAGGGTGAACAGG
STK11-Ex7-F	AGGAGTGGAGTGGCCTCTGT
STK11-Ex7-R	AACAGGACACTGCCAGAGA
STK11-Ex8-F	ATGGCTGAGCTTCTGTGGTC
STK11-Ex8-R	CCACACCTTTTCAGCCATGT
STK11-Ex9-F	GCAGCATTTTCAGGCTGGATA
STK11-Ex9-R	ACGTAGGCCTCCATGACCA

STK11: Serine/threonine kinase 11.

Sequencing FS Ready Reaction Kit (Life Technologies). The cycle sequencing was hot-started at 96 °C for 30 s, followed by 25 cycles of denaturation at 96 °C for 10 s, annealing at 50 °C for 5 s, and extension at 60 °C for 4 min using 1 pmol PCR forward or reverse primer. Sequencing reaction solutions were purified using Sephadex G-50 superfine columns (Amersham Pharmacia Biotech), followed by drying and sequencing of the samples with an ABI Prism 3100 Genetic Analyzer (Life Technologies). All of the coding exons of the *STK11* gene, its boundary regions, and the promoter region were amplified by PCR in accordance with the standard literature methods. PCR was carried out in a total volume of 100 µL containing 200 ng of genomic DNA, 80 pmol of each primer, 100 µmol/L of each deoxyribonucleoside triphosphate, 1.5 µmol/L of magnesium chloride, 10 µL of 10X PCR buffer and 1.0 U of Taq DNA polymerase. The amplification conditions were 95 °C for 5 min, followed by 30 cycles of 94 °C for 30 s, 55 °C for 45 s, 72 °C for 1 min, with a final extension at 72 °C for 10 min in a thermal cycler.

Statistical analysis

Data were shown as mean and range.

RESULTS

The proband in Family I was a 52-year-old male (Case 1) without malignancy, who underwent a laparotomy for polypectomy of small intestinal polyps. His 26-year-old daughter was diagnosed as having cervical cancer, and subsequently underwent hysterectomy (Case 2). In addition, this daughter also underwent laparotomy four times for polypectomy of small intestinal polyps and related intussusceptions. Another daughter, who is 22 years old, has had no reported malignancies as of the present time (Case 3), although she has undergone laparotomy for polypectomy of small intestinal polyps. In Family II, a 65-year-old female (Case 4) was diagnosed with pancreatic cancer, and underwent pancreatoduodenectomy. After further being diagnosed with intraepithelial neoplasia, she underwent an endoscopic submucosal dissection, and had a laparotomy for polypectomy of small intestinal polyps. Her 37-year-old daughter (Case 5) was diagnosed with colon cancer, and had a colectomy. Subsequently, she was also found to have a benign ovarian tumor, in addition to undergoing laparotomy on three separate occasions for polypectomy of small intestinal polyps and related intussusceptions. In Family III, a laparotomy was performed in a 27-year-old female who at the present time has exhibited no malignancies (Case 6).

Magnified endoscopic findings

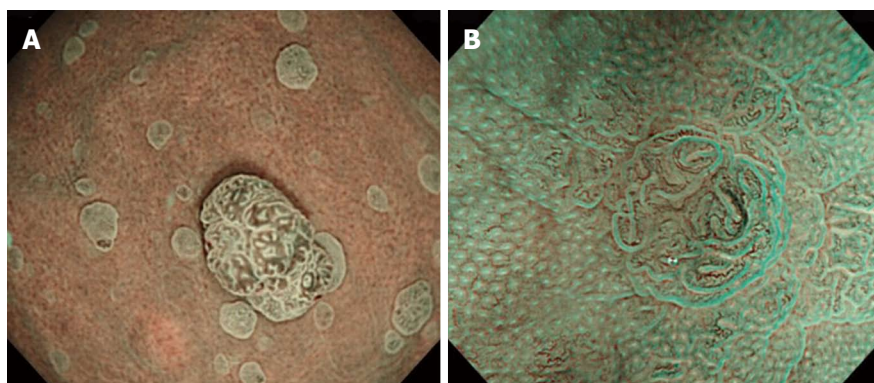
Table 2 summarizes the NBI magnification endoscopic findings. Overall, we found 5 cases of type A (Figure 3A) and one case without the examination for the gastric polyps, while there were 4 cases of type B (Figure 3B) and 2 case of type A for the colorectal polyps.

Polypectomy

As seen in Table 3, we resected a total of 79 small-bowel polyps over 27 sessions, with a mean number of resected polyps per patient of 13.2 (range 1 to 31). The only delayed complication noted in the PJS patients was the occurrence of bleeding in Case 6, and this was successfully managed with hemoclips. Otherwise, there were no serious complications related to the therapeutic DBE. A total of 115 colorectal polyps were resected over 27 sessions, with the mean number of resected polyps per patient calculated to be 19.2 (range 0 to 39). There were also no complications associated with the colorectal pol-

Table 2 Numbers of gastrointestinal polyps in the stomach, small intestine and colorectum, and narrow-band imaging magnification endoscopic findings of the gastric and colorectal lesions

Family	Case No.	Polyps			Narrow-band imaging magnification type	
		Stomach	Small intestine	Colorectum	Stomach	Colorectum
I	1	Sporadic	Multiple	Multiple	NE	A
	2	Multiple	Multiple	Multiple	A	B
	3	Sporadic	Sporadic	Multiple	A	B
II	4	Multiple	Multiple	Multiple	A	B
	5	Multiple	Multiple	Multiple	A	B
III	6	Multiple	Solitary	Sporadic	A	A

**Figure 3** Narrow-band imaging-magnification gastroscopic picture. A: Narrow-band imaging (NBI)-magnification gastroscopic picture showing type A of the classification; B: NBI-magnification colonoscopic picture showing type B of the classification.**Table 3** Numbers and sizes of the small-bowel and colorectal polyps that were resected endoscopically and session times of polypectomy

Family	Case No.	Polypectomy for the small intestinal polyps			Polypectomy for the colorectal polyps		
		Times	<i>n</i>	Size (mm)	Times	<i>n</i>	Size (mm)
I	1	5	21	10-35	6	10	5-15
	2	7	31	10-25	6	39	5-10
	3	1	1	20	1	3	5
II	4	6	10	10-20	10	54	5-10
	5	7	15	10-30	4	9	5-10
III	6	1	1	50	0	0	-

ypectomies. The resected polyps varied in size among the PJS patients, and histopathologically, no malignant components were found within these resected polyps.

STK11 gene mutation

All 3 cases in Family I exhibited the +658C>T nonsense mutation in exon 5 (Figure 4), which resulted in the production of a truncated protein (Q220X). In Family II, Case 4 had -252C>A and -193C>A in the promoter region, while no germline mutations were noted for Case 5. In Family III, Case 6 was found to have the +1062C>G (F342L) mutation in exon 8.

DISCUSSION

Mutations in the *STK11* gene on chromosome 19p13.3 have been identified as the cause of PJS^[3,5,6]. *STK11* is a highly conserved gene that extends over 23 kb and con-

sists of nine exons, and one non-coding exon, coding for a 433-amino acid coding sequence and one non-coding exon^[1,3,5,6]. *STK11* protein is primarily composed of three major domains, including an N-terminal non-catalytic domain, a catalytic kinase domain and a C-terminal regulatory domain^[1,3,5-9]. Although the exact function of *STK11* as of yet remains unclear, prior studies have demonstrated that a mutation in the *STK11* gene can lead to a loss of kinase activity^[1,3,5-9,31]. This loss of activity is most likely responsible for the development of the PJS phenotype. Codons 50-337 are responsible for encoding the catalytic kinase domain. It has been proposed that the *STK11* gene may act as a tumor suppressor gene and thus, could be involved in early development of the pathogenesis in which hamartomas are converted into adenocarcinoma^[32-34]. In our study, we identified *STK11* mutations in both Families I and III. These mutations have never been reported in any database or in any pre-

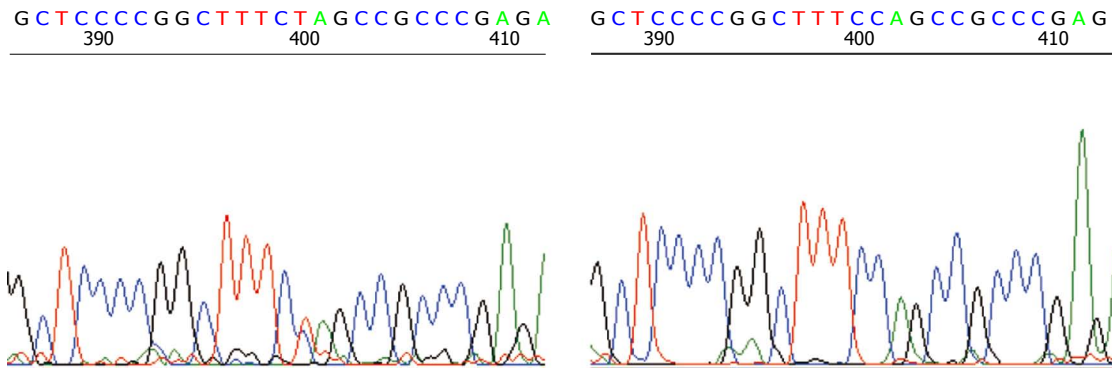


Figure 4 Serine/threonine kinase 11 germline mutation of +658C>T in exon5 that was identified in all the 3 Peutz-Jeghers syndrome patients in Family I.

viously published articles, which indicates that they are novel mutations. In particular, the +658C>T nonsense mutation that was found in exon 5 in the Family I results in a truncated protein that may be non-functional due to a loss of the kinase activity. More recently, Salloch *et al.*^[35] have shown that patients who have a truncating mutation in the *STK11* gene were more severely affected from the disease as compared with the patients with a non-truncating mutation. These findings suggest when the mutation is present, there is a tendency to have more carcinomas and polyps, in addition to having a significantly increased number of surgical interventions. In a further study that examined a larger number of subjects, a total of 240 PJS patients with the *STK11* mutation were analyzed^[3]. Even though no differences were seen between individuals with missense and truncating mutations, or between familial and sporadic cases, the results did suggest that there was a higher risk of cancer in individuals with mutations in exon 3 of the gene^[3]. On the other hand, a larger study found that the type and site of *STK11* mutation did not influence cancer risk^[36]. Since we only examined a small series of PJS patients, it was not possible to assess the potential genotype-phenotype correlations in the current study.

The +1062C>G (F342L) mutation seen in exon 8 in Case 6 is a missense mutation that results in the F342L amino acid substitution. Since this mutation was not involved in the codons that encode the catalytic kinase domain, it might not affect the *STK11* functions. This may explain the relatively indolent phenotypes, including the sparse distribution and paucity of the gastrointestinal polyps that were seen in Case 6. Amos *et al.*^[37] suggested that individuals with these missense mutations have a later onset of symptoms as compared to those individuals with the other *STK11* mutations. Clearly, further studies are warranted in order to be able to definitively clarify the biologic significance of these non-truncating mutations.

Family II patient cases had multiple gastrointestinal polyps and more serious, complicated malignancies. Nevertheless, we could not detect any mutations in these subjects. While the absence of *STK11* mutations does occasionally occur in some PJS patients, the reason for this remains unclear at the present time. *STK11/LKB1* gene mutation is found in approximately 30%-70% of

sporadic cases of PJS and 70% of affected individuals with a family history of the condition^[1]. Recent studies have attempted to use the multiplex ligation dependent probe amplification analysis to screen for gene and exon scale mutations in a set of PJS cases in which the *STK11* mutations could not be detected. These studies showed that the detection rates of *STK11* mutations in PJS patients tended to be higher, with rates reaching nearly 80%-94%^[10-12]. It is likely that with continued improvements in genetic testing that mutation detection rates will improve further, making genetic heterogeneity even less likely. The lack of identification of a *STK11* gene mutation also suggests genetic mosaicism or additional PJS loci^[1,38,39].

PJS is associated with an increased risk of gastrointestinal and nongastrointestinal malignancies^[1,3,4,28,36]. The most common sites for malignancy include colorectal, breast, stomach, small bowel, and pancreas. Since gastrointestinal hamartomatous polyps are benign, they were not initially thought to represent a premalignant condition^[1,3,4]. However, several studies have shown that the distribution of the gastrointestinal cancers in PJS patients is similar to that of the hamartomatous polyps, in addition to clearly documenting that carcinoma arises in hamartomas^[40,41]. As a result, surveillance GI endoscopy is now recommended for detection of cancer^[3]. Moreover, the ability to be able to predict the histologic grade and invasion depth of gastrointestinal neoplastic lesions is of clinical importance. The NBI magnification classification scheme that was proposed by Kanao *et al.*^[17] has proven to be useful for both predicting the histology and for selecting optimal therapeutic strategies. In Kanao's study, they examined the sensitivity and specificity of the various lesions for diagnosing carcinomas. Their results showed that the sensitivities and specificities of the type A lesions for hyperplastic polyps were 100% and 98.9%, while the type B lesions for tubular adenoma were 85.5% and 71.0%, respectively. The sensitivities and specificities of the type C1 lesions for diagnosis of tubular adenoma or mucosal/minimally invasive colorectal cancer diagnosis were 80.0% and 89.4%, while for the type C3 lesions for the diagnosis of carcinoma with massive submucosal invasion, they were 63.8% and 100%, respectively. Based on these findings, endoscopic resection should be select-

ed when type B and C1 lesions are present, while surgical resection should be selected for type C3 lesions. In the current study, we diagnosed the gastric polyps observed in our patients according to the NBI-based classification. As seen in Table 2, all of these polyps were classified as type A in each of the cases and thus, they did not require further treatment. This suggests all of these polyps were of a hyperplastic (hamartomatous) histology type. On the other hand, the colorectal polyps were classified as B type polyps, and since they were larger than 5 mm in size, they were endoscopically resected. Regardless of the treatment, there were no complications noted in our series.

Small-bowel polyps are the most significant clinical feature of PJS^[1,3,4,19]. These hamartomas can lead to complications such as bowel obstruction and severe GI bleeding, which necessitates multiple emergency laparotomies and bowel resections^[20,21]. In the present study, 5 out of 6 cases had one or more laparotomies due to intussusception or other significant symptoms. Therefore, when small-bowel polyps were more than 10 mm in size in PJS patients, we performed endoscopic resection using DBE. In the current study, a total of 79 small-bowel polyps were safely resected without serious complications in any of the patients. However, in another study that examined a larger number of PJS cases, the total complication rate after therapeutic DBE was performed was relatively higher, with 6.8% of the patients exhibiting complications^[19]. When taken together with the findings for our small case series, these results justify performing a future prospective multicenter study that is specifically designed to examine PJS patient treatment protocols.

We report two novel mutations of STK11 that are associated with PJS. Endoscopic management of GI polyps in PJS patients using DBE or colonoscopy appears to be both safe and effective, and may help to prevent emergency laparotomies and reduce the cancer risk. Additionally, NBI magnification endoscopic observation provides helpful information that can be used to select optimal therapeutic strategies for GI tumors in PJS.

COMMENTS

Background

Peutz-Jeghers syndrome (PJS) is an autosomal-dominant hereditary condition characterized by gastrointestinal (GI) hamartomatous polyps and mucocutaneous pigmentation. Mutations in the serine/threonine kinase 11 (*STK11*) gene play a causal role in PJS. Endoscopic polypectomy of GI polyps may help to prevent emergency laparotomies and reduce PJS-related cancer risk.

Research frontiers

PJS occurrence is primarily associated with germline mutations in the *STK11/LKB1* gene, which are localized on the chromosomal segment 19p13.3. The gene spans 23 kb, and consists of nine coding exons and a final noncoding exon. The coded protein plays a role in cellular energy metabolism, cell polarization, p53-dependent apoptosis, and Wnt signal transduction. The germline mutation detection rates in PJS patients vary among reports, but recent studies which have searched for germline mutations using state-of-art techniques demonstrate between 80% and 94%. Most mutations are single base substitutions/insertions or small deletions that result in an abnormal truncated protein.

Innovations and breakthroughs

Although the exact function of STK11 as of yet remains unclear, prior studies have demonstrated that a mutation in the *STK11* gene can lead to a loss of

kinase activity. This loss of activity is most likely responsible for the development of the PJS phenotype. Codons 50-337 are responsible for encoding the catalytic kinase domain. In the study, the authors identified *STK11* mutations in two families. These mutations have never been reported in any database or in any previously published articles, which indicates that they are novel mutations. In particular, the +658C>T nonsense mutation that was found in exon 5 results in a truncated protein that may be non-functional due to a loss of the kinase activity. The +1062C>G (F342L) mutation seen in exon 8 is a missense mutation that results in the F342L amino acid substitution. Since this mutation was not involved in the codons that encode the catalytic kinase domain, it might not affect the *STK11* functions, suggesting that individuals with these missense mutations have a later onset of symptoms.

Applications

It has been proposed that the *STK11* gene may act as a tumor suppressor gene and thus, could be involved in early development of the pathogenesis in which hamartomas are converted into adenocarcinoma. It is useful in clinical management of PJS and to predict its clinical course to assess this gene mutations.

Terminology

The *STK11* gene is located on chromosome 19p13.3 and the mutations in *STK11* gene have been identified as the cause of PJS. *STK11* is a highly conserved gene that extends over 23 kb and consists of nine exons, and one non-coding exon, coding for a 433-amino acid coding sequence and one non-coding exon. *STK11* protein is primarily composed of three major domains, including an N-terminal non-catalytic domain, a catalytic kinase domain and a C-terminal regulatory domain. PJS is a rare autosomal-dominant hereditary condition with incomplete penetrance that is characterized by hamartomatous polyps of the gastrointestinal tract and pigmented lesions of the buccal mucosa, perioral region and other sites. Variable penetrance and clinical heterogeneity make it difficult to determine the exact frequency of PJS. Most PJS patients develop significant hamartomatous polyps of the small bowel, with these polyps commonly arising in the stomach and colorectum.

Peer review

This is a good study in which authors explore mutations in *STK11* gene in PJS with GI hamartomatous polyps. The results are interesting and suggest that endoscopic polypectomy of GI polyps in PJS patients appears to be useful to prevent emergency laparotomies and reduce the cancer risk.

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Diagnosis of the jejunoileal lymphoma by double-balloon endoscopy

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$n = 2$), enteropathy associated T cell lymphoma (ETL, $n = 1$) and anaplastic large cell lymphoma (ALCL, $n = 1$).

RESULTS: Ten cases showed accumulation by FDG-PET (50%). FDG-PET was positive in 3 of 12 FL cases (25%) while in 7 of 8 non-FL cases (88%, $P < 0.05$). Intestinal FL showed a significantly lower rate of positive FDG-PET, in comparison with other types of lymphoma. Cases with endoscopically elevated lesions ($n = 10$) showed positive FDG-PET in 2 (20%), but those with other type NHL did in 8 of 10 (80%, $P < 0.05$). When the cases having elevated type was compared with those not having elevated type lesion, the number of cases that showed accumulation of FDG was significantly smaller in the former than in the latter.

CONCLUSION: In a significant proportion, small intestinal involvement cannot be pointed out by FDG-PET. Especially, FL is difficult to evaluate by FDG-PET but essentially requires DBE.

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Abstract

AIM: To investigate the feasibility of double-balloon endoscopy (DBE) to detect jejunoileal lymphoma, compared with fluorodeoxyglucose positron emission tomography (FDG-PET).

METHODS: Between March 2004 and January 2011, we histologically confirmed involvement of malignant lymphoma of the jejunoileum in 31 patients by DBE and biopsy. In 20 patients of them, we performed with FDG-PET. We retrospectively reviewed the records of these 20 patients. Their median age was 64 years (range 50-81). In the 20 patients, the pathological diagnosis of underlying non-Hodgkin's lymphoma (NHL) comprised follicular lymphoma (FL, $n = 12$), diffuse large B cell lymphoma (DLBCL, $n = 4$), mantle cell lymphoma (MCL,

Key words: Double-balloon endoscopy; Non-Hodgkin's lymphoma; Jejunoileum; Fluorodeoxyglucose positron emission tomography; Follicular lymphoma

Ibuka T, Araki H, Sugiyama T, Nakanishi T, Onogi F, Shimizu M, Hara T, Takami T, Tsurumi H, Moriawaki H. Diagnosis of the jejunoileal lymphoma by double-balloon endoscopy. *World J Gastrointest Endosc* 2013; 5(3): 111-116 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i3/111.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i3.111>

INTRODUCTION

The clinical stage of non-Hodgkin's lymphoma (NHL) is usually determined by imaging modalities such as com-

puted tomography (CT) and 18F-fluorodeoxyglucose positron emission tomography (FDG-PET). FDG-PET has become a routine measure for staging and follow-up of patients with malignant lymphoma^[1]. Staging parameters include extranodal involvement, and the gastrointestinal tract is the most common site. Although the actual incidence of small intestinal involvement is unknown, surgical pathology estimates that small intestinal lymphoma accounts for 4%-12% of all reported NHL^[2-4]. Since small intestinal involvement of NHL easily leads to perforation, peritonitis, and subsequent poor outcome after chemotherapy, investigations into the small intestine are important to determine the most appropriate treatment strategy for patients with NHL. However, there is a limitation in the diagnosis by FDG-PET for this aim, since biologic characteristics of specific histologic subtypes of lymphoma result in different degrees of FDG uptake^[5]. Capsule endoscopy or double-balloon endoscopy (DBE) can detect such lesions of lymphoma, but biopsy samples can be obtained only by using DBE. DBE is a novel diagnostic and therapeutic modality that was originally described by Yamamoto *et al.*^[6]. The procedure allows high-resolution images, as well as diagnostic sampling and therapeutic interventions in all segments of the small intestine. Thus, DBE developed non-surgical evaluation of the small intestine. Here, we examined the feasibility of DBE to detect small intestinal involvement of NHL, in comparison with FDG-PET.

MATERIALS AND METHODS

Patients

Between March 2004 and January 2011, we histologically confirmed involvement of malignant lymphoma of the jejunum in 31 patients by DBE and biopsy. In 20 patients of them, we performed with FDG-PET. We retrospectively reviewed the records of these 20 patients. Their median age was 64 years (range 50-81 years). Their demographic and clinical characteristics are summarized in Table 1. In the 20 patients, the pathological diagnosis of underlying NHL comprised follicular lymphoma (FL, $n = 12$), diffuse large B cell lymphoma (DLBCL, $n = 4$), mantle cell lymphoma (MCL, $n = 2$), enteropathy associated T cell lymphoma (ETL, $n = 1$) and anaplastic large cell lymphoma (ALCL, $n = 1$) (Table 2).

Eligibility criteria for DBE in lymphoma patients

Eligibility criteria for DBE in lymphoma patients were: (1) lymphoma infiltration of the stomach, duodenum or colon proven by gastrointestinal endoscopy or colonoscopy which are routine evaluation of lymphoma patients in our institution; (2) intraabdominal lesion suspected from CT or gallium-scintigraphy/FDG-PET imaging; or (3) any gastrointestinal symptoms such as a bloated sensation in the abdomen, abdominal pain, diarrhea, constipation, protein-losing syndrome or hematochezia. Exclusion criterion was poor performance status of grade 3 or 4 assessed by Eastern Cooperative Oncology Group

Table 1 Demographic and clinical characteristics of the patients with confirmed involvement of malignant lymphoma in the jejunum by double-balloon endoscopy and who also underwent fluorodeoxyglucose positron emission tomography

Total number of patients	20
Gender	
Male	14
Female	6
Median age (yr)	64
(range)	(50-81)
Observation	
Jejunum + ileum	11
Jejunum	4
Ileum	5
Location	
Jejunum + ileum	9
Jejunum	6
Ileum	5
Number of lesions	
Solitary	2
Multiple	16
Diffuse	2

classification^[7]. We conducted DBE from both oral and anal routes in principle. However, in the patients who did not give consent to this dual approach mainly due to the examination burden, we selected only one-sided insertion according to the information of preceding gastrointestinal endoscopy and colonoscopy.

Locations and multiplicity of lymphoma lesions confirmed by DBE

We observed jejunum and ileum in 11 cases by the combination of both oral and anal approach, only jejunum in 4 cases by oral approach, and only ileum in 5 cases by anal approach. Six, five and nine patients had lesions in the jejunum, ileum, and in both, respectively. We observed multiple lesions in 16 cases, solitary lesion in 2 cases, and diffuse lesion in 2 cases.

DBE

DBE was carried out in the Endoscopy Unit of Gifu University Hospital using a Fujinon system (EN450-T5/W, Fujinon Corporation, Saitama, Japan). The whole procedure is similar to that described in detail elsewhere^[8-10]. In brief, the system comprises an endoscope and a flexible overtube that are both provided with soft latex balloons connected through a built-in air route to a controlled pump system. Patients ingested 2 L of a polyethylene glycol-based solution on the day before the examination. The small intestine was examined endoscopically using a combination of antegrade (oral) and retrograde (anal) DBEs. We obtained biopsy specimens of all lesions detected during the procedure.

Statistical analysis

Pretreatment characteristics were compared between FDG-PET-positive and -negative patients by the Fisher's exact test or Student's *t*-test. *P* values of < 0.05 indicated significance.

Table 2 Characteristics of fluorodeoxyglucose positron emission tomography-positive or -negative patients

	All cases	FDG-PET		P value
		Positive	Negative	
All cases	20	10	10	
Histology				
FL	12	3	9	
DLBCL	4	3	1	
MCL	2	2	0	
ETL	1	1	0	
ALCL	1	1	0	
FL	12	3	9	< 0.05 ¹
Others	8	7	1	
Endoscopic findings				
Elevated	5	1	4	
Ulcerative	5	4	1	
MLP	3	2	1	
Diffuse infiltration	1	1	0	
Diffuse infiltration + ulcerative	1	1	0	
Elevated + MLP	5	1	4	
Including elevated	10	2	8	< 0.05 ¹
Not including elevated	10	8	2	
Clinical Stage				
I	1	1	1	
II	5	3	2	
III	3	1	2	
IV	9	5	5	
I / II	6	4	3	NS
III / IV	12	6	7	
Abdominal symptom				
Present	6	5	1	NS
Absent	14	5	9	
B symptom				
Present	10	5	5	NS
Absent	10	5	5	
Other gastrointestinal tract lesions				
Absent	10	6	4	NS
Present	10	4	6	
Esophagus	2	2	0	
Stomach	6	4	2	
Duodenum	12	5	7	
Colon	2	2	0	
PS				
0	18	9	9	NS
1	2	1	1	
Hemoglobin (g/dL)				
Median	13.7	13.1	14.1	NS
(range)	(7.8-17.1)	(7.8-16.3)	(12.1-17.1)	
Lactate dehydrogenase (IU/L)				
Median	196	197	187	NS
(range)	(108-1195)	(108-342)	(126-1195)	
Soluble interleukin-2 receptor (U/mL)				
Median	1350	2302	802	NS
(range)	(363-7410)	(371-6880)	(363-7410)	

¹By Fisher's exact test. FDG-PET: Fluorodeoxyglucose positron emission tomography; DLBCL: Diffuse large B-cell lymphoma; FL: Follicular lymphoma; MCL: Mantle cell lymphoma; ETL: Enteropathy associated T-cell lymphoma; ALCL: Anaplastic large cell lymphoma; MLP: Multiple lymphomatous polyposis; PS: Performance status; NS: Not significant.

RESULTS

Histopathological classification

Ten of 20 cases with malignant lymphoma confirmed by DBE showed accumulation by FDG-PET (50%). In

these 10 cases, histopathological classification was FL in 3 cases, DLBCL in 3, MCL in 2, ETL in 1 and ALCL in 1. In the cases which did not show FDG accumulation, histopathological classification was FL in 9 cases and DLBCL in 1. Thus, intestinal FL showed a significantly lower rate of positive FDG-PET, in comparison with other types of lymphoma ($P < 0.05$) (Table 2).

Endoscopic findings

Macroscopically, 5 tumors were classified as elevated type (5 FL cases), 5 as ulcerative type (4 DLBCL cases, 1 FL case), 3 as multiple lymphomatoid polyposis (MLP) type (2 MCL cases, 1 FL case), 1 as diffuse-infiltrating type (1 ETL case), 1 as diffuse infiltration+ulcerative (1 ALCL case) and 5 as elevated + MLP type (5 FL cases). Thus, the cases with elevated type all belonged to FL.

In the 10 cases that showed accumulation of FDG, 4 tumor was classified as ulcerative type (Figure 1), 2 as MLP type, 1 as elevated type (Figure 2), 1 as diffuse-infiltrating type, 1 as diffuse infiltration+ulcerative and 1 as elevated + MLP type. In other 10 cases that did not show accumulation of FDG, 4 tumors were classified as elevated type (Figure 3), 1 as ulcerative type, 1 as MLP type, and 4 as elevated + MLP type. When the cases having elevated type was compared with those not having elevated type lesion, the number of cases that showed accumulation of FDG was significantly smaller in the former than in the latter ($P < 0.05$) (Table 2).

Other parameters

Clinical stage, abdominal symptom, B symptom, other gastrointestinal tract lesions, performance status (PS), lactate dehydrogenase (LDH), hemoglobin (Hb) or soluble interleukin-2 receptor (sIL-2R) did not produce significant difference in the accumulation of FDG (Table 2).

Adverse events of DBE

We had no complications associated with DBE in all twenty cases.

DISCUSSION

NHL frequently involves the gastrointestinal tract and forms multiple tumors^[11-14]. Since the small intestine is a preferential site of such involvement^[2-4] and could be complicated with perforation following chemotherapy, it is important to diagnose NHL invasion into the small intestine in advance. For this aim, DBE is invasive while FDG-PET is not. Thus, FDG-PET is now a routine measure for staging and follow-up of patients with malignant lymphoma^[1], since it has been proven as useful to clinically evaluate these patients^[15]. In our study, however, FDG-PET could not detect small intestinal involvement in 10 (50%) of the 20 patients with confirmed small intestinal involvement. Therefore, we emphasize that DBE is essential for the diagnosis of such involvement of lymphoma and for the subsequent management of the patients. Less invasive capsule endoscopy can image the

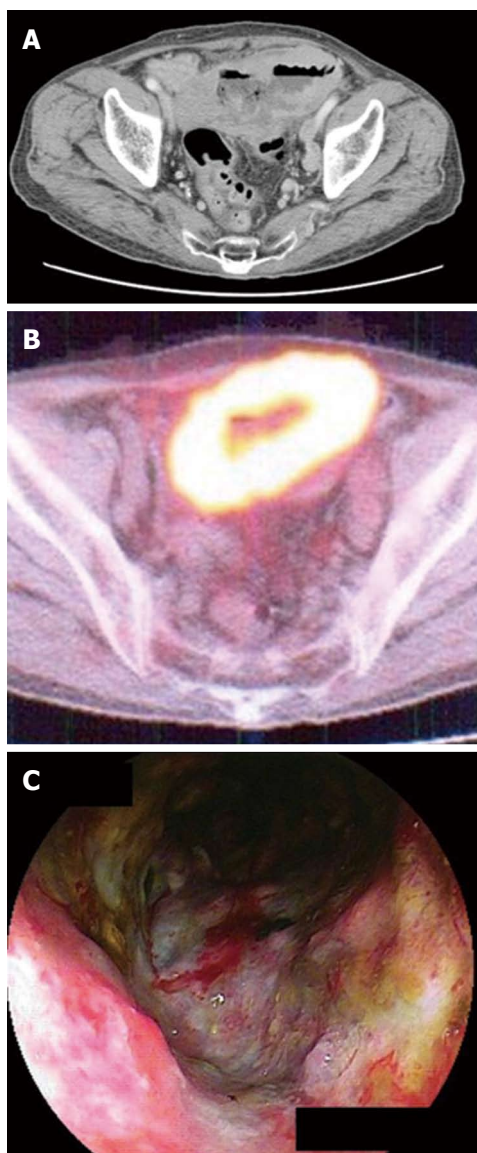


Figure 1 In the 10 cases that showed accumulation of fluorodeoxyglucose, 4 tumor was classified as ulcerative type. A: The isolated dilation and wall thickening of the small intestine was recognized by computed tomography in a 78-year-old man with anemia and abdominal tumor; B: At the same site, fluorodeoxyglucose accumulated; C: The ulcerative tumor was observed by double-balloon endoscopy. The histopathological diagnosis was diffuse large B-cell lymphoma.

entire gastrointestinal tract and thus might also be useful to detect small intestinal involvement of lymphoma^[16,17]. However, application of this method is limited, because biopsy specimens cannot be obtained. Although invasive, DBE is the sole endoscopic approach that enables biopsy of small intestine.

The good diagnostic ability of FDG-PET for extra-nodal lymphoma lesions has been demonstrated with sensitivity of 67%-100%^[18-22]. Our sensitivity of FDG-PET was lower than previous reports, probably because the number of FL cases was large.

Yamamoto *et al.*^[23] reported that in 14 of 16 FL cases of the small intestine, there were no obvious accumula-

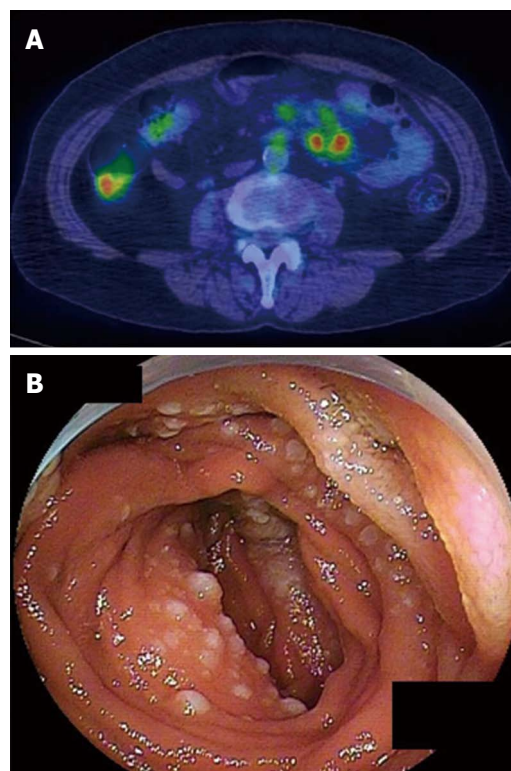


Figure 2 In the 10 cases that showed accumulation of fluorodeoxyglucose, 1 as elevated type. A: Multiple foci of abnormally increased fluorodeoxyglucose uptake were recognized in a 64-year-old female case of follicular lymphoma; B: Small intestinal involvement was confirmed by double-balloon endoscopy.

tions of 18F-FDG in the primary lesions, giving a low diagnostic sensitivity of 12.5%. In our study, the proportion of patients with positive FDG-PET was significantly lower in FL cases when compared to other types of lymphoma (Table 2). On the other hand, it is reported that FDG-PET detected disease on at least one site in 98% of FL patients^[5], supporting its usefulness for staging of patients with FL^[24]. However, in another report of duodenal FL, 18F-FDG accumulated in the mesenteric lymph nodes but not in the primary duodenal site^[25]. Hoffmann *et al.*^[26] also reported that FDG-PET is not useful for clinical assessment of primary duodenal FL. Higuchi *et al.*^[27] further reported that increased uptake of 18F-FDG was not observed in the confirmed jejunoileal FL lesions in their 6 patients. We also experienced FL case that 18F-FDG accumulated in the intraabdominal lymph nodes, whereas there was no obvious uptake in the jejunoileum site (Figure 3). We thus think that FDG-PET is not useful for clinical assessment of jejunoileum FL and DBE is essential to diagnose the gastrointestinal involvement of FL. Thus, as reported by Tanaka *et al.*^[28], intestinal FL seems to have distinct clinicopathological characteristics from other intestinal lymphoma.

The morphological features of small intestinal involvement were basically the same as those in the stomach or duodenum^[11-14]. We identified a variety of morphologies, such as ulcerative, MLP, diffuse infiltration,

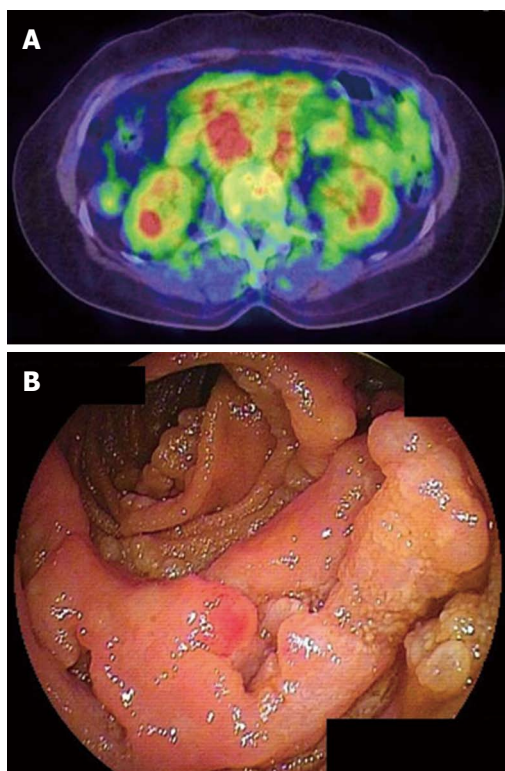


Figure 3 In other 10 cases that did not show accumulation of fluorodeoxyglucose, 4 tumors were classified as elevated type. A: In a 64-year-old female with follicular lymphoma, we identified abnormally increased fluorodeoxyglucose uptake only in the intraabdominal lymph nodes, but not in the small intestine; B: However, small intestinal involvement was confirmed by double-balloon endoscopy.

and elevated types. The most typical finding in FL was multiple whitish small nodules. Nakamura *et al*^[29] showed that endoscopic findings of primary intestinal FL by DBE were varied, including mass formation, swelling of folds, and stenosis of intestine. In our analysis, multiple whitish small nodules, mass formation and swelling of folds were included in elevated type.

In the cases including elevated type, accumulation of FDG appeared in significantly fewer cases than in those without elevated type (Table 2). For the reason, we suppose that majority of FL patients showed elevated type of small intestinal involvement.

Although we had no complications associated with DBE in all twenty cases, it is reported that 40 adverse events were experienced in 2362 DBE procedure (1.7%)^[30], including pancreatitis in 7 patients (0.3%), bleeding in 19 patients (0.8%), perforation in 6 patients (0.3%), and others in 8 (0.3%). However, only regarding diagnostic DBE (1728 patients), the incidence of complication was 0.8%^[30]. We think that DBE is a safe and well-tolerated method, but it is necessary to take care about adverse events.

In conclusion, in a significant proportion of lymphoma cases, small intestinal involvement cannot be pointed out by FDG-PET. Especially, the small intestinal FL is difficult to evaluate by FDG-PET but essentially requires DBE.

COMMENTS

Background

Presence of small intestinal involvement is important to determine the clinical stage and subsequent most appropriate treatment strategy in patients with malignant lymphoma. However, there is a limitation in the currently recommended diagnostic modality of fluorodeoxyglucose positron emission tomography (FDG-PET). Here, the authors examined the feasibility of double-balloon endoscopy (DBE) to detect small intestinal involvement of lymphoma, in comparison with FDG-PET.

Research frontiers

The good diagnostic ability of FDG-PET for extranodal lymphoma lesions has been generally agreed. However, the diagnostic power of FDG-PET is significantly low for primary duodenal follicular lymphoma.

Innovations and breakthroughs

Many papers report the usefulness of FDG-PET to detect the small intestinal involvement of lymphoma, but limitation also exists as described above. The authors examined the feasibility of DBE to detect small intestinal involvement of lymphoma in comparison with FDG-PET and broke-through that limitation.

Applications

In a significant proportion of lymphoma cases, small intestinal involvement cannot be pointed out by FDG-PET. Especially, the small intestinal follicular lymphoma is difficult to evaluate by FDG-PET but essentially requires DBE.

Terminology

DBE is an innovative fiber endoscopy equipped with double balloon function that enables observation and biopsy of deep small intestine. DBE actually covers the whole small intestine when used with both oral and anal insertion routes. Non-Hodgkin's lymphoma (NHL) shares about 95% of malignant lymphoma in Japan. Major subtypes of NHL include diffuse large B-cell lymphoma and follicular lymphoma.

Peer review

In this article, the authors described the better diagnostic yield of using DBE than using PET scan in the diagnosis of small bowel follicular lymphoma. The results are interesting and potentially clinically meaningful.

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Clinical usefulness of single-balloon endoscopy in patients with previously incomplete colonoscopy

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Abstract

AIM: To evaluate the clinical usefulness of single-balloon endoscopy (SBE) in patients in whom a colonoscopy was technically difficult to insert previously.

METHODS: The study group comprised 15 patients (8 men and 7 women) who underwent SBE for colonoscopy (30 sessions). The number of SBE sessions was 1 in 7 patients, 2 in 5 patients, 3 in 1 patient, 4 in 1 patient, and 6 in 1 patient. In all patients, total colonoscopy was previously unsuccessful. The reasons for difficulty in scope passage were an elongated colon in 6 patients, severe intestinal adhesions after open surgery in 4, an elongated colon and severe intestinal adhesions in 2, a left inguinal hernia in 2, and multiple diverticulosis of the sigmoid colon in 1. Three endoscopists were responsible for SBE. The technique for inserting SBE in the colon was basically similar to that in the small intestine. The effectiveness of SBE was assessed on the basis of the success rate of total colonoscopy and the presence or absence of complications. We also evaluated the diagnostic and treatment outcomes of colonoscopic examinations with SBE.

RESULTS: Total colonoscopy was successfully accomplished in all sessions. The mean insertion time to the cecum was 22.9 ± 8.9 min (range 9 to 40). Abnormalities were found during 21 sessions of SBE. The most common abnormality was colorectal polyps (20 sessions), followed by radiation colitis (3 sessions) and diverticular disease of the colon (3 sessions). Colorectal polyps were resected endoscopically in 15 sessions. A total of 42 polyps were resected endoscopically, using snare polypectomy in 32 lesions, hot biopsy in 7 lesions, and endoscopic mucosal resection in 3 lesions. Fifty-six colorectal polyps were newly diagnosed on colonoscopic examination with SBE. Histopathologically, these lesions included 2 intramucosal cancers, 42 tubular adenomas, and 2 tubulovillous adenomas. The mean examination time was 48.2 ± 20.0 min (range 25 to 90). Colonoscopic examination or endoscopic treatment with SBE was not associated with any serious complications.

CONCLUSION: SBE is a useful and safe procedure in patients in whom a colonoscopy is technically difficult to insert.

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Key words: Single-balloon endoscopy; Colonoscopy; Difficult to insert; Diagnosis; Endoscopic treatment

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INTRODUCTION

Colonoscopy is playing an increasingly important part

in the diagnosis and treatment of colorectal diseases. Its diagnostic role has been enhanced by the development of improved imaging techniques such as magnifying endoscopy and narrow band imaging. Therapeutically, progress in resection techniques such as endoscopic mucosal resection and endoscopic submucosal dissection has contributed to the widespread application of colonoscopic therapy. The availability of improved devices such as variable stiffness and small-caliber colonoscopes allows instruments optimally suited for individual patients to be selected^[1,2]. Despite recent progress, however, the passage of a colonoscope is often difficult in subjects who have an elongated colon or severe adhesions.

Balloon endoscopy was originally developed to facilitate insertion of an endoscope deep into the small intestine. First, double-balloon endoscopy (DBE) was developed by Yamamoto *et al*^[3]. Subsequently, single-balloon endoscopy (SBE) was developed and applied clinically^[4-6]. A balloon at the tip of a sliding tube or an overtube is inflated to grip the intestine, and both the scope and the sliding tube are simultaneously withdrawn, thus shortening the intestine. By repeating these maneuvers, the endoscope can be inserted more deeply into the small intestine.

We performed colonoscopy by SBE in patients in whom a conventional colonoscope was technically difficult to insert because of an elongated colon or severe adhesions and retrospectively evaluated the clinical usefulness of this procedure.

MATERIALS AND METHODS

Patients

The study group comprised 15 patients (8 men and 7 women) who underwent SBE for colonoscopy (30 sessions) in our hospital from July 2007 through June 2012. The number of SBE sessions was 1 in 7 patients, 2 in 5 patients, 3 in 1 patient, 4 in 1 patient, and 6 in 1 patient. The mean age at examination was 65.7 ± 8.7 years (range 38 to 81). Seven patients concurrently had cardiovascular diseases such as arrhythmias and hypertension, 1 had diabetes mellitus, and 1 had a history of cerebral infarction. Six patients had a history of open surgery (total hysterectomy in 5 and cholecystectomy in 2). Two patients who had undergone total hysterectomy had received radiotherapy to treat uterine cancer.

Total colonoscopy was technically difficult to perform in all patients. In 5 patients, total colonoscopy was unable to be performed by their previous physicians. In the other 10 patients, total colonoscopy was not successfully accomplished at the previous examination in our hospital. In 9 of these patients, the first author of this paper, who has more than 20 years of experience in colonoscopy, was charge of the previous examinations. The deepest part of the colon reached on previous unsuccessful colonoscopic examinations was the sigmoid colon in 7 patients, followed by the transverse colon in 3, the descending colon in 2, and the ascending colon in 2. The details



Figure 1 External appearance of the tip of a single-balloon endoscope.

were unknown for 1 patient in whom colonoscopy was performed by a previous physician. The mean time from starting scope insertion to the unsuccessful discontinuation of examination was 30.7 ± 6.4 min (range 19 to 38 min) in 10 patients for whom the details were provided by their previous physicians; the details of examination were unavailable for 5 patients. The reasons for difficulty in scope passage were an elongated colon in 6 patients (40%), severe intestinal adhesions after open surgery in 4 (27%), an elongated colon and severe intestinal adhesions in 2 (13%), a left inguinal hernia in 2 (13%), and multiple diverticulosis of the sigmoid colon in 1 (7%).

Methods

Among 30 sessions of SBE, the objective was follow-up after endoscopic resection of colorectal polyps in 21 sessions (70%), endoscopic resection of colorectal polyps in 5 sessions, confirmation of colorectal polyps suspected on barium enema examination in 3 sessions, and screening for colorectal disease in 1 session. Three endoscopists were responsible for SBE. The first author was in charge of 26 sessions (87%). Twenty-three sessions (77%) were performed on an outpatient basis, and 7 sessions (23%) were performed after hospitalization.

As premedication, antispasmodic drugs such as scopolamine butylbromide (10 mg) were administered before 24 sessions (80%). Sedatives and analgesic agents were concurrently used in 28 sessions (93%), including 14 sessions in which multiple drugs were used. The used drugs were diazepam in 25 sessions, pethidine hydrochloride in 15, propofol in 2, and midazolam in 1.

SBE was performed with an enteroscope with an effective length of 2000 mm, an outer diameter of 9.2 mm, and a forceps channel diameter of 2.8 mm, allowing the use of conventional endoscopic devices (Figure 1). The SBE system consisted of a dedicated sliding tube with a silicone balloon attached to its tip. Single-balloon colonoscopy was performed by the two-operator technique under fluoroscopic guidance. The basic insertion procedure was similar to that of conventional enteroscopy. The balloon attached to the sliding tube was inflated to grip the intestine, and both the scope and the sliding tube were withdrawn in tandem to shorten the intestine. By

repeating these steps, the endoscope was inserted deeper into the intestine^[4-6]. To insert the endoscope into the large intestine, the abdomen was compressed manually or body position was changed as required. During colonoscopic examination with SBE, air was insufflated 25 times, and carbon dioxide was insufflated 5 times at the discretion of the endoscopist in charge.

The primary variable used to evaluate SBE was the success rate of total colonoscopy, which was defined as insertion of the endoscope into the cecum. Secondary variables were the presence or absence of complications related to colonoscopy with SBE. We also evaluated the diagnostic and treatment outcomes of colonoscopic examinations with SBE.

This study was approved by the Institutional Ethics Committees of Kitasato University School of Medicine. Before performing colonoscopy with SBE, we provided all patients with a detailed explanation of the objectives and methods of examination, possible complications, and the possibility to select other procedures, such as barium enema. The decision to undergo colonoscopy with SBE was in accordance with the free will of each patient. Written informed consent for examination was obtained from all subjects. Continuous data are expressed as means \pm SD.

RESULTS

Success rate of total colonoscopy

Total colonoscopy was successfully performed by SBE in all sessions. The mean time required to reach the cecum was 22.9 ± 8.9 min (range 9 to 40 min).

Safety

The main complication associated with SBE was mild redness of the colorectal mucosa in some patients, caused by insertion of the sliding tube and pressure applied by the balloon. However, there were no serious complications associated with colonoscopic examination with SBE.

Diagnosis and treatment outcomes

Abnormal findings were found during 21 (70%) sessions of SBE. The most common abnormality was colorectal polyps (20 sessions), followed by radiation colitis (3 sessions) and diverticular disease of the colon (3 sessions). Finally, 56 colorectal polyps were newly diagnosed on colonoscopy with SBE. Colorectal polyps were resected endoscopically in 15 sessions. A total of 42 polyps were resected endoscopically, using snare polypectomy in 32 lesions, hot biopsy in 7 lesions, and endoscopic mucosal resection in 3 lesions. The 14 other polyps underwent biopsy with histopathological evaluation. The final histopathological diagnoses were intramucosal cancer in 2 lesions, tubular adenoma in 42, tubulovillous adenoma in 2, hyperplastic polyp in 8, and inflammatory polyp in 2. There were no complications associated with endoscopic resection or biopsy of the colorectal polyps. The mean

examination time was 48.2 ± 20.0 min (range 25 to 90 min).

DISCUSSION

Colonoscopy is essential for the diagnosis and treatment of colorectal disease. In particular, the indication range of colonoscopic treatment has been broadened owing to improved techniques for the endoscopic resection of colorectal tumors, endoscopic hemostasis, and endoscopic balloon dilatation of intestinal stenosis. As for colonoscopic devices, image quality as well as insertability has improved considerably. However, total colonoscopy is still technically difficult to perform in about 10% to 15% of subjects^[7-10]. Even though our hospital specializes in gastrointestinal endoscopy, we still encounter patients in whom total colonoscopy is technically difficult to perform. Excluding follow-up examinations after colorectal surgery or other procedures, we performed 3140 sessions of colonoscopy during the year of 2011. A conventional colonoscope could not be inserted to the cecum in 32 sessions (1.0%). In many patients with difficulty in scope insertion, barium enema examination was performed to evaluate sites of the colon that could not be assessed on endoscopy. Factors related to technical difficulty in colonoscope insertion have been reported to include advanced age, female sex, a low body mass index, an elongated colon or adhesions, multiple diverticula, and inadequate bowel preparation^[7-11]. In our series, the main factors that precluded colonoscope passage during SBE were an elongated colon and severe adhesions.

Patients in whom colonoscope insertion is expected to be technically difficult, especially those who are sensitive to discomfort and pain associated with colonoscopy, should receive adequate doses of analgesics and sedatives before examination. Manual compression of the abdomen by an assistant and the use of an overtube may facilitate scope passage in patients in whom insertion is difficult because of an elongated colon^[11]. In such patients, a variable stiffness colonoscope or a colonoscope with a long effective length should be used. Lichtenstein *et al*^[12] reported that the use of a small-caliber, push-type enteroscope with an effective length of greater than 2000 mm allowed total colonoscopy to be performed in about half of all patients in whom scope passage was difficult. If colonoscopy is performed in patients with severe adhesions in the colon after open surgery, a small-caliber colonoscope should be used. At present, very small-caliber colonoscopes with an outer diameter of 10 mm or less are commercially available. We previously reported that the use of a colonoscope with an outer diameter of 9.2 mm and an effective length of 1600 mm (CF-PQ260L[®], Olympus Co., Tokyo, Japan) allowed total colonoscopy to be performed in the majority of patients in whom scope insertion was precluded by an elongated colon and adhesions^[13]. Preliminary studies have suggested that the use of a guide-wire-directed endoscope or a spiral overtube can facilitate colonoscope insertion when difficulty is en-

countered^[14,15].

During colonoscope insertion, the scope may bend or form large loops in patients with an elongated colon. The presence of bowel adhesions can restrict mobility of the colon and cause sharp bends, which preclude scope passage. Excessive force to promote passage can injure the intestine. We performed colonoscopic examination by SBE in patients with a history of difficulty in scope insertion even by experienced endoscopists. A balloon attached to a sliding tube was inflated to grip and shorten the intestine, thereby preventing overextension of the intestine during the procedure and facilitating passage of the endoscope through regions with adhesion. Because the outer diameter of the SBE was only 9.2 mm, pushing the scope and distension of the intestine caused only mild discomfort to patients. Subsequent shortening of the intestinal tract with a sliding tube was also easily accomplished. In our study, SBE permitted total colonoscopy in all patients with a history of difficulty in colonoscope insertion. There were no serious complications associated with colonoscope insertion or endoscopic treatment. Eight patients (53%) underwent repeated examinations, and total colonoscopy was successfully accomplished at all sessions, confirming that SBE is consistently effective. During SBE, the mean time required for scope insertion into the cecum was 22.9 min. This prolonged insertion time was attributed to the extra time required for insertion of a sliding tube and shortening of the intestine.

Balloon endoscopy has previously been reported to be useful for colonoscopy in patients with a history of difficulty in colonoscope insertion^[16-23]. Most studies used a DBE, but two studies conducted in the United State and Holland reported the results of SBE^[22,23]. Keswani^[22] randomly assigned 30 patients with a history of difficulty in colonoscope insertion to undergo SBE or conventional colonoscopy. The success rate of total colonoscopy was significantly higher in the SBE group (93%) than in the conventional colonoscopy group (50%), with no examination-related complications. Teshima *et al*^[23] reported that total colonoscopy was successfully accomplished in 22 (96%) of 23 sessions of SBE performed in 22 patients with a history of difficulty in colonoscope insertion. In contrast to DBE, SBE does not require a balloon attached to the tip of the scope. Consequently, intestinal gripping strength might be lower with SBE than with DBE. However, our results suggest that SBE with only one balloon attached to the sliding tube was able to adequately shorten the large intestine, allowing total colonoscopy to be successfully accomplished.

Because SBE does not require attachment of a balloon to the scope tip, the preparation time is shorter and insertion of the scope is easier than with DBE. One study reported that the single-balloon technique performed with a DBE, in which a balloon was attached only to the overtube, facilitated scope insertion in patients in whom a colonoscope had been technically difficult to insert^[17]. DBE with a short effective length of 1520 mm are now available and have been reported to be

useful^[21].

In addition to diagnostic procedures such as biopsy, SBE allowed colorectal polyps to be endoscopically resected with no problems or complications. In contrast to a standard colonoscope, the opening of the forceps channel of SBE is located in the 8 o'clock direction. The field of vision is thus similar to that during upper gastrointestinal endoscopy. Because the scope is long, twisting maneuvers applied by the operator are sometimes not transmitted to the scope tip, making it difficult to accurately position endoscopic devices relative to target lesions. Because the forceps channel diameter was 2.8 mm, which is smaller than that of a standard colonoscope, it was difficult to aspirate intestinal juice and air after the insertion of endoscopic devices. Many lesions located at curvatures of the large intestine or on the proximal sides of folds were difficult to view endoscopically. When the intestine was shortened with the use of a sliding tube, the region surrounding lesions was straightened, facilitating lesion inspection as well as endoscopic therapy.

Our results showed that SBE facilitated total colonoscopy in patients in whom scope passage was difficult, confirming that SBE is useful and safe in Japanese subjects. However, this was a retrospective study in a small number of patients, and 1 endoscopist with many years of experience in colonoscopy performed most of the examinations. To clarify whether the technical ability of the operator affects the performance of SBE, prospective studies performed by endoscopists with different levels of experience are needed.

COMMENTS

Background

Colonoscopy is playing an increasingly important part in the diagnosis and treatment of colorectal diseases. Therapeutically, progress in resection techniques such as endoscopic mucosal resection and endoscopic submucosal dissection has contributed to the widespread application of colonoscopic therapy. Despite recent progress, however, the passage of a colonoscope is often difficult in subjects who have an elongated colon or severe adhesions.

Research frontiers

Colonoscopy's diagnostic role has been enhanced by the development of improved imaging techniques such as magnifying endoscopy and narrow band imaging. Therapeutically, progress in resection techniques such as endoscopic mucosal resection and endoscopic submucosal dissection has contributed to the widespread application of colonoscopic therapy.

Applications

The results showed that single-balloon endoscopy (SBE) facilitated total colonoscopy in patients in whom scope passage was difficult, confirming that SBE is useful and safe in Japanese subjects. However, this was a retrospective study in a small number of patients, and 1 endoscopist with many years of experience in colonoscopy performed most of the examinations.

Peer review

The manuscript describes an interesting technique in the diagnosis and treatment of colorectal diseases. It is an excellent article on single balloon endoscopy.

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Yield, etiologies and outcomes of capsule endoscopy in Thai patients with obscure gastrointestinal bleeding

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Abstract

AIM: To investigate the yield, etiologies and impact of capsule endoscopy (CE) in Thai patients with obscure gastrointestinal bleeding (OGIB).

METHODS: The present study is a retrospective cohort study. All patients with OGIB who underwent CE in Siriraj Hospital, Bangkok, Thailand during 2005-2009 were included in the study. All the patients' medical records and results of the CE videos were reviewed. CE findings were classified as significant, suspicious/equivocal and negative. Sites of the lesions were located to duodenum, jejunum, jejunoileum, ileum and diffuse lesions by the localization device of the CE. Impact of CE on the patients' management was defined by any investigation or treatment given to the patients that was more than an iron supplement or blood transfusion. Patients' outcomes (rebleeding, persistent bleeding, anemia or requirement of blood transfusion) were collected from chart reviews and direct phone interviews with the patients.

RESULTS: Overall, there were 103 patients with OGIB

included in the study. Mean age of the patients was 64 ± 16 years (range 9-88 years) and 57 patients (55%) were male. Types of OGIB were overt in 80 (78%) and occult in 23 patients (22%). The median time interval of CE after onset of OGIB was 10 d (range 1-180 d). The median time of follow-up was 19 mo (range 1-54 mo). Capsules reached caecum in 77 patients (74%) and capsule retention was found in 1 patient (1%). The diagnostic yield of CE revealed significant lesions in 37 patients (36%), suspicious/equivocal lesions in 15 patients (15%) and 51 patients (49%) had negative CE result. Among the significant lesions, the bleeding etiologies were small bowel ulcers in 44%, angiodysplasia in 27%, small bowel tumor in 13%, miscellaneous in 8% and active bleeding without identifiable causes in 8%. Patients with small bowel ulcers were significantly associated with the use of non-steroidal anti-inflammatory drugs (48%, $P = 0.034$), while patients with small bowel tumors were more commonly female (86%, $P = 0.043$) compared to the other etiologies. The rate of rebleeding, persistent bleeding or anemia in patients with positive, equivocal and negative CE results were 5%, 0% and 18%, respectively ($P = 0.078$). All the 9 patients with rebleeding after negative CE were subsequently found to be from hematologic disorders (4), colonic diverticulosis (2), colonic Dieulafoy's (1), hemorrhoid (1) and hemosuccus pancreaticus (1). Results of CE had a positive impact on the patients' management in 35% of the patients whose results were positive, but none on the patients whose results were equivocal or negative CE ($P < 0.001$).

CONCLUSION: In Thai OGIB patients, CE had low yield and small bowel ulcer was most common. Positive CE impacted managements and outcomes. Negative CE caused low rebleeding.

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Key words: Angiodysplasia; Etiology; Gastrointestinal Bleeding; Obscure; Capsule Endoscopy; Outcome; Small bowel ulcer; Wireless

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INTRODUCTION

Obscure gastrointestinal bleeding (OGIB) is defined as a persistent or recurrent gastrointestinal bleeding without a source being identified by standard evaluations, including esophagogastroduodenoscopy and colonoscopy. It is further classified into overt and occult gastrointestinal bleeding^[1]. OGIB accounts for an approximately 5% of all gastrointestinal bleeding and the most common site of bleeding is in the small intestine^[1]. The difficulty in examining the entire small intestine has made an assessment of small intestinal sources of bleeding problematic.

Capsule endoscopy (CE) has recently been developed as a non invasive method for examining the small bowel. CE provides opportunity to obtain images from the entire length of the small intestine in most patients, thus has been accepted as a first-line investigation of patients with OGIB^[1,2]. Recent meta-analysis showed that CE provided the highest diagnostic yield for OGIB (61%-63%)^[3,4], comparable to double-balloon enteroscopy^[5], but much higher than push enteroscopy (28%) and small bowel radiography (8%)^[3]. The most common cause of OGIB identified by CE in most studies was angiodysplasia^[6,7] and results of CE were shown to impact management in 50%-70% of cases^[8].

However, there are some debates on the long-term outcome of patients with negative CE, whether negative CE predicts low or substantial rebleeding remains controversial. Furthermore, data of CE in OGIB in Asia is limited and the etiology of OGIB among Asians may be different from Westerners. This study aims to evaluate the etiologies of OGIB among Thai patients, and to determine the diagnostic yield and the impacts on patient management and outcomes in association with the results of CE.

MATERIALS AND METHODS

Patients

All patients with OGIB who had CE done at the Division of Gastroenterology, Siriraj Hospital during 2005-2009 were identified and included in the study. The study was approved by Siriraj Institute Review Board. OGIB was defined as an evidence of melena, hematochezia, drop of hemoglobin (Hb) level for at least 2 g/dL or a positive fecal occult blood test, accompanied by negative EGD and colonoscopy.

CE

CE studies (PillCam®, Given Imaging, Israel) were performed according to standard protocol, which included an overnight fast, the use of bowel preparation (2 sachets

of polyethylene glycol in 2 L of fluid), a prokinetic agent (metoclopramide 10 mg intravenous injection) for immobilized patients, patients with longstanding diabetes or patients with known slow transit. A second recorder technique was done periodically to check the position of the capsule^[9]. All videos were reviewed by 2 readers, one of which is an experienced reader who had officially reviewed more than 500 cases of CE (SP).

CE findings

CE findings were classified as highly significant lesions (P2) which was likely to explain source of bleeding, suspicious or equivocal lesions (P1) and negative for any lesions (P0) according to the report by Saurin *et al*^[10]. Examinations that demonstrated one or more P2 lesions were recorded as positive studies, whereas those with P1 and P0 lesions were considered equivocal and negative, respectively.

Location of the lesions

Location of the lesions was classified using the localization device on the screen of the CE platform. Duodenum was located right after the capsule entered duodenum and quickly moved along the path of C-loop from right- to left-side of the of the localization device. Jejunum was located when capsule was in the left side of the localization device or the proximal third of the small bowel transit. Ileum was located when capsule was in the right side of the localization device or the distal third of the small bowel transit. Capsule located in the mid abdomen or in the middle third of the small bowel was classified as jejunoileal lesion.

Change of patient management

Change of patient management was defined by any treatment other than iron supplement and blood transfusion. They included any of the followings, *i.e.*, surgery, further endoscopy and specific medications.

Patient outcomes

Long-term outcomes were evaluated by the presence of persistent or rebleeding episodes. Rebleeding was defined as an evidence of melena, hematochezia, a documented fall of Hb 2 g/dL from baseline or more and the need for blood transfusion. Follow-up data were obtained from the medical records and direct phone interview with the patients.

Statistical analysis

All the data collected were subjected to a descriptive analysis. For numerical variables, the results were expressed as a mean \pm SD. For quantitative variables, percentages are shown with 95%CI. The comparison of numerical variables between groups was accomplished by using the Student's *t*-test or the Mann-Whitney test, as appropriate. For comparison of percentages, the χ^2 test or the Fisher's exact test were used together with the calculation of the odds ratio and its 95%CI. Long-term outcome was analyzed by using Kaplan-Meier analysis. The value of *P* < 0.01 was

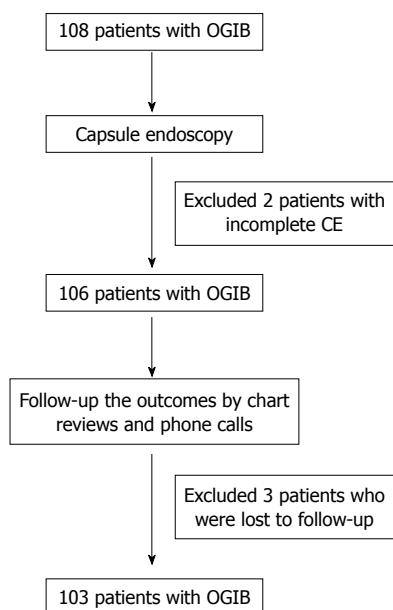


Figure 1 Flow chart of the trial. OGIB: Obscure gastrointestinal bleeding; CE: Capsule endoscopy.

considered significant. The SPSS 13.0 for windows was used for the statistical analysis.

RESULTS

Overall, there were 108 patients, who underwent CE for OGIB at Siriraj Hospital during the 5-year periods from 2005-2009. Five patients were excluded because 2 of them failed to complete the procedures, and 3 patients lost contact and were impossible to follow their clinical outcomes. Finally, 103 patients were included in the analysis (Figure 1).

The baseline characteristics of the studied population are shown in Table 1. Mean age was 64 ± 16 years (range 9-88 years) and 57 patients (55%) were male. Types of OGIB were found to be overt in 80 (78%) and occult in 23 patients (22%). Median time interval of CE after onset of OGIB was 10 d (range 1-180 d). The proportions of patients who had CE done within 2 d, 3-7 d, 8-14 d and more than 14 d were 7%, 30%, 31% and 32%, respectively. The median time of follow-up was 19 mo (range 1-54 mo).

Findings and diagnosis yield of CE

Capsules reached caecum in 77 patients (74%) and capsule retention was found in 1 patient (1%) due to undiagnosed stricture in Crohn's disease. However, the capsule passed beyond the stricture spontaneously 3 d after initiating corticosteroid treatment. Diagnostic yield of CE revealed significant lesions which could explain GI bleeding in 37 patients (36%), suspicious or equivocal lesions in 15 patients (15%) while 51 patients (49%) had negative CE result. Among the significant lesions, the bleeding etiologies were found to be small bowel ulcers in 44%, angiodysplasia in 27%, small bowel tumor in 13%, miscellaneous in 8% and

Table 1 Demographic data of 103 patients with obscure gastrointestinal bleeding *n* (%)

Parameters	Type of OGIB			<i>P</i> value
	Total (<i>n</i> = 103)	Overt (<i>n</i> = 80)	Occult (<i>n</i> = 23)	
Age (yr), mean \pm SD	64 \pm 16	62 \pm 16	69 \pm 14	0.059
Male, <i>n</i>	57 (55)	51 (64)	6 (26)	0.001
Episode, <i>n</i>				
First	79 (77)	56 (70)	23 (100)	0.003
Recurrent	24 (23)	24 (30)	0	
Hb (g/dL), mean \pm SD	8.5 \pm 2.4	8.7 \pm 2.5	8.2 \pm 1.9	0.371
Drugs, <i>n</i>				
NSAIDs	30/100 (30)	22/77 (29)	8/23 (35)	0.568
Anticoagulants	4/100 (4)	2/77 (3)	2/23 (9)	0.226

Hb: Hemoglobin; NSAIDs: Nonsteroidal anti-inflammatory drugs; OGIB: Obscure gastrointestinal bleeding.

Table 2 Capsule endoscopy findings in patients with overt and occult obscure gastrointestinal bleeding *n* (%)

Parameters	Type of OGIB			<i>P</i> value
	Total (<i>n</i> = 103)	Overt (<i>n</i> = 80)	Occult (<i>n</i> = 23)	
Reaching caecum, <i>n</i>	77 (74)	60 (75)	17 (74)	0.916
Capsule endoscopy findings, <i>n</i>				
Positive (P2)	37 (36)	28 (35)	9 (39)	0.792
Equivocal (P1)	15 (15)	11 (14)	4 (17)	
Negative (P0)	51 (49)	41 (51)	10 (43)	
Etiologies, <i>n</i> ¹				
Ulcers	23 (44)	15 (38)	8 (61)	0.462
Angiodysplasia	14 (27)	12 (31)	2 (15)	
Tumors	7 (13)	6 (15)	1 (8)	
Miscellaneous	4 (8)	3 (8)	1 (8)	
Active bleeding	4 (8)	3 (8)	1 (8)	
Location of lesions, <i>n</i> ²				
Duodenum	6 (13)	4 (11)	2 (17)	0.969
Jejunum	15 (31)	11 (31)	4 (33)	
Jejunum-ileal	12 (25)	9 (25)	3 (25)	
Ileum	14 (29)	11 (30)	3 (25)	
Diffuse	1 (2)	1 (3)	0	

¹Among 52 patients with P2 or P1 lesions; 39 were overt and 13 were occult obscure gastrointestinal bleeding (OGIB); ²Data was available in 48 patients; 36 with overt and 12 with occult OGIB.

active bleeding without identifiable causes in 8% (Table 2). Natures of the small bowel ulcers were caused by non-steroidal anti-inflammatory drugs (NSAIDs)-induced in 8 (35%), CD in 3, radiation in 1, chemotherapy-induced in 1 and undetermined cause in 10 patients.

Characteristics of patients according to the etiology

Patients' characteristics according to their etiology were demonstrated in Table 3. Patients' age and type of OGIB were similar in all etiologies, however, patients with small bowel tumors were more commonly female (86%, *P* = 0.043) as compared to other etiologies. History of NSAIDs use was more common in patients with small bowel ulcers (48%, *P* = 0.034) but their sensitivity, specificity, positive predictive value and negative predictive value were 48%, 75%, 37% and 83%, respectively.

Table 3 Characteristics of patients according to their etiologies *n* (%)

	Ulcers (<i>n</i> = 23)	Angiodysplasia (<i>n</i> = 14)	Tumors (<i>n</i> = 7)	Negative CE (<i>n</i> = 51)
Age (yr), mean ± SD	68 ± 14	66 ± 12	60 ± 8	64 ± 16
Male, <i>n</i>	16 (70)	8 (57)	1 (14) ¹	29 (57)
Overt bleeding, <i>n</i>	15 (65)	12 (86)	6 (86)	41 (80)
NSAIDs use, <i>n</i>	11 (48) ²	5 (36)	0	12 (24)

¹*P* = 0.043; ²*P* = 0.034. CE: Capsule endoscopy; NSAIDs: Nonsteroidal anti-inflammatory drugs.

Results of CE on patient management

The results of CE finally determined patient management in 13 (35%) of the 37 patients with positive CE result. Surgery was performed in 8 patients, immunosuppressive therapy for inflammatory bowel disease was initiated in 4 patients and anti-parasitic agent was administered in 1 patient. On the other hand, none of the patients with equivocal or negative CE resulted in changing of management plan (*P* < 0.001) and all were treated with iron supplement and blood transfusion.

Long-term outcomes

Rebleeding, persistent bleeding or persistent anemia occurred in 5%, 0% and 18% of patients with positive, equivocal and negative CE results, respectively (*P* = 0.078, Figure 2). Positive CE resulted in fewer rebleeding as compared to patients with negative CE (hazards ratio 0.31, 95%CI 0.07-1.43). Causes of rebleeding in all CE-negative patients (*n* = 9) were subsequently found to be associated with hematologic disorders, *i.e.*, myelodysplastic syndrome in 4 patients, colonic diverticulosis in 2 patients, colonic Dieulafoy's in 1 patient, hemorrhoid in 1 patient and hemosuccus pancreaticus in 1 patient.

DISCUSSION

In the present study, the diagnostic yield, etiology and outcomes of 103 patients with OGIB who underwent CE in a single institution in Thailand were reported. This is the largest study on capsule endoscopy in OGIB in Thai patients. The main information obtained from this study was that the diagnostic yield for significant lesions of OGIB was substantially low (36%). The most common etiology was small bowel ulcers (44%). The long-term rebleeding rate in patients with negative CE results was low (18%) and most rebleedings were from non-small bowel etiologies.

The diagnostic yield of CE in OGIB in the present study (36%) was lower than those reported in western literatures (42%-71%)^[6,7,10-16] and those reported in meta-analyses (61%-63%)^[3,4]. There are many possible reasons. Firstly, the timing of CE after onset of OGIB varied, particularly the overt OGIB group of patients might be different from other studies. The study by Pennazio *et al*^[6] showed that the yield of CE was highest in patients with ongoing overt bleeding, while the yield could be as low as 13% in patients without ongoing bleeding, particularly, if

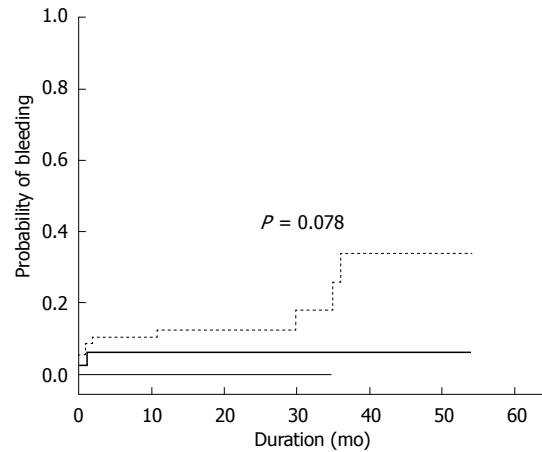


Figure 2 Probability of persistent or rebleeding after capsule endoscopy according to the results of capsule endoscopy; positive (thick solid line), equivocal (thin solid line) and negative (dotted line). Rebleedings were found in 5%, 0% and 18%, respectively (*P* = 0.078).

CE was performed after 2 wk of bleeding. The median time interval of CE after onset of OGIB in the present study was 10 d but they ranged from 1-180 d. This wide range of interval was because most patients were referred from other institutes where significant delay in CE was problematic. The late performance of CE in this study might underdiagnose small bowel ulcers caused by NSAIDs as suggested by a recent study^[17] which were found to be the most common cause of OGIB in this study. Most small bowel ulcers were able to heal spontaneously within days to weeks. Secondly, the low diagnostic yield might be due to the low prevalence of angiodysplasia in Thai patients (27%) which is the major cause of OGIB in other studies (33%-79%)^[6,7,10-16].

The finding that small bowel ulcer, instead of angiodysplasia was the most common cause of OGIB in this study needs attention. Angiodysplasia is well-known to be the most common cause of OGIB among Western patients but no convincing data to show that this holds true among Asians^[18-21]. Some^[18,20] reported angiodysplasia as a main cause of OGIB, while others^[19,21] report ulcers to be the main etiology. However, when considered large studies that include more than 100 patients, one study from India^[21] and two double-balloon enteroscopy studies from Japan^[22,23], all showed that small bowel ulcers were the most common cause of OGIB (41%-53%), more common than angiodysplasia (23%-24%). These yielding rates are much closer to the results of our study (44% and 27% for ulcers and angiodysplasia, respectively). Therefore, small bowel ulcer is likely the most common cause of OGIB among Asians.

In the present study, the demographic data of patients with OGIB from various etiologies were mostly indistinguishable. Although we found significantly more small bowel tumors in female, many recent larger studies of small bowel tumors did not confirm this finding and most demonstrated male predominance in 60%-65%^[24-26]. Thus, the finding in our study might be from type I error. We found that history of NSAID use correlated with the finding of small bowel ulcers, which is straightforward.

However, it was also common in other causes of OGIB and the predictive values were too low to have significant clinical implication.

Information regarding to the site of the lesions obtained from this study can be helpful to guide the route of balloon-assisted enteroscopy (BAE) if it needs to be done. Assuming from the location of the lesions by CE and findings from recent studies on the predictive role of CE for the route of enteroscopy^[27,28], antegrade BAE would reach the lesions in 79%, whereas retrograde BAE would do so in 56%. Thus, antegrade route may have higher yield than retrograde route for patients with OGIB in Thailand.

Positive CE results in this study also lead to change in patient management plans in 35% of patients. They were given either specific medication, BAE with or without specific interventions or surgery. Patients with equivocal or negative CE results obviously had no change in their management plan. The change in patient management plan in this study is slightly lower than the 50%-70% rate of management changes reported in the recent review^[8]. The explanation might be because the criteria of the change of management in these studies were different from ours and the findings in our study that large proportion of OGIB was NSAID-induced small bowel ulcers. Such small bowel ulcer can often heal spontaneously without any specific treatment and thus the rate of change in patient management would be low.

Patient outcome after CE was another important significant finding in the present study. The very low rebleeding rate in patients with positive CE results (together with appropriate management according to the CE findings) is found to be lower than those reported from the West^[6,7,10-16]. The low rebleeding in our study could be due to the spontaneously improved nature of the disease (*i.e.*, NSAID-induced ulcers) and the ability to provide specific treatments, *i.e.*, surgery for small bowel tumors, which were also prevalent in this study. In contrast, the main cause of OGIB found in the West is angiodysplasia which is often difficult or impossible to completely eradicate and the natural course is often not well-understood^[1]. These similar reasons may also explain the substantially low rebleeding rate in the CE-negative group in the present study. Another important finding from this study that all rebleeding in the CE-negative patients were finally found to be non-small bowel lesions, strongly supports CE as an important tool to rule out small bowel source of OGIB. It also emphasizes the importance of thorough evaluation of non-small bowel causes before heading to investigate with capsule endoscopy.

The strong aspect of present study is its large number of sample size and that all CE videos were reviewed by 2 reviewers. However, the main drawback of this study is its retrospective design and some clinical outcomes might not be completely recorded as retrospective phone interview might not be completely accurate.

In conclusion, the diagnostic yield of CE for OGIB in Thai patients seems to be lower than those in Westerners. Small bowel ulcers are the most common causes of

OGIB, while angiodysplasia is less common. Positive CE strongly impacted on management plan and outcomes of OGIB. Negative CE was associated with a substantially low rebleeding rate and all etiologies were from non-small bowel origins. However, further studies, *i.e.*, randomized controlled trial, are necessary in order to confirm these results.

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COMMENTS

Background

Capsule endoscopy (CE) is now accepted as the first line investigation of obscure gastrointestinal bleeding (OGIB). The yield is high, angiodysplasia is the most common cause in Westerners but impact on patients' outcome is controversial. Data in Asians is limited.

Research frontiers

Knowledge on the yield, etiologies and impact of CE on outcomes of OGIB in Asians are lacking and may be different from those in the Westerners.

Innovations and breakthroughs

Yield of CE in Thai OGIB is lower than the Westerners. Small bowel ulcers are more common than angiodysplasia and tumors are quite common. CE impacts management and outcomes. Rebleeding is low and most are from non-small bowel causes.

Applications

CE should be used as first-line investigation of OGIB in Asians because of the noninvasiveness, the high yield, the positive impacts on management and the ability to rule-out small bowel causes of OGIB when negative.

Terminology

OGIB is gastrointestinal bleeding that the etiology is not detected by both upper endoscopy and colonoscopy.

Peer review

This is the first manuscript on Thai patients with OGIB managed by CE. Figures and results are well made and easy to be understood for readers.

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Endoscopic submucosal dissection of multiple flat adenomas in the radiated rectum

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Abstract

We report a case of multiple flat adenomas and cancer of the rectum that occurred 15 years after pelvic irradiation following surgery for uterine cancer. Adenoma borders were diagnosed accurately by magnifying chromoendoscopy, leading to their adequate excision using endoscopic submucosal dissection. This enabled minimal dissection of the irradiated pelvis that would have otherwise been difficult. Furthermore, our approach probably helped minimize loss of bowel function, thereby preserving the patient's quality of life as much as possible. Pathology of the resected specimens revealed thickened walls of the submucosal layer vessels, indicating chronic radiation proctitis. Pelvic irradiation of the bowel carries a high risk of causing flat adenomas and cancer. Close and long-term surveillance may be useful in such cases, using not only conventional colonoscopy but also chromoendoscopy with indigo carmine dye spray and magnifying endoscopy.

Key words: Flat adenoma; Endoscopic submucosal dissection; Magnifying chromoendoscopy; Radiation proctitis; Pelvic irradiation

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INTRODUCTION

Pelvic irradiation is frequently used as a definitive or adjunctive treatment for pelvic malignancy, and development of cancer in this region is considered a late complication^[1-4]. We recently experienced a case of multiple flat adenomas and cancer in the rectum that occurred 15 years after pelvic irradiation following surgery for uterine cancer. The borders of these adenomas could be accurately diagnosed by magnifying chromoendoscopy, leading to their adequate excision using endoscopic submucosal dissection (ESD). This enabled us to minimize the extent of surgical dissection in the irradiated pelvis when removing the remaining neoplasm.

To our knowledge, there have been no similar reports of endoscopic resection of multiple flat adenomas in the irradiated rectum. The superficial neoplastic lesions were described according to the Paris endoscopic classification of superficial neoplastic lesions^[5].

CASE REPORT

A 46-year-old woman presented with bloody stools in November 2010. She had undergone radical hysterectomy followed by pelvic irradiation (total 54 Gy) for uterine cancer 15 years earlier. There was no family history of colorectal cancer. On physical examination, her lower abdomen was slightly hard because of the surgical scar,

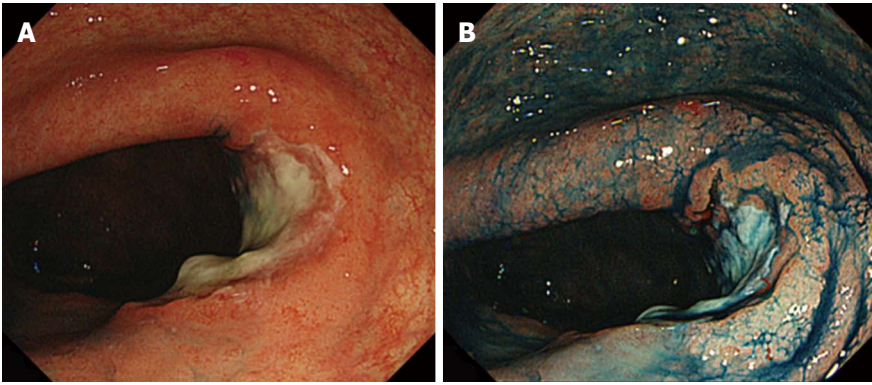


Figure 1 An advanced neoplasm, 35 mm in size, in the rectum. A: Colonoscopy shows an ulcerative lesion in the rectum, the biopsy of which proved to be well differentiated adenocarcinoma; B: Chromoendoscopy with indigo carmine dye spray shows the lesion clearly.

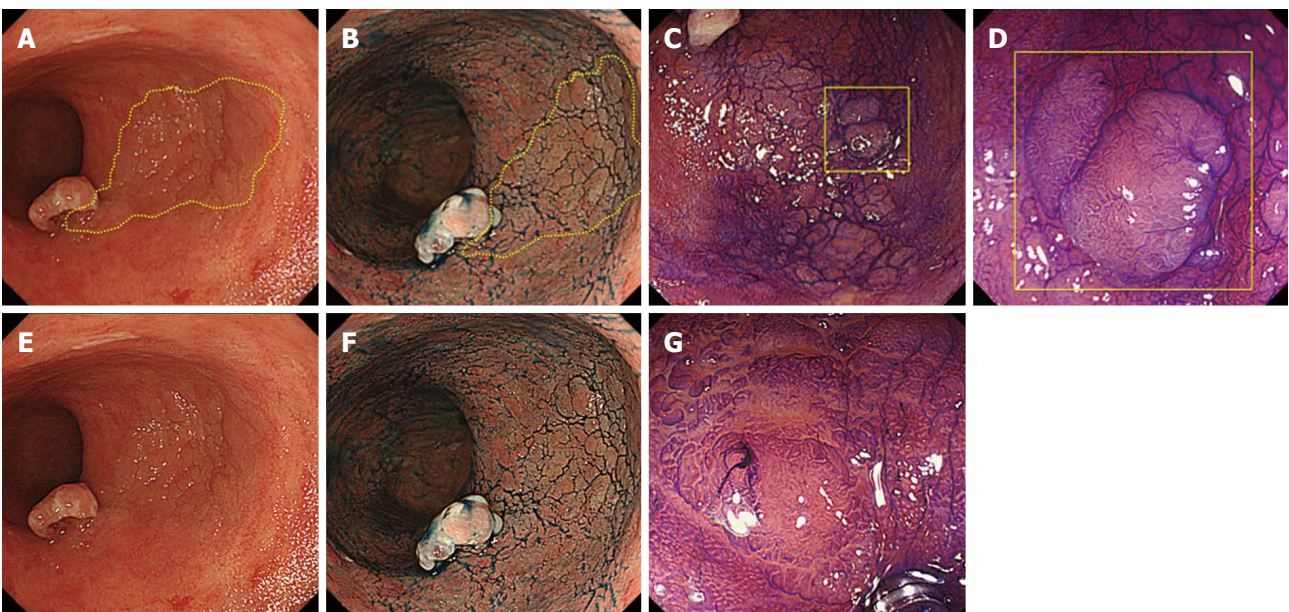


Figure 2 A flat adenoma, 35 mm in size, in the anterior wall of the low rectum. A: The lesion was detected as a slight decline in vascular permeability on routine observation; B: Although we could highlight the irregular surface by spraying indigo carmine solution, it was difficult to trace the margin of the lesion; C, D: The surface structure of the lesion is composed mainly of IIIIL pits with partially mixed IV pits on magnifying endoscopy with crystal violet staining; E: Figure A showing lesion borders without the aid of yellow lines; F: Figure B showing lesion borders without the aid of yellow lines; G: Magnifying endoscopy with crystal violet staining effectively delineates the margin of the lesion.

bowel sound was normal, and superficial lymph nodes were not palpable. All other physical examinations were unremarkable. Laboratory studies, including complete blood cell counts, serum electrolytes, blood biochemistry, carcinoembryonic antigen, and CA19-9 were within normal limits.

Colonoscopy using a magnifying videoscope (CF H260-AZI high vision scope, Olympus, Tokyo, Japan) revealed five lesions: a 35-mm flat adenoma in the sigmoid colon, an advanced cancer, a 30-mm flat adenoma in the rectum (Figure 1), and two flat adenomas (35 mm and 10 mm) in the lower rectum. Although we could highlight the irregular surface by spraying indigo carmine solution, it was difficult to trace the lesion margin. On magnifying endoscopy with crystal violet staining, the surface structure

of the four lesions was found to be composed mainly of IIIIL and IV pits, which suggested adenomas. Magnifying chromoendoscopy helped to delineate the borders of these lesions distinctly (Figures 2, 3). ESD was performed for two rectal flat lesions, which minimized the extent of dissection in the subsequent anterior resection of the rectal cancer (pT3 N0 M0) in January 2011.

Pathological examination revealed the two flat lesions in the lower rectum to be tubular adenomas. The resected specimens measured 52 mm × 30 mm and 18 mm × 18 mm with sufficient margins (Figure 4A, B). In the resected rectum specimen, wall-thickening of the vessels in the submucosal and subserosal layers was evident (Figure 4C), indicating chronic radiation proctitis^[6]. No recurrence was observed during follow-up.

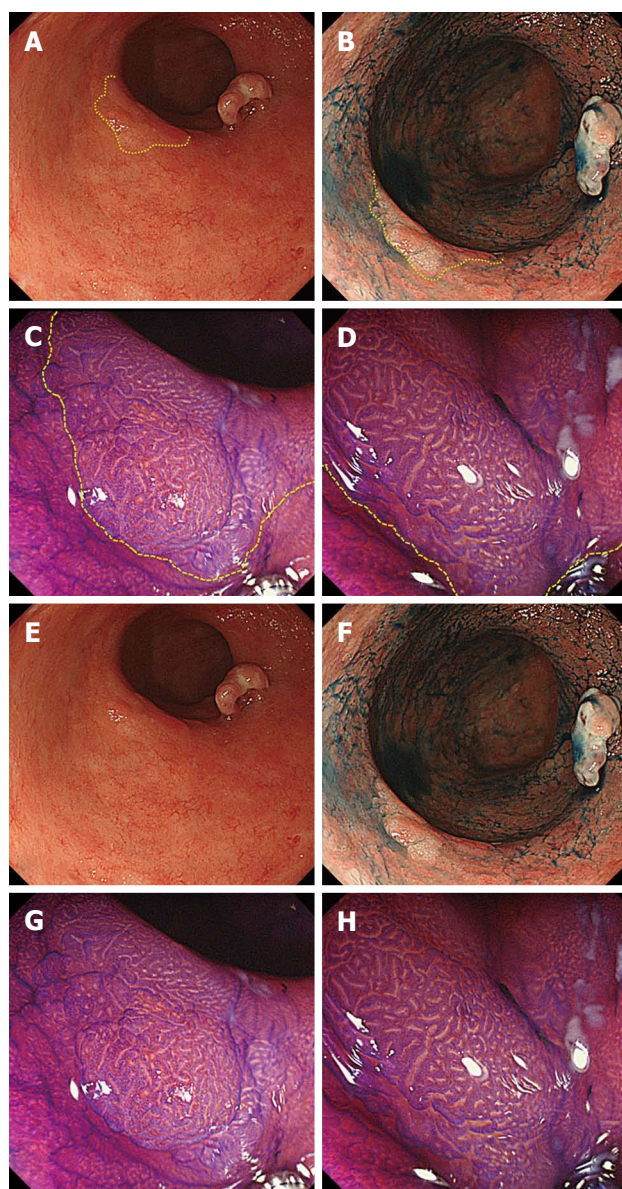


Figure 3 A slightly elevated adenoma, 10 mm in size, in the posterior wall of the low rectum. A: The lesion was detected with a slight decline in vascular permeability on routine observation; B: Although we could highlight the irregular surface by spraying indigo carmine solution, it was not possible to determine the area of the lesion; C: Regarding surface structure, the lesion is composed mainly of ILL pits with partially mixed IV pits on magnifying endoscopy with crystal violet staining; D: Magnifying endoscopy with crystal violet staining effectively delineates the margin of the lesion; E: Figure A showing lesion borders without the aid of yellow lines; F: Figure B showing lesion borders without the aid of yellow lines; G: Figure C showing lesion borders without the aid of yellow lines; H: Figure D showing lesion borders without the aid of yellow lines.

DISCUSSION

To our knowledge, no cases of endoscopic removal of flat adenomas arising in the radiated rectum have been reported. The current case is particularly interesting not only because the patient developed advanced rectal cancer 15 years after pelvic irradiation therapy, but also because she simultaneously developed multiple sizeable flat adenomas that would have been extremely difficult to diagnose on routine colonoscopy alone. In fact, magnifying

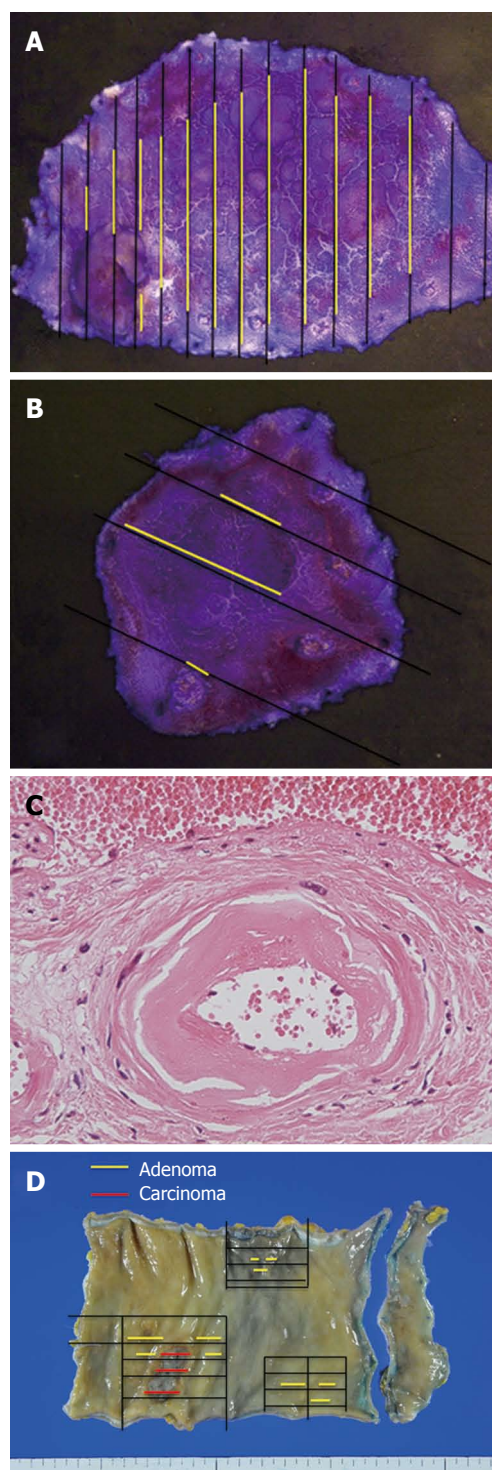


Figure 4 Resected specimens. A: A complete one-piece resection of 52 mm × 30 mm in size with tumor-free margins was achieved; B: Complete one-piece resection with tumor-free margins 18 mm × 18 mm; C: Microscopy of the resected specimens revealed increased vessel wall thickness in the submucosal layer and the serous coat of the large intestine around the tumors, indicating chronic radiation proctitis; D: A well-differentiated adenocarcinoma, 35 mm × 18 mm, invading beyond the muscularis propriae (pT3). None of the 10 lymph nodes retrieved were involved (pN0). Moreover, adenomatous change, which endoscopic observation failed to detect, was found.

chromoendoscopy proved useful for accurate diagnosis, and led to adequate resection using ESD. Chromoendos-

copy with crystal violet is indeed time-consuming. However, magnifying chromoendoscopy enabled accurate diagnosis of the surface structure of the lesions. Narrow-band imaging (NBI) is a recent development designed to enhance standard endoscopy with superior delineation of mucosal surface capillaries. In the present case, we did not estimate these lesions by using NBI. However, the features of NBI suggest that it is more useful than conventional colonoscopy for evaluating flat adenomas. Pathology of the resected specimens revealed thickened vessel walls in the submucosal layer, indicating chronic radiation proctitis^[6].

We predicted that using endoscopic mucosal resection it would be difficult to achieve complete one-piece resection with tumor-free margins because adequate lifting of the lesions after submucosal injection was not obtained due to severe submucosal fibrosis after the previous radiation therapy. Therefore, we performed ESD for two flat adenomas in the lower rectum. By adequately removing the adenomas in the low rectum by ESD, we were able to minimize the extent of dissection of the irradiated pelvis which would have otherwise been difficult. Furthermore, it is likely that this approach helped minimize the loss of bowel function, thereby minimizing the impact on quality of life.

Flat adenomas are generally hard to detect on routine colonoscopy. Moreover, background radiation proctocolitis, resulting in flat lesions, makes accurate diagnosis more difficult. In fact, the pathology of the surgically resected specimen revealed a cancer-associated adeno-

matous component which endoscopic observation had failed to detect (Figure 4D). It is important to bear in mind that patients who have undergone pelvic irradiation may be at high risk of developing flat adenomas or neoplasms in the irradiated bowel^[1-4]. Close and long-term surveillance using not only conventional colonoscopy but also chromoendoscopy with indigo carmine dye spray and magnifying endoscopy may therefore prove useful in such patients.

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Endoscopic lithotripsy with peroral direct cholangioscopy using a conventional endoscope

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Abstract

Recently, peroral direct cholangioscopy (PDCS) using an ultra-slim endoscope has come into the spotlight. However, the working channel is too small to use various devices for lithotripsy. We report a case of endoscopic lithotripsy with PDCS using a conventional endoscope as a cholangioscope. Computed tomography scan on an 80-year-old female who was admitted with acute cholangitis showed two large stones in the bile duct. Endoscopic retrograde cholangiopancreatography was attempted first. However, mechanical lithotripsy failed because the stone was too large for the basket catheter. Finally, electric hydraulic lithotripsy with PDCS using a conventional endoscope was performed allowed the stones to be cleared completely. In conclusion, PDCS using a conventional endoscope can be an alternative solution for endoscopic lithotripsy for patients with large stones in the dilated bile duct.

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Key words: Peroral direct cholangioscopy; Electric hydraulic lithotripsy; Conventional endoscope; Bile duct stone; Transpapillary lithotripsy

Nakaji S, Hirata N, Shiratori T, Kobayashi M, Inase M. Endoscopic lithotripsy with peroral direct cholangioscopy using a conventional endoscope. *World J Gastrointest Endosc* 2013; 5(3): 132-134 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i3/132.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i3.132>

INTRODUCTION

The peroral direct cholangioscopy (PDCS) procedure was first reported by Urakami *et al*^[1] 3 decades ago. Recently, PDCS has come into the spotlight with the development of ultra-slim endoscopes. However, the working channel is too small to use various devices for lithotripsy. We report a case in endoscopic lithotripsy with PDCS using a conventional endoscope as the cholangioscope was used to avoid this problem. This is the first case of transpapillary lithotripsy using a conventional endoscope on a patient without a history of gastrectomy or gastro-jejunal anastomosis.

CASE REPORT

An 80-year-old female was admitted with acute cholangitis. Her past medical history included cholelithiasis and recurrent choledocholithiasis. Cholecystectomy had been performed at the age of 27. Choledocholithiasis had been treated endoscopically and endoscopic sphincterotomy (EST) had been already performed. At the time of this admission, computed tomography (CT) scan showed two large stones in the bile duct. One was in the common bile duct (36.7 mm in diameter), while the other was in the left hepatic bile duct (21 mm in diameter). Endoscopic retrograde cholangiopancreatography was attempted first. However, mechanical lithotripsy failed because the stone was too large for the basket catheter. After we had obtained the patient's consent, electric hydraulic lithotripsy (EHL) (Nortech AUTOLITH lithotripter with a 1.9F

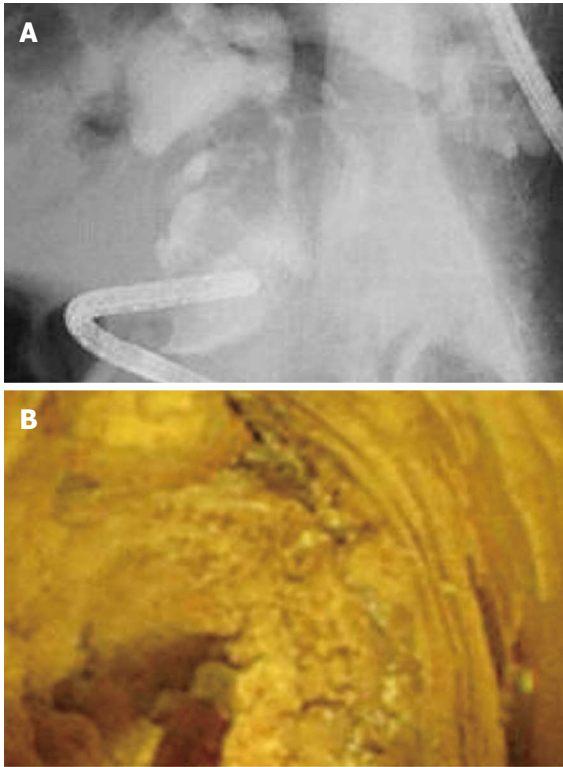


Figure 1 The ultra-slim endoscope was inserted into the common bile duct (A), electric hydraulic lithotripsy was performed (B).

probe; Northgate Technologies, Illinois, United States) was performed with PDCS using an ultra-slim endoscope (GIF-XP260N; Olympus Medical Systems, Tokyo, Japan) (Figure 1). During the procedure, carbon dioxide was used to insufflate the bile duct. EHL was performed under saline solution irrigation. Although the stone was partially crushed, the view quickly deteriorated because of the presence of the fragments. Having had difficulty in lithotripsy with an ultra-slim endoscope, we changed to a conventional endoscope (GIF-Q260; Olympus Medical Systems) with a larger working channel (2.8 mm in diameter) to strengthen the suction power and to enable use of various devices. Both procedures were carried out under conscious sedation while monitoring the respiratory and circulatory dynamics with the patient in a prone position. Both endoscopes were inserted by the freehand method without balloon-assist or an overtube. After insertion, the crushing by EHL and suction were repeated. The fragments were removed using a retrieval net (Roth Net; Olympus Medical Systems) (Figure 2). In this way, stones were cleared completely. It took thirteen minutes to carry out the procedure.

DISCUSSION

At present, there are two types of scope used in peroral cholangioscopy: the single endoscope and the mother-baby type^[2,3]. Both have advantages and disadvantages. For example, the mother-baby type is easier to insert into the bile duct, but is more difficult to handle. The

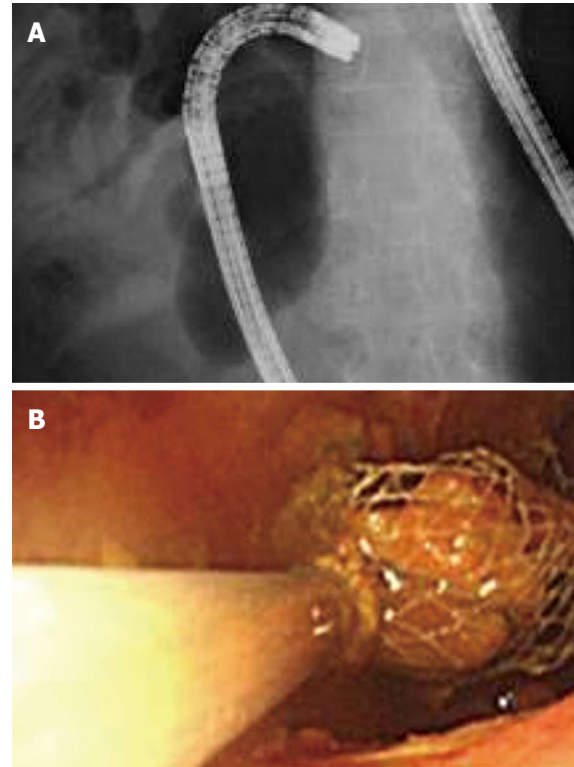


Figure 2 The conventional endoscope was inserted into the bile duct (A), fragments were removed by a retrieval net (B).

Spy Glass System (Boston Scientific, Natick, MA, United States), a new mother-baby type cholangioscope that was developed recently, has improved insertability and handleability, but has drawbacks in actual lithotripsy, such as the small size of the working channel and the absence of an independent suction channel during lithotripsy.

The biggest problem of PDCS is the difficulty of insertion into the bile duct. The several techniques, such as the use of a sliding tube and a balloon catheter, were reported to facilitate insertion, but have not become well established. Moreover, a dedicated direct peroral cholangioscope has been developed recently^[4]. PDCS using a conventional endoscope is usually more difficult to insert than an ultra-slim endoscope because of the diameter. However, endoscopic papillary large balloon dilation after EST may make insertion easier^[5]. It also has the advantage of preventing increase in intra-biliary pressure during the procedure. Once a conventional endoscope has been inserted, various devices can be inserted through the 2.8 mm working channel: a mechanical lithotriptor (crusher catheter; Zeon Medical, Tokyo, Japan), a retrieval net, *etc.* Therefore, the lithotripsy can be easily completed in a short time. It is important to remember that this procedure should be performed under carbon dioxide insufflation to prevent air embolism^[6]. There are no previous reports of transpapillary lithotripsy using a conventional endoscope, other than in patients the history of gastrectomy or gastro-jejunal anastomosis^[7].

In conclusion, PDCS using a conventional endoscope can be an alternative solution for endoscopic lithotripsy

in patients with large stones in the dilated bile duct. Although we have described one successful case further studies are needed to evaluate the safety and effectiveness of this procedure.

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Massive gastric antral vascular ectasia successfully treated by endoscopic band ligation as the initial therapy

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also provided a good treatment outcome and less sessions.

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Key words: Gastric antral vascular ectasia; Non variceal hemorrhage; Endoscopic band ligation; Water melon stomach; Treatment

Prachayakul V, Aswakul P, Leelakusolvong S. Massive gastric antral vascular ectasia successfully treated by endoscopic band ligation as the initial therapy. *World J Gastrointest Endosc* 2013; 5(3): 135-137 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i3/135.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i3.135>

Abstract

Gastric antral vascular ectasia (GAVE) accounted for 4% of non-variceal gastrointestinal hemorrhage. Even though unclear pathogenesis, GAVE often associated with chronic renal failure, autoimmune diseases and cirrhosis. Asymptomatic lesions were reasonably not to treated. The treatment options for GAVE are non-endoscopic and endoscopic treatments. For the pharmacological treatment, some success were reported for the use of octreotide, thalidomide and tranexamic acid. While the endoscopic treatment is the mainstay for treatment of symptomatic lesions. The endoscopic ablative therapies such as argon plasma coagulation was reported with good clinical outcomes. However, these treatment options had some limitation due to the need of special equipment and multiple sessions needed to control the bleeding. We reported another treatment option using the routine-achievable instrument such as endoscopic band ligation as an initial treatment which

INTRODUCTION

Gastric antral vascular ectasia (GAVE), or water melon stomach, is an uncommon cause of non variceal gastrointestinal hemorrhage. This condition was firstly reported as "an erosive type of gastritis with marked veno-capillary ectasia" by Rider *et al*^[1,2] in 1953. Up to the present, there had been more data regarding of the epidemiology, pathology including the outcomes of variable treatment modalities for this condition^[1]. Interestingly, there have been many hypotheses regarded the pathophysiology of GAVE which seem to be linked to cirrhosis or portal hypertension. By the way, the other theories such as GAVE and achlorhydria or mechanical stress at the antral area thus caused the detachment of the distal gastric mucosa to the pyloric ring were still be under investigated^[1]. Considering the treatment options for GAVE, the non-endoscopic treatment which aimed to reduce the bleeding without ablative therapy such as beta-blocker, octreotide, Thalidomide or even tranexamic acid reported of only little benefit. The endoscopic therapies had been reported since 1980s^[2-4], using heater probe, followed by

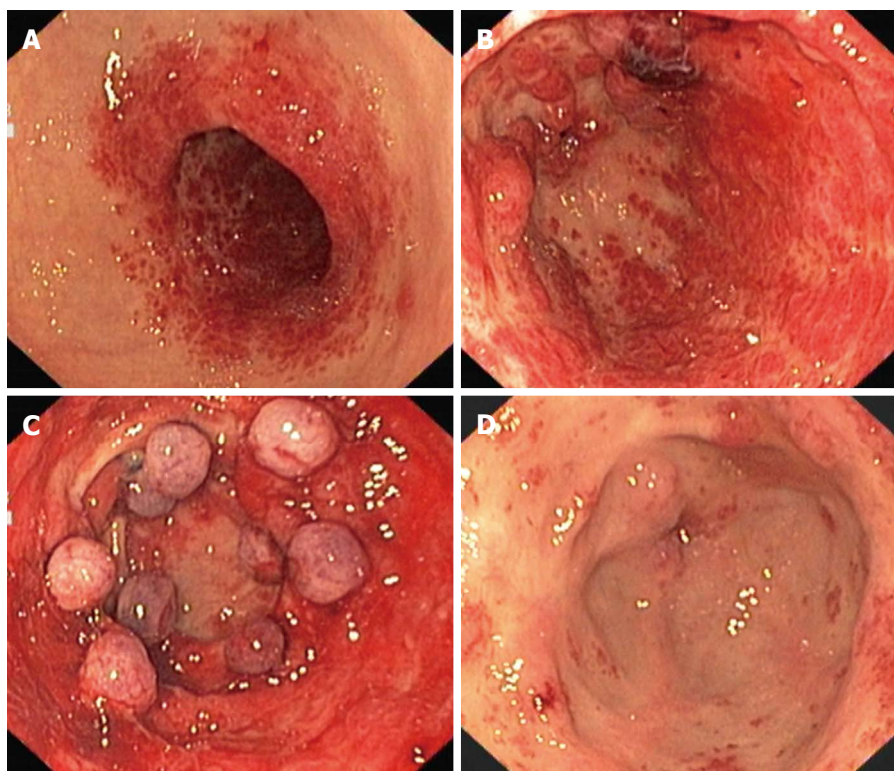


Figure 1 Esophagogastroscope was done using gastroscope. A, B: The finding revealed raised erythematous stripes radiating from pylorus up to the lower part of gastric body; C: Using endoscopic band ligation as the initial treatment for this particular patient; D: The endoscopic view showed much improvement of the lesions.

many reports of ablative treatment such as argon plasma coagulation (APC), cryotherapy and endoscope-mounted ablative device (HALO⁹⁰). Those ablative therapies reported as high as 80%-100% clinical response, which determined as no further blood transfusion required, after 2-4 years follow up period^[1-6]. However, this treatment options do have some limitations due to requirement of more sessions and the expensive equipments which might be not available in every hospital especially developing countries. Therefore, we reported of another treatment modality which provided an acceptable clinical outcome with less expensive equipment.

CASE REPORT

A 73-years-old female, known case of hypertension and Diabetes mellitus without documented evidence of cirrhosis, presented with chronic progressive anemia with intermittent melena for 4 mo. The bleeding was very severe that weekly blood transfusion required. She underwent esophagogastroscope (EGD) at the community hospital, the endoscopic finding showed fiery red gastric mucosa, diffusely found at entire antrum and extended to lower portion of gastric body. The biopsy was taken, the pathology revealed GAVE. She was referred to our endoscopic unit. Her blood works showed leukocytosis with anemia (hemoglobin 80 mg/L), otherwise were unremarkable. In the endoscopic suite, the patient was under total intravenous anesthesia (TIVA) with full anesthetic monitoring. EGD was done using gastroscope

(GIF-Q180, Olympus, Tokyo, Japan) the finding revealed raised erythematous stripes radiating from pylorus up to the lower part of gastric body (Figure 1A and B). The endoscopist who performed the procedure decided to use endoscopic band ligation (EBL), using MBL (Wilson-Cook Medical, Winston-Salem, NC, United States), as the initial treatment for this particular patient (Figure 1C). The sequential EBL, which 8-10 bands were applied per session, was scheduled as 4 wk interval for another 2 sessions. The patient responded very well after the first session, only mild gastric discomfort was reported and she was discharged without complication two days later. After seven months followed-up, her hemoglobin level was stable at 110 mg/L, no further blood transfusion required. The endoscopic view showed much improvement of the lesions (Figure 1D).

DISCUSSION

GAVE could be correctly diagnosed from the typical endoscopic finding, however the histopathology might be necessary in some atypical or severe cases such as the present case. There had been many reports regarded of endoscopic treatment options for GAVE, in our opinion; were classified into two groups, which were ablative and non-ablative therapy. The clinical outcomes of ablative therapy such as APC treatment or HALO⁹⁰ system were reported as high as 80%-100% success rate^[1,5,6]. However, these treatments needed special equipment which might not be available in all situations. The non-ablative treat-

ment options which was mentioned here was the EBL. EBL was firstly reported as the treatment for refractory GAVE in the patients who failed other treatment modalities such as APC or hormonal therapy by Sinha *et al*^[7]. Wells *et al*^[8] also reported a case series of 9 patients showed superiority of EBL over endoscopic thermal therapy, which were APC and Bipolar thermal probe therapy, for re-bleeding, hospitalization and post procedure transfusion. The number of treatment sessions was less in the EBL group (1.9 ± 0.6 sessions) than those reported using APC (4.6 ± 4.6 sessions), though it was not a head-to-head comparison^[7,8]. The complications reported for this procedure were very small^[6-10]. Regarding of the extensive involvement of the lesion in the present patient, the endoscopist who performed the procedure chose EBL as the first treatment option. According to the result of the treatment mentioned above, we proposed that EBL could be considered as first line treatment options for the GAVE patients especially for extensive area of involvement.

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Detection of active bleeding from gastric antral vascular ectasia by capsule endoscopy

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vessels may be diminished in an inflated stomach. Therefore, GAVE may be prominent in CE. We herein describe a case of active bleeding from GAVE detected by CE and would like to emphasize a possibility that CE can improve diagnostic yields for GAVE.

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Key words: Gastrointestinal bleeding; Gastrointestinal endoscopy; Capsule endoscopy; Gastric antral vascular ectasia; Argon plasma coagulation

Ohira T, Hokama A, Kinjo N, Nakamoto M, Kobashigawa C, Kise Y, Yamashiro S, Kinjo F, Kuniyoshi Y, Fujita J. Detection of active bleeding from gastric antral vascular ectasia by capsule endoscopy. *World J Gastrointest Endosc* 2013; 5(3): 138-140
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Abstract

Gastric antral vascular ectasia (GAVE) has been recognized as one of the important causes of occult and obscure gastrointestinal bleeding. The diagnosis is typically made based on the characteristic endoscopic features, including longitudinal row of flat, reddish stripes radiating from the pylorus into the antrum that resemble the stripes on a watermelon. These appearances, however, can easily be misinterpreted as moderate to severe gastritis. Although it is believed that capsule endoscopy (CE) is not helpful for the study of the stomach with its large lumen, GAVE can be more likely to be detected at CE rather than conventional endoscopy. CE can be regarded as "physiologic" endoscopy, without the need for gastric inflation and subsequent compression of the vasculature. The blood flow of the ecstatic

TO THE EDITOR

Although gastric antral vascular ectasia (GAVE) has been recognized as the uncommon cause of chronic anemia, its active bleeding has been documented very rarely. We present a case of active bleeding from GAVE detected by capsule endoscopy (CE).

A 77-year-old woman who had had mitral valve replacement with warfarin presented with dyspnea. Heart failure due to anemia was diagnosed. Fecal occult blood test was positive and repeated blood transfusion was required. The diagnosis of superficial gastritis was made by first endoscopy and was not regarded as the bleeding source (Figure 1A). Colonoscopy was negative. CE was performed for the examination of the small intestine, which disclosed active bleeding from GAVE (Figure 1B). Repeated endoscopy showed the classical "watermelon

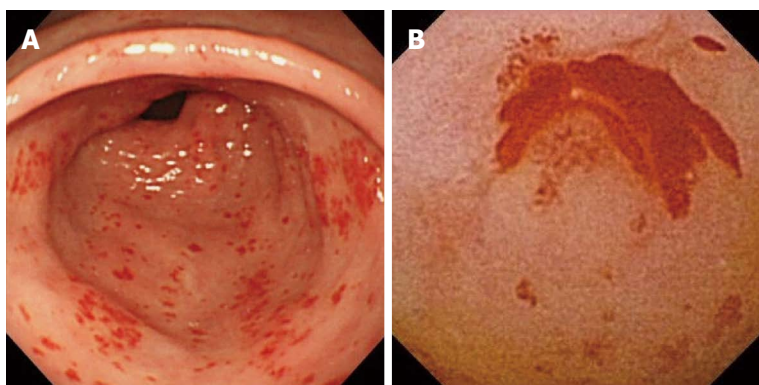


Figure 1 Conventional and capsule endoscopy. A: Conventional endoscopy showing non-bleeding gastric antral vascular ectasia (GAVE), mislabeled as superficial gastritis; B: Capsule endoscopy showing active bleeding from GAVE.

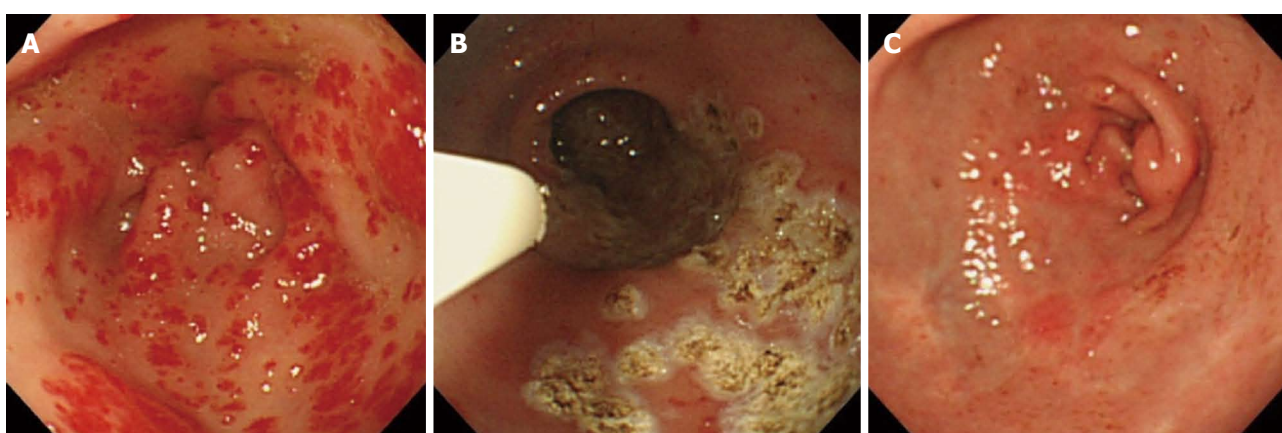


Figure 2 Endoscopy showing gastric antral vascular ectasia. A: Endoscopy showing gastric antral vascular ectasia (GAVE) with the classical "watermelon stomach" appearance just before the treatment with argon plasma coagulation (APC); B: Endoscopy showing GAVE during the treatment with APC; C: Endoscopy showing the improvement of GAVE with scar formation.

stomach" appearance of GAVE (Figure 2A). GAVE was then treated with repeated endoscopic argon plasma coagulation (APC), abolishing blood transfusion (Figure 2B). Follow-up endoscopy disclosed the improvement of GAVE with scar formation (Figure 2C).

GAVE has been described in association with various diseases, including liver cirrhosis and chronic renal failure^[1]. It is one of the important causes of occult and obscure gastrointestinal bleeding^[2]. The diagnosis is typically made based on the characteristic endoscopic appearance. The endoscopic features include longitudinal row of flat, reddish stripes radiating from the pylorus into the antrum that resemble the stripes on a watermelon or a diffuse pattern of small, punctuate spots primarily in the antrum. These appearances, however, can easily be misinterpreted as moderate to severe gastritis^[3], as in this case. Recent studies indicated that GAVE can be more likely to be detected at CE rather than conventional endoscopy^[4-7]. CE can be regarded as "physiologic" endoscopy, without the need for gastric inflation and subsequent compression of the vasculature^[5]. The blood flow of the ecstatic vessels may be diminished in

an inflated stomach^[6]. Therefore, GAVE may be prominent in CE. Our case illustrates a possibility that CE can improve diagnostic yields for GAVE. Appropriate diagnosis and treatments including APC are critical for the favorable outcome.

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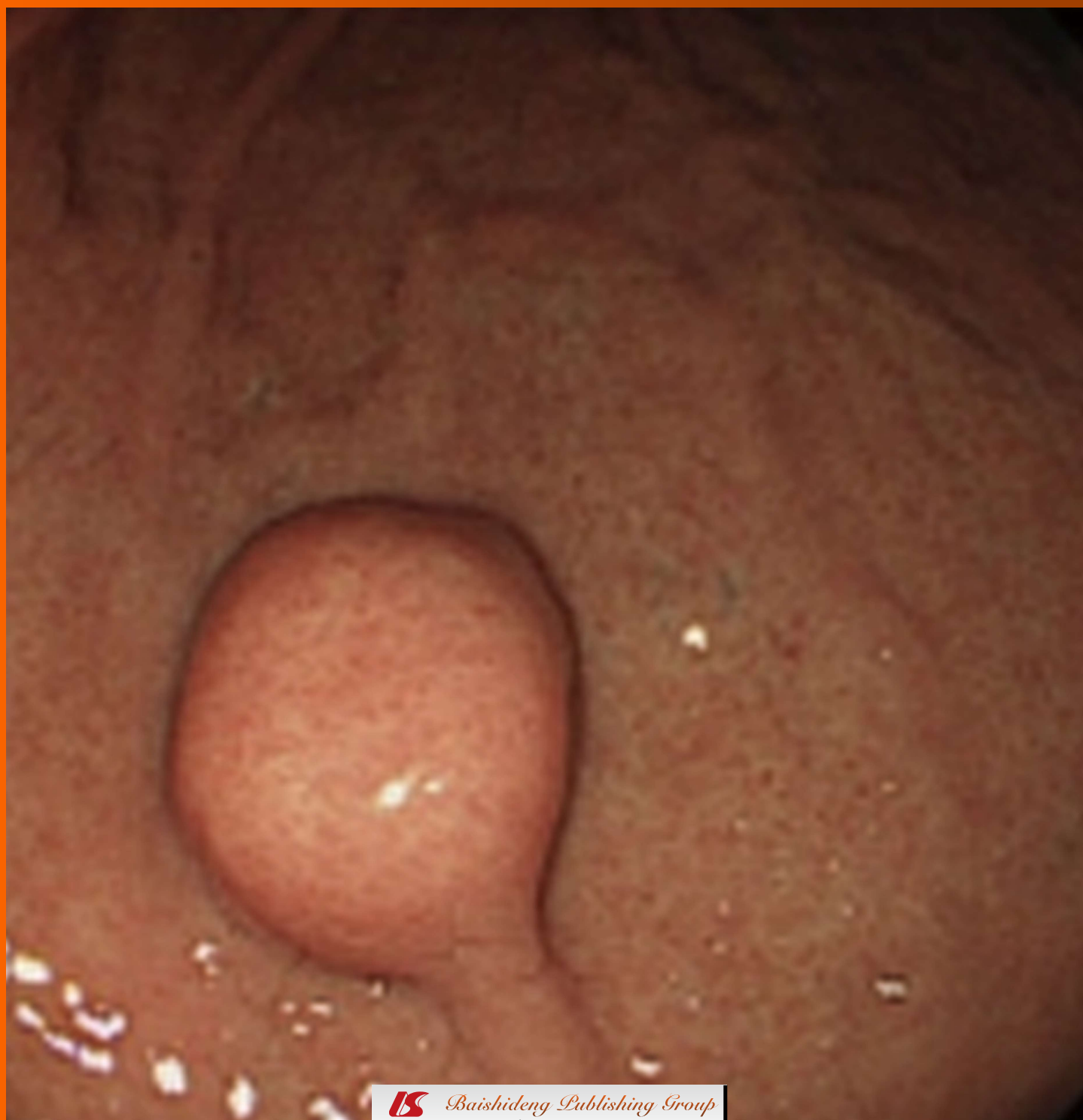
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Tumors and new endoscopic ultrasound-guided therapies

Silvia Carrara, Maria Chiara Petrone, Pier Alberto Testoni, Paolo Giorgio Arcidiacono

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Abstract

With the advent of linear echoendoscopes, endoscopic ultrasound (EUS) has become more operative and a new field of oncological application has been opened up. From tumor staging to tissue acquisition under EUS-guided fine-needle aspiration, new operative procedures have been developed on the principle of the EUS-guided puncture. A hybrid probe combining radiofrequency with cryotechnology is now available, to be passed through the operative channel of the echoendoscope into the tumor to create an area of ablation. EUS-guided fine-needle injection is emerging as a method to deliver anti-tumoral agents inside the tumor. Ethanol lavage, with or without paclitaxel, has been proposed for the treatment of cystic tumors in non-resectable cases and complete resolution has been recorded in up to 70%-80%. Many other chemical or biological agents have been investigated for the treatment of pancreatic adenocarcinoma: activated allogenic lymphocyte culture (Cytoimplant), a replication-deficient adenovirus vector carrying the tumor necrosis factor- α gene, or an oncolytic attenuated adenovirus (ONYX-015). The potential advantage of treatment under EUS control is the real-time imaging guidance into a deep target like

the pancreas which is extremely difficult to reach by a percutaneous approach. To date there are no randomized controlled trials to confirm the real clinical benefits of these treatments compared to standard therapy so it seems wise to reserve them only for experimental protocols approved by ethics committees.

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Key words: Endoscopic ultrasound; Pancreatic cancer; Endoscopic ultrasound guided ablation; Alcohol injection; Anti-tumoral injection

Core tip: New operative procedures have been developed on the principle of the endoscopic ultrasound (EUS)-guided puncture. A hybrid probe combining radiofrequency with cryotechnology is now available, to be passed through the operative channel of the echoendoscope into the tumor to create an area of ablation. The potential advantage of an ablation device employed under EUS control is the real-time imaging guidance into a deep target like the pancreas which is extremely difficult to reach by a percutaneous approach.

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INTRODUCTION

Endoscopic ultrasound (EUS) has seen significant growth in its applications in oncology in recent years^[1-9]. With the advent of linear array therapeutic probes with a large working channel EUS has become more operative. From tumor staging to tissue acquisition under EUS-guided fine-needle aspiration (FNA), new procedures have been

developed on the principle of the EUS-guided puncture: if we can puncture a lesion to acquire a cytological specimen, in the same way we can puncture a tumor to carry chemical, biological, or physical therapy inside it. New accessories have been developed, and clinical research on applications in oncological patients has expanded, especially for pancreatic diseases^[10-16].

ABLATIVE TECHNIQUES

Radiofrequency and cryotechnology

Ablative therapies such as radiofrequency (RF) and cryotechnology (CT) are widely used in oncology, though not in the pancreas because of the high operative risks. Retrospective and prospective studies have, however, shown the feasibility of water-cooled monopolar RF ablation in patients with stage III pancreatic cancer in an open, percutaneous, or laparoscopic setting^[17,18]. They confirmed that ablation in the pancreas is dangerous without additional cooling of adjacent tissue, real-time image control, and currently available ablation systems^[19-22]. Italian surgeons applied an RF probe in locally advanced pancreatic cancer during laparotomy, demonstrating the feasibility and safety of the technique^[23].

The potential advantage of an ablation device employed under EUS control is the real-time imaging guidance into a deep target like the pancreas which is extremely difficult to reach by a percutaneous approach. A minimally invasive technique to selectively ablate tumor masses could improve the efficacy of neoadjuvant treatments in patients not eligible for any other therapy. The precision of EUS in establishing the location and size of pancreatic masses could be exploited to estimate and follow up the area of ablation and help avoid damage to surrounding structures^[24-26].

A new flexible bipolar hybrid ablation system has been developed (ERBE Elektromedizin GmbH, Tübingen, Germany) (Figures 1, 2). This hybrid cryotherm probe (CTP) combines bipolar RF ablation with CT. A bipolar system is believed to create ablations with less collateral thermal damage than monopolar systems but the trade-off is some loss of overall efficiency^[27,28]. The CTP combines the advantages of the two technologies and overcomes the loss of efficiency: the more effective cooling by cryogenic gas permits more RF-induced interstitial devitalizing effects than heat alone^[29]. Less power (16 W) is needed than with conventional RF ablation systems (30-60 W) to obtain the same result, so there should be less collateral damage.

The CTP has an active electrical part with a diameter of 1.8 mm. The entire probe is covered by a protection tube that can be safely passed through the operative channel of the echoendoscope without any risk for the instrument. Basically this is an internally CO₂-cooled RF-ablation probe which ensures efficient cooling according to the Joule-Thomson effect. The distal tip of the probe is sharp, pointed and stiff in order to penetrate the gut wall and pancreatic parenchyma. Parameters like the

Total length of the active part = 24 mm (1 + 3 + 2 + 4)
Length of each electrode = 8 mm (1 and 2)
Length of the isolation part = 4 mm (3)
Length of the tip = 4 mm (4)
Diameter of the active part = 1.8 mm
Diameter of the protection tube = 2 mm (5)



Figure 1 The tip of the ERBE hybrid cryotherm probe with the active electrical part.

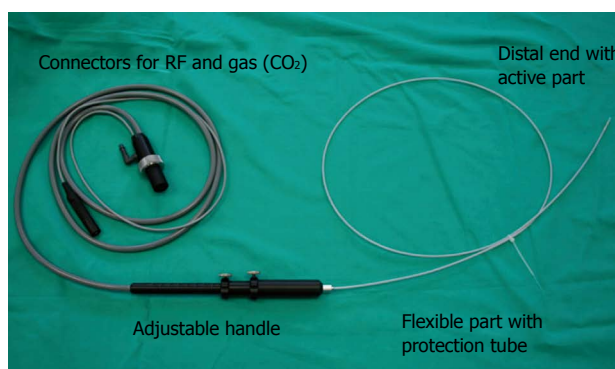


Figure 2 The ERBE flexible probe used for endoscopic ultrasound-guided ablation of the parenchymal organs. The probe, covered with a protection tube, is passed through the operative channel of the echoendoscope.

power setting of the generator, the pressure of the gas through the expansion vessel, and the duration of application can be set independently.

Transluminal RF ablation in the pancreas under EUS control was feasible in an animal model^[30]. The power (16 W) and pressure (650 psi) settings were standardized on the basis of previous experiments. Under real-time EUS-guidance the CTP was clearly visualized as a hyperechoic line moving out of the working channel until it reached its place in the pancreatic parenchyma. During the application a hyperechoic elliptic area appeared around the distal tip of the probe, surrounded by a hypoechoic border (most likely edema) (Figure 3). There was a positive correlation between lesion size and application time: the longer the application time the more the lesion size varied, reflecting the fact that a 900-s application induces high complication rates in a healthy pancreas.

On histological examination a sharp demarcation was visible between the ablated area and the untreated pancreatic parenchyma. Coagulative necrosis was evident in the center of the lesion one week after the ablation; after two weeks the lesions showed less edema and more fibrotic transformation (Figure 4).

After the animal model experiments the efficacy of the CTP was evaluated in an *ex vivo* study for destroying neoplastic tissue of explanted pancreas from patients with resectable pancreatic adenocarcinoma. Again, histological examination found a positive correlation between

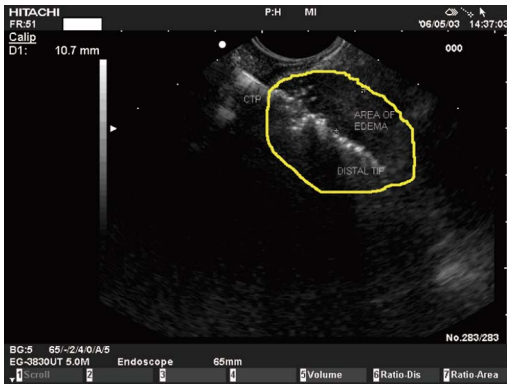


Figure 3 The cryotherm probe applied in the porcine pancreas: the probe is seen as an hyperechoic line. Initially an hyperechoic elliptic area appears around the distal tip of the probe, surrounded by a hypoechoic border (most likely edema).

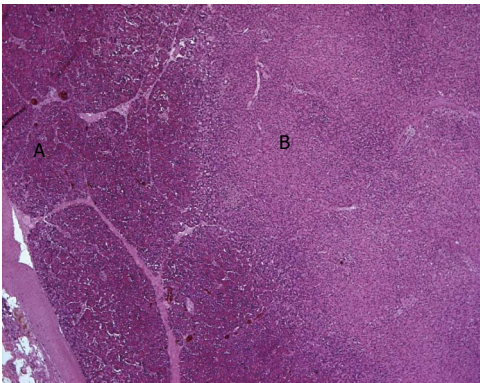


Figure 4 Histopathologic section from the first pig: Normal pancreatic tissue (A) surrounds the central treated area (B).

the size of the ablated area and the application time^[31].

In the animal model the complications were related to the ablation time: all but histochemical pancreatitis occurred with ablations longer than 300 s. Pancreatic tissue is very heat-sensitive and the thermal ablation of a normal pancreas usually leads to an inflammatory response with consecutive edema, fibrotic and sometimes cystic transformation. The tissue response should be different and less pronounced in a tumor mass surrounded by a capsule where a desmoplastic reaction limits the damage to the capsule to a certain extent.

Patients with unresectable, locally advanced pancreatic adenocarcinoma were recently enrolled in a prospective case study to investigate the feasibility of EUS-guided CTP application *in vivo* and to assess to what extent progression of the disease was slowed^[32]. The inclusion and exclusion criteria are listed in Table 1. From September 2009 to May 2011, 22 patients (11 males and 11 females, mean age 61.9 years) with unresectable stage III pancreatic adenocarcinoma were enrolled. The cryotherm ablation was feasible in 16 patients (72.8%). The probe was clearly visible throughout the procedure. No severe complications arose during or immediately after the ablation. Three patients reported post-interventional abdominal

Table 1 Inclusion and exclusion criteria of patients treated with endoscopic ultrasound-guided cryotherm ablation

Inclusion criteria	Exclusion criteria
Age > 18 yr	Severe alteration of hemostasis
Able to give consent for the procedure	Unwilling or unable to give consent
PLT > 100 000/μL	Pregnancy
INR < 1.5	Infection and/or severe leucopenia
Unresectable locally advanced pancreatic adenocarcinoma already treated with neoadjuvant chemotherapy	Acute pancreatitis
	Distant metastasis

PLT: Platelet count; INR: International normalized ratio.

pain, which responded well to analgesic drugs. Only one patient experienced a minor bleed in the duodenal lumen after the procedure, which was treated by endoscopic placement of hemostatic clips and did not require blood transfusion. Late complications arose in four cases: three were related mainly to tumor progression. A computed tomography scan was done in all patients but only in 6/16 was it possible to clearly define the tumor margins after ablation. In these patients the tumor seemed smaller than the initial mass ($P = 0.07$).

For experts familiar with the EUS-FNA procedure, the EUS-guided placement of the CTP and the ablation itself should not present any technical challenge.

A hepatocellular carcinoma of the caudate lobe unsuitable for surgery was treated with EUS-guided neodymium: yttrium-aluminium-garnet (Nd:YAG) laser ablation. A 300-μm optical fiber was passed through a 22-G needle which was then positioned in the tumor under EUS guidance. After two months computed tomography scan showed uniform hypo-attenuation without enhancement in the ablated zone^[33].

Ablation of cystic lesions

Only few studies have examined the role of ethanol injection in ablation of the lining epithelium of cystic tumors. Pancreatic cystic tumors encompass a wide spectrum of histopathologies and biological behaviors (from benign to borderline to malignant) and can be differentiated essentially as mucinous or non-mucinous. They are often detected by chance in asymptomatic patients during radiological examinations for non-specific gastrointestinal complaints. For the treatment of mucinous cystic tumors, surgical resection is usually the first choice, but EUS-guided ethanol lavage has been proposed as an alternative for patients not suitable for surgery. The rationale for the use of ethanol is that it can sclerose the lining epithelium and reduce the influx of fluid. The cyst is punctured with a 22-G fine needle under EUS-guidance, the fluid is aspirated, then ethanol is injected into the cyst and re-aspirated after 3-5 min (Figure 5). In the initial pilot study the Boston group showed the feasibility and safety of EUS-guided ethanol lavage for pancreatic cystic tumors in 25



Figure 5 Endoscopic ultrasound-guided puncture of a cystic tumor. The cyst is punctured with a 22-G fine needle under endoscopic ultrasound guidance, the fluid is aspirated, then ethanol is injected into the cyst and re-aspirated after 3-5 min.

patients^[34]. They obtained complete resolution of the cysts in eight (33%), with variable degrees of epithelial ablation observed at histological examination of resected specimens in patients who subsequently underwent surgery.

Other studies used taxol for lavage after the ethanol. Paclitaxel is a viscous, hydrophobic chemotherapeutic agent that is believed to have prolonged action in the cyst. In a preliminary study 11 out of 14 patients showed complete cyst resolution after ethanol lavage and paclitaxel injection^[35,36].

A more recent cohort study determined the duration of successful cyst resolution after EUS-guided ethanol lavage. Computed tomography scans at a median of 26 mo suggested resolution lasted well^[37]. In the Editorial commenting this study, Goodman *et al.*^[38] suggest that until we have better randomized controlled trials EUS-guided ethanol ablation of pancreatic cysts is best reserved for experimental protocols and for patients who cannot undergo surgery.

EUS-guided injection of anti-tumoral agents

EUS-guided fine-needle injection is emerging as a method to deliver anti-tumoral agents inside pancreatic tumors. Many chemical or biological agents have been investigated for the treatment of pancreatic adenocarcinoma: activated allogenic lymphocyte culture (Cytoimplant)^[39], a replication-deficient adenovirus vector carrying the tumor necrosis factor- α gene^[40,41], and an oncolytic attenuated adenovirus (ONYX-015)^[42]. The procedure was developed on the principle of EUS-guided FNA: the needle is passed through the operative channel of the echoendoscope and is followed in real time while it punctures the tumor and the agent is delivered inside the mass. A Doppler signal helps avoid interposing vessels and makes the procedure safer.

Allogenic mixed lymphocyte culture (Cytoimplant): The first study, by Chang *et al.*^[40], assessed the technical feasibility and safety of EUS-guided injection of allo-

genic mixed lymphocyte culture (Cytoimplant) in locally advanced pancreatic adenocarcinoma. Eight patients with unresectable pancreatic cancer were given a single EUS-guided injection of Cytoimplant. The first two received three billion cells, the next three six billion cells and the last three nine billion cells. The procedures were safe and there were no severe complications. The only side effect reported was low-grade fever. Median survival was 13.2 mo. No other studies have followed this first phase I trial.

Replication-deficient adenovirus vector carrying the tumor necrosis factor- α gene: Chang *et al.*^[40] also tested EUS-guided TNFerade injection in patients with locally advanced pancreatic cancer. TNFerade is a replication-deficient adenovector that contains the human tumor necrosis factor (TNF)- α gene. Patients received five weekly EUS-guided intratumoral injections of TNFerade (4×10^9 , 4×10^{10} , and 4×10^{11} particle units in 2 mL). This was combined with *iv* chemotherapy (fluorouracil, 5-FU) and radiation. The rationale for this triple strategy lies in the synergism between the three therapies. 5-FU is directly toxic to malignant cells and is also a radiosensitizer; radiation therapy destroys tumor cells and up-regulates TNF production; and TNFerade, which is also a radiosensitizer, kills the tumor cells. The procedure was well tolerated. Patients who received the higher doses had better locoregional control of the disease, better median survival rates, and a higher percentage of resective surgery after the treatment^[41,42].

Adenovirus ONYX-015: Another anti-tumoral viral therapy schedule is ONYX-015, a replication selective adenovirus with a deletion in the E1B-55 kDa gene, which preferentially replicates in tumoral cells and kills them. Twenty-one patients were given EUS-guided injections of ONYX-015 over an eight-week period. Complications were more severe than in the previous studies described: two patients had sepsis and two had duodenal perforation. None showed tumor regression with the ONYX-015 injection alone after five weeks, but two patients had a partial response after the combination with gemcitabine^[42].

Although EUS-guided antitumoral injection seems feasible and safe, and the results of these studies seem promising, the efficacy in phase III randomized controlled trials has still to be demonstrated and published.

PLACEMENT OF EUS-GUIDED FIDUCIAL MARKERS AND BRACHYTHERAPY

EUS guidance can also be used to place fiducial markers or radioactive seeds inside a tumor. Fiducial markers are radiopaque spheres, coils, or seeds that are implanted in or near the tumor in order to demarcate the borders of the tumor to facilitate image-guided radiation therapy. Many studies have been published on EUS-guided placement of these markers in different tumors^[43-47].

The fiducials are passed through a 19-G or 22-G

Table 2 Potential applications of therapeutic endoscopic ultrasound for pancreatic cancer

Ref.	Year of publication	Type of cancer	n	Materials	Results	Complications
Arcidiacono <i>et al</i> ^[32]	2012	Adeno-carcinoma	22	Cryotherm probe	Feasible (72%), and safe	Pain (3 pts); minor bleeding (1 pt)
Gan <i>et al</i> ^[34]	2005	Cystic tumors	25	Ethanol lavage	Complete resolution (35%)	No complications
Oh <i>et al</i> ^[36]	2008	Cystic tumors	52	Ethanol lavage + paclitaxel	Complete resolution (62%)	Mild pancreatitis and splenic vein obliteration (1 pt)
Chang <i>et al</i> ^[39]	2000	Adeno-carcinoma	8	Cytoimplant	2 partial responses and 1 minor response	Low-grade fever (86%); GI toxicities (37%)
Hecht	2012	Adeno-carcinoma	50	TNFrade	1 complete response; 3 partial responses; 12 stable diseases	Pancreatitis and cholangitis (3 pts)
Hecht <i>et al</i> ^[42]	2003	Adeno-carcinoma	21	ONYX-015 + iv gemcitabine	Partial response (2 pts)	Sepsis (2 pts); duodenal perforation (2 pts)
Jin <i>et al</i> ^[50]	2008	Adeno-carcinoma	22	iodine 125-seeds	Successful implantation in all pts; partial remission (13%); stable disease (45%)	No complications

GI: Gastrointestinal.

needle and deployed with different techniques into the mass, using the stylet, or by injecting sterile water into the needle^[46]. The fact that the 19-G needle is stiffer can make it harder to position the fiducials in pancreatic head tumors with the echoendoscope placed in the second portion of the duodenum, while with the smaller-caliber 22-G needle it may be easier to place the fiducials in the deepest portions of the pancreas^[48].

Few trials have evaluated EUS-guided implantation of radioactive seeds (iodine-125) in patients with unresectable pancreatic cancer^[49,50]. Patients treated with a combination of radioactive seeds and chemotherapy showed tumor regression and reported some relief of pain^[50].

CONCLUSION

EUS, born as an extremely accurate imaging technique, is emerging as a tool to guide interventional endoscopy in oncological patients, from EUS-guided FNA, to EUS-guided injection of anti-tumoral agents, to EUS-guided ablation devices. Table 2 summarizes the potential oncological applications of therapeutic EUS.

Many case series and reports have confirmed the feasibility and safety of EUS-guided operative procedures, but there are still no randomized controlled trials to confirm the real clinical benefits of these treatments compared to standard therapy. At the moment it seems wise to reserve them only for experimental protocols approved by ethics committees.

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Safety of endoscopic retrograde cholangiopancreatography in pregnancy: Fluoroscopy time and fetal exposure, does it matter?

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Abstract

AIM: To estimate the fetal radiation exposure using thermoluminescent dosimeters (TLD's) in pregnant patients undergoing endoscopic retrograde cholangiopancreatography (ERCP) and assess its relevance.

METHODS: Data on thirty-five therapeutic ERCPs conducted in pregnant patients from 2001 to 2009 were retrieved from a prospective database. Techniques to minimize fluoroscopy time were implemented and the fluoroscopy times captured. TLD's were placed on the mother to estimate the fetal radiation exposure and the results were compared to the maximum allowed dose of radiation to the fetus [0.005 gray (Gy)]. Obstetrics consultations were obtained and the fetus was monitored before and after the ERCP. Fluoroscopy was

performed at 75 kVp. ERCP was performed with the patients supine by dedicated biliary endoscopists performing more than 500 cases a year.

RESULTS: A total of 35 pregnant patients underwent ERCP and biliary sphincterotomy (14 in first trimester, 11 in second trimester, and 10 in third trimester). Mean maternal age was 25 years (range 16-37 years) and mean gestational age was 18.9 wk (range 4-35 wk). Mean fluoroscopy time was 0.15 min (range 0-1 min). For 23 women, the estimated fetal radiation exposure was almost negligible (< 0.0001 Gy) while for 8 women, it was within the 0.0001-0.0002 Gy range. Three women had an estimated fetal radiation exposure between 0.0002 and 0.0005 Gy and 1 woman had an estimated fetal radiation exposure greater than 0.0005 Gy. Complications included 2 post-sphincterotomy bleeds, 2 post-ERCP pancreatitis, and 1 fatal acute respiratory distress syndrome. One patient developed cholecystitis 2 d after ERCP.

CONCLUSION: ERCP with modified techniques is safe during pregnancy, and estimating the fetal radiation exposure from the fluoroscopy time or measuring it *via* TLD's is unnecessary.

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Key words: Endoscopic retrograde cholangiopancreatography; Pregnancy; Fluoroscopy; Fetal exposure; Pancreaticobiliary disease

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INTRODUCTION

Choledocholithiasis can occur in as many as 12% of pregnant women and increases with gestational age^[1]. It may be associated with cholangitis and/or gallstone pancreatitis, both of which have an increased morbidity for the mother and fetus^[2]. Therefore choledocholithiasis is the most common indication for endoscopic retrograde cholangiopancreatography (ERCP) during pregnancy^[3]. For pancreaticobiliary diseases in pregnancy, ERCP has been suggested as an effective alternative to surgery^[4]. Suggestions have been made that ERCP is likely best performed during the second trimester, though the procedure appears reasonably safe to be performed throughout the entire period of pregnancy^[5]. ERCP is currently exclusively indicated for therapeutic reasons in light of the endoscopic risks (such as bleeding, pancreatitis or perforation) as well as the ionizing radiation exposure to the fetus^[6]. ERCPs are therapeutic when one or more of the following is performed: endoscopic sphincterotomy, removal of stones, stent placement, dilation of strictures. Efforts to minimize ionizing radiation, measured in rads (radiation absorbed dose)^[5] or in rem (radiation equivalent man) or in international units gray (Gy)^[7], should be undertaken. During neuron development, the threshold for malformations appears to be 0.001 Gy^[5] and the overall maximum allowed dose of radiation to the fetus is 0.005 Gy^[7]. The International Commission of Radiological Protections recommends specific calculations of fetal radiation exposure when doses are suspected to exceed the threshold of 0.01 Gy^[8]. Our study sought to estimate the fetal radiation exposure using thermoluminescent dosimeters (TLD's) in pregnant women undergoing therapeutic ERCP with modified techniques as well as look at the outcome of the ERCP in those patients.

MATERIALS AND METHODS

All pregnant woman undergoing ERCP between 2001 till 2009 were captured in a dedicated prospective database. A total of thirty-five pregnant women were entered. The records were reviewed to determine the procedure indications and outcome in terms of success and eventual morbidity. Also, existing perinatal records were reviewed. The institutional review board approved the study protocol.

Preprocedure characteristics and evaluation

Pre-ERCP diagnosis included gallstone pancreatitis (17), choledocholithiasis (11), symptomatic cholelithiasis (6) and cholangitis (1). Obstetrics consultations were obtained and the fetus was monitored before and after the ERCP. Antibiotics were administered prophylactically. The modified technique involved the patients being placed supine on the fluoroscopy table, and the lower abdomen and pelvis being shielded with a 0.5- to 1.0-mm thickness of lead or its equivalent^[7]. The uterus was positioned outside the primary X-ray beam. Four pairs of TLD's were taped to the skin; one pair on the abdomen over the uterus shielded by lead, one pair on the upper



Figure 1 Fluoroscopy view of stone in common bile duct in a pregnant patient.

abdomen in the primary beam, one pair on the lower back beneath the uterus shielded by lead and one pair on the upper back in the primary beam^[7]. Fluoroscopy was performed at 75 kVp. A TLD reader was used and its readings were converted to milliamps (mrads) of dose received at the skin surface by using a calibration curve^[7]. TLDs on the upper back in the primary beam recorded the highest dose; about 10% of this dose was estimated to be the fetal dose^[7]. The fetus was considered to be 10 cm from the posterior surface, and percentage depth dose at 10 cm was taken as approximately 10%. The depth dose varies with body habitus and gestational age and hence the dose estimation was an approximation^[7].

ERCP techniques

ERCP was performed with the patients supine by dedicated biliary endoscopists performing more than 500 cases a year^[7]. Free biliary cannulation was obtained by using a sphincterotome and was confirmed by aspiration of bile, after which a biliary sphincterotomy was performed^[7]. An 11.5-mm diameter retrieval balloon was advanced into the bile duct^[7]. Contrast medium was injected, and a balloon occlusion cholangiogram was obtained to confirm the presence and location of stones, as well as cystic duct patency, after which the balloon was used to extract stones (Figures 1 and 2)^[7].

RESULTS

A total of 35 pregnant patients underwent ERCP and biliary sphincterotomy (14 in first trimester, 11 in second trimester, and 10 in third trimester). Mean maternal age was 25 years (range 16-37 years) and mean gestational age was 18.9 wk (range 4-35 wk). Mean fluoroscopy time was 0.15 min (range 0-1 min). For 23 women, the estimated fetal radiation exposure was negligible (< 0.0001 Gy) while for 8 women, it was within the 0.0001-0.0002 Gy range. Three women had an estimated fetal radiation exposure between 0.0002 and 0.0005 Gy and one woman had an estimated fetal radiation exposure greater than 0.0005 Gy (Figure 3). Mean values for biochemical tests obtained before ERCP were the following: aspartate



Figure 2 Endoscopic view of impacted stone in a pregnant patient.

aminotransferase 179 IU/L (range: 25-310 IU/L); alanine aminotransferase 210 IU/L (27-561 IU/L); alkaline phosphatase 162 IU/L (44-394 IU/L); and total bilirubin 2.4 mg/dL (0.2-5 mg/dL). Four patients prior to pregnancy had cholecystectomy, one patient had a cholecystectomy during the pregnancy and prior to ERCP, and four patients required cholecystectomy post-ERCP during their pregnancy.

The patients' final diagnosis was made based on ERCP findings, that is, extraction of stone or stone fragments after biliary sphincterotomy. Final diagnosis included the following: choledocholithiasis (18), gallstone pancreatitis (14), cholelithiasis, microlithiasis, and cholestasis. Complications of the ERCP procedure included post-sphincterotomy bleeding in two patients (controlled by hemoclip placement), post-ERCP pancreatitis (pancreatitis that developed within a week after ERCP) in two patients that necessitated one and two days of hospitalization, and acute respiratory distress syndrome in one patient who passed away as a result. One patient had cholecystitis requiring laparoscopic cholecystectomy 2 d post-ERCP. Two patients had contractions post-ERCP that resolved with hydration and terbutaline administration, respectively. Four mothers were at term and 2 mothers were preterm. Labor was induced in 2 mothers with non eventful delivery.

DISCUSSION

The incidence of gallstone disease during pregnancy has been estimated to be between 4.5% to 12%^[1,3]. Choledocholithiasis may lead to potentially life-threatening cholangitis and/or gallstone pancreatitis. Given the necessity of treating cholangitis and gallstone pancreatitis during pregnancy^[3] with therapeutic ERCP, an estimate of the radiation exposure to the fetus from an uncomplicated ERCP procedure should be known. Several published studies have investigated post-ERCP complications (preterm births, pancreatitis, sphincterotomy bleed) in pregnant women with a few capturing the mean time of fluoroscopy.

The mean fluoroscopy time was 14 s (range 1-48 s) and with use of TLDs the fetal radiation exposure was

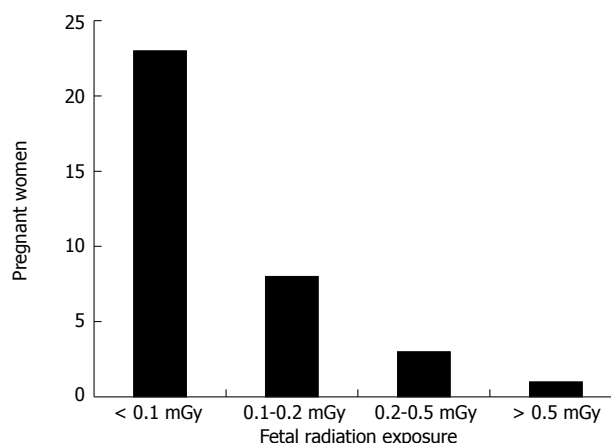


Figure 3 Bar graph representing estimated fetal radiation exposure. Gy. Gray.

estimated to be 0.0004 Gy (range 0.0001-0.0018 Gy) in Kahaleh *et al*^[7]. Despite there being a correlation between fluoroscopy time and radiation exposure, each fluoroscopy time corresponded with a wide range of radiation exposures. Complications included one post-sphincterotomy bleed and one post-ERCP pancreatitis. Two of the 17 women developed third-trimester preeclampsia, and labor was induced in both. Thirteen of the 15 patients who delivered were contacted and they confirmed that their child was in good health. Similar but limited complications were seen in Jamidar *et al*^[9]. Twenty-three pregnant patients underwent a total of 29 ERCPs with one post-ERCP pancreatitis. Also, there was one spontaneous abortion (3 mo after ERCP) and one neonatal death; however, casual relationship to ERCP was not clear.

In Tang *et al*^[10] in 2009, the largest retrospective study on ERCP in pregnant women, 68 ERCPs were performed on 65 pregnant women. The median fluoroscopy time was 1.45 min (range 0-7.2 min) and 11 patients (16%) had post-ERCP pancreatitis. Term pregnancy was achieved in 53 patients (89.8%). Patients having ERCP in the first trimester had the lowest percentage of term pregnancy (73.3%) and the highest risk of preterm delivery (20.0%) and low-birth-weight newborns (21.4%). None of the 59 patients with long-term follow-up had spontaneous fetal loss, perinatal death, stillbirth, or fetal malformation.

Gupta *et al*^[11] reported on one of the longest follow-up periods on fetal outcome after ERCP. Eighteen pregnant women underwent ERCP and sphincterotomy (4 in the first trimester, 6 in the second, and 8 in the third) in which the location of the cannula in the bile duct was confirmed using ultrasound guidance in 5 patients and bile aspiration in 2 patients. Indications included elective ERCP in 14 and symptomatic choledocholithiasis in 4. Complications included a post-sphincterotomy bleed and a mild post-ERCP pancreatitis in another, who also had preterm delivery. Eleven of 18 patients had healthy children without any developmental or congenital abnormalities 11-years post ERCP follow-up.

Tiwari *et al.*^[12] conducted a systematic review of 19 studies including 214 ERCPs in pregnant women and the procedure related complications included spontaneous abortion (0.9%), fetal distress (0.6%) and post procedure pancreatitis (4.6%). Preterm birth occurred in 4.6% with majority of the APGAR score greater than 8. Post-procedure pancreatitis risk factors include: young age, female sex, history of pancreatitis, sphincter of oddi dysfunction, difficult cannulation and precut sphincterotomy^[6]. Thus, post-ERCP pancreatitis does not adversely affect pregnancy-related outcomes, as reported previously^[10]. Cholecystectomy was performed in a few of the patients reviewed and most likely does not appear to lead to pre-term delivery and low birth weight^[10].

In a few studies, biliary stents were placed not only when residual stones or fragments were present, but also in an effort to limit total fluoroscopy time^[10]. Farca *et al.*^[13] placed 10-French biliary stents without sphincterotomy in 10 patients, all of which had uncomplicated pregnancies and deliveries. Daas *et al.*^[4] in 2009 (17 ERCPs in 10 patients) placed plastic biliary stents when large (> 10 mm) biliary stones were encountered or when there was doubt regarding complete stone clearance. Fluoroscopy was used in 6 cases with mean exposure time of 8 s. Most of the 10 pregnant women in the study required repeat ERCPs with one woman receiving 3 subsequent ERCPs without fluoroscopy and had to return postpartum for a definitive stone extraction.

Barthel *et al.*^[14] performed biliary sphincterotomy in 3 patients with gallstone pancreatitis despite the absence of choledocholithiasis; one patient had post-ERCP pancreatitis and none had recurrent pancreatitis and all pregnancies had healthy outcome. Tang *et al.*^[10] showed that prophylactic sphincterotomy during ERCP can effectively reduce the risk of recurrent biliary pancreatitis during pregnancy. Therefore, ERCP with biliary sphincterotomy was performed in all 35 patients in our study.

Some have advocated eliminating radiation exposure by biliary cannulation with a sphincterotome, confirmation of access by bile aspiration^[9] followed by sphincterotomy and stone extraction with a balloon catheter^[5]. With this technique of using wire-guided cannulation techniques to achieve bile duct access without use of fluoroscopy^[15], there is lack of ductal system definition and additional stones may be missed^[5]. Importantly, aspiration of bile into the catheter does not necessarily confirm whether the CBD or the cystic duct has been cannulated^[5]. Although it is important to minimize radiation exposure during ERCP, without fluoroscopy, residual stones or debris can be left in the CBD and might lead to recurrent cholangitis with more serious effects on both the fetus and mother^[5].

In Sharma *et al.*^[16] in 2008, 11 pregnant women underwent biliary sphincterotomy and stenting without fluoroscopy and had definitive ERCP and stone clearance after pregnancy. One patient with large common bile duct stone required mechanical lithotripsy while another required surgery. Of note, the indication for the ERCP

in the study was choledocholithiasis not cholangitis or gallstone pancreatitis which carry an increased mortality to the mother and fetus and likely necessitate definitive ERCP during the pregnancy. Further studies are required to prove that the clinical efficiency of nonradiating ERCP remains at the same level with conventional fluoroscopically guided ERCP^[15]. Girotra *et al.*^[17] described an alternative management strategy to conventional ERCP in pregnant women with choledocholithiasis and cholangitis detected using EUS and choledochoscopy.

Fluoroscopy time can be utilized in ERCPs performed in pregnant patients and limiting fluoroscopy time is one of the most efficient methods to reduce radiation dose^[3]. Lead shielding should be used^[6] hard copy radiographs should be avoided^[5] and anterior posterior beam projection should be used as it results in lower fetal dosing^[6,8]. The radiation risks include fetal death, growth retardation especially during organogenesis and malformations^[7]. Exposures over 0.001 Gy during neuron development and migration may be associated with microcephaly, mental retardation and childhood cancers^[5]. The maximum allowed dose of radiation to the fetus is 0.005 Gy^[7].

The International Commission of Radiological Protections recommends specific calculations of fetal radiation exposure when doses are suspected to exceed the threshold of 0.01 Gy^[8]. Surprisingly, ERCP-induced fetal radiation exposure from ERCPs carried out in pregnant patients have been reported in the literature to vary from 0.0001 to 0.003 Gy per procedure^[1,3,7,9,18,19]. In our study, the ERCP-induced fetal radiation ranged from less than 0.0001 to greater than 0.0005 Gy. For the majority of the women (88.6%), the estimated fetal radiation exposure was no more than 0.0002 Gy; while only one woman's estimated fetal radiation exposure was greater than 0.0005 Gy. The fetal radiation exposure values in our study are below the threshold established by the International Commission of Radiological Protections needing specific calculations of fetal radiation exposure and the maximum allowed dose of radiation to the fetus.

Thus, for a routine ERCP with modified techniques, estimating the fetal radiation exposure from the fluoroscopy time and measuring it with the use of TLD's is unnecessary. The threshold may be exceeded in complicated long-lasting ERCPs^[3] and in these complicated long-lasting ERCPs, dosimetry may be used to estimate the fetal radiation exposure, such as patients with altered anatomy, failed prior ERCP or complex bile leak. By placing TLD's on the pregnant patient over and above the uterus, one can obtain a good estimate of the fetus doses from calculations based on a TLD reading. The value is an approximation, probably an underestimate of the real value, as the principal source of radiation to the fetus during the ERCP comes from scattered radiation absorbed within the mother's body^[3]. Tham *et al.*^[1] attempted to attain a better estimate using nonanthropomorphic phantom to estimate the entrance skin dose and estimated the fetal dose exposure at 0.003 Gy.

The safety and efficacy of therapeutic ERCP has been

demonstrated in many studies^[1,7,9,11,13,20-31]. For a routine ERCP, the reported fetal radiation exposure falls below the maximum allowed dose of radiation to the fetus of 0.005 Gy^[7], therefore estimating the fetal radiation exposure from the fluoroscopy time or by measuring it from the use of TLD's is unnecessary.

COMMENTS

Background

For pancreaticobiliary diseases in pregnancy, endoscopic retrograde cholangiopancreatography (ERCP) has been suggested as an effective alternative to surgery. ERCPs are therapeutic when one or more of the following is performed: endoscopic sphincterotomy, removal of stones, stent placement, dilation of strictures.

Research frontiers

Fluoroscopy time can be utilized in ERCPs performed in pregnant patients and limiting fluoroscopy time is one of the most efficient methods to reduce radiation dose.

Innovations and breakthroughs

The fetal radiation exposure values in the authors' study are below the threshold established by the International Commission of Radiological Protections needing specific calculations of fetal radiation exposure and the maximum allowed dose of radiation to the fetus.

Peer review

The aim of the present article is the estimation of the fetal radiation exposure using TLD's in pregnant women undergoing ERCPs. The article is sound and deserves publication.

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Accuracy of community based video capsule endoscopy in patients undergoing follow up double balloon enteroscopy

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Abstract

AIM: To determine the test characteristics of community based video capsule endoscopy (VCE) in patients undergoing sequential VCE and double balloon enteroscopy (DBE).

METHODS: Eighty-nine patients (34 females, 55 males, mean age 66) who underwent both VCE and DBE from 2008-2010 were retrospectively reviewed. Lesions detected at VCE were categorized. Capsule directed DBE followed and included 44 antegrade, 11 retrograde and 34 combined antegrade and retrograde procedures. Lesions detected were compared utilizing the McNemar's test.

RESULTS: Angiectasia detection with VCE was 25% and with DBE 35% ($P < 0.03$) with a calculated sensitivity and specificity of 58% and 93% respectively. Polyps were detected by VCE in 22% and in DBE 20%, ($P = 0.6$), with a sensitivity and specificity for VCE of 61% and 87%. Small bowel diverticula were only seen in 1% of VCE but in 12% of DBE patients ($P < 0.002$) with a calculated sensitivity and specificity of VCE of 9% and 100%.

CONCLUSION: VCE would be moderately sensitive

and specific overall with considerable variation by lesion. Furthermore, VCE cannot be relied upon to diagnose small bowel diverticula.

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Key words: Video capsule endoscopy; Double balloon enteroscopy; Angiectasia; Diverticulosis; Obscure gastrointestinal bleeding

Core tip: Advances in endoscopic technology have revolutionized the evaluation of small intestinal disorders. Non-invasive imaging utilizing video capsule endoscopy (VCE) offers the potential to safely visualize the entire small bowel with a high diagnostic yield. It is limited by a lack of therapeutic ability, imprecise localization, failure to reach the colon in all cases and inconsistent visualization of the entire small bowel. Deep enteroscopy, utilizing double balloon enteroscopy (DBE), enables diagnostic and therapeutic endoscopy of the small bowel. Although total enteroscopy can be accomplished, it typically requires antegrade and retrograde approaches. In most clinical situations, VCE is performed initially. By using DBE as the criterion (gold) standard, the sensitivity and specificity of community based VCE can be assessed for individual lesions, offering a more informative comparison than diagnostic yield.

Tenembaum D, Sison C, Rubin M. Accuracy of community based video capsule endoscopy in patients undergoing follow up double balloon enteroscopy. *World J Gastrointest Endosc* 2013; 5(4): 154-159 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i4/154.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i4.154>

INTRODUCTION

Advances in endoscopic technology have revolutionized

the evaluation of small intestinal disorders. Non-invasive imaging utilizing video capsule endoscopy (VCE) offers the potential to safely visualize the entire small bowel with a high diagnostic yield^[1,2]. It is limited by a lack of therapeutic ability, imprecise localization, failure to reach the colon in all cases and inconsistent visualization of the entire small bowel^[3]. Deep enteroscopy, utilizing double balloon enteroscopy (DBE), enables diagnostic and therapeutic endoscopy of the small bowel. Limitations of DBE include its invasive nature, limited availability and the need for anesthesia^[4]. Although total enteroscopy can be accomplished, it typically requires antegrade and retrograde approaches. The rate of total enteroscopy varies between 11%-66%^[5,6]. In most clinical situations, VCE is performed initially^[3]. The results can then be used to determine the need for deep enteroscopy as well as the entry route (antegrade or retrograde)^[7,8]. Studies comparing the relative abilities of VCE and DBE, are based on “diagnostic yield” which refers to the proportion of examinations in which any abnormality is detected. Two recent meta-analyses of studies comparing VCE and DBE have demonstrated comparable diagnostic yields^[1,2]. Few studies, however, compared the individual abnormalities detected at VCE with those subsequently confirmed at DBE^[9]. We propose to evaluate the test characteristics of VCE for each type of lesion by comparing the results of community based VCE to the findings at follow up DBE for each patient. By using DBE as the criterion (gold) standard, the sensitivity and specificity of community based VCE can be assessed for individual lesions, offering a more informative comparison than diagnostic yield.

MATERIALS AND METHODS

Patients

Eighty-nine patients, 34 females and 55 males with a mean age of 66, who underwent sequential VCE and DBE exams between 2008-2010 were retrospectively reviewed (Table 1). The study was approved by the New York Hospital Queens institutional review board. All VCE studies but one were performed with the Given Imaging Pillcam SB2[®] system. VCE studies were read by both community and full-time academic gastroenterologists in the New York metropolitan area. A formal second review of VCE studies by a single expert was not performed. Preparation for VCE was variable and depended on the preferences of the referring physician. Findings were not correlated with use and type of preparation. No attempt was made to correlate VCE findings with pre-procedure preparation since the effect of preparation on diagnostic yield remains controversial^[10-12]. All patients undergoing antegrade DBE were NPO for eight hours prior to the exam. All patients undergoing retrograde DBE were prepped with a combination of 2 L of polyethylene glycol and Bisacodyl 120 mg.

DBE

DBE studies were performed with the Fujinon EN-450T5 enteroscope with a methodology described previously^[13].

Table 1 Demographics *n* (%)

Total patients	89
Male	55 (62)
Female	34 (38)
Median days from VCE to DBE	29 (8-64)
Age (range) (yr)	66 (19-93)
Antegrade DBE	44 (49)
Retrograde DBE	11 (12)
Antegrade and retrograde DBE	34 (38)

VCE: Video capsule endoscopy; DBE: Double balloon enteroscopy.

All DBE procedures were performed by one attending (MR) and a gastroenterology fellow at New York Hospital Queens Weill-Cornell Medical College. The approach to DBE was guided by VCE findings. Patients with positive VCE findings in the proximal and mid small-bowel underwent antegrade DBE initially. If the lesion was not found, a retrograde procedure was then performed. Patients with lesions seen in the distal small bowel at VCE underwent a retrograde DBE as the initial procedure. If the lesion was not found, an antegrade procedure was then performed. In total 44 patients underwent antegrade DBE, 11 retrograde DBE and 34 underwent both. Sixteen of the 34 had complete enteroscopy^[5,6]. In patients with obscure gastrointestinal bleeding (OGIB) and negative VCE exams, DBE was guided by the patient's history. A second DBE was only performed if no lesion was found. The median time interval between the performance of VCE and the initial DBE was 29 d.

Descriptive statistics such as means, SD, medians and interquartile range were used to characterize the age distribution and time between VCE and DBE. Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV), along with their corresponding 95% confidence intervals, were calculated to evaluate the accuracy of VCE for identification of lesions using DBE as criterion standard. McNemar's test for paired data was used to compare detection rates between VCE and DBE. In addition to investigating detection rates for the overall presence of any lesion, separate analyses were also performed according to the type of lesion (angioectasia, diverticula, mass, polyps, ulcers/erosions). All analyses were performed using SAS version 9.2 (SAS Institute, Cary, NC). A result was considered statistically significant at the $P < 0.05$ level of significance.

Statistical analysis

Abnormalities identified by VCE and DBE were categorized into 5 groups to facilitate the comparison of VCE to DBE by lesion type. These groups include: (1) Angioectasia; (2) Diverticula; (3) Mass; (4) Polyps; and (5) Ulcers/Erosions.

RESULTS

Indication

Indications for VCE included OGIB ($n = 78$, 88%), suspicion of Crohn's disease ($n = 10$, 11%), and suspicion

Table 2 Diagnostic yield by lesion

	VCE	DBE	P value
Angioectasia	25%	35%	0.03
Diverticula	1%	12%	0.002
Mass	2%	2%	NA
Polyps	22%	20%	0.62
Ulcers	17%	14%	0.44
All Lesions	64%	66%	0.72

VCE: Video capsule endoscopy; DBE: Double balloon enteroscopy; NA: Not available.

of Whipples disease ($n = 1$, 1%).

Diagnostic yield

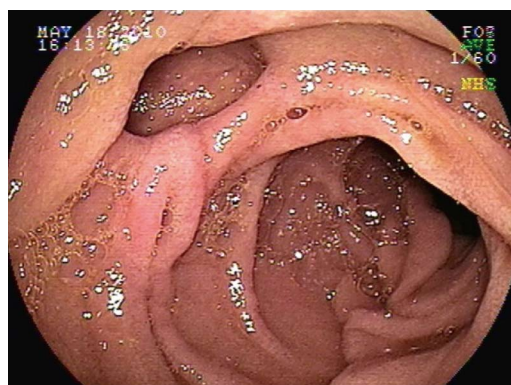
The overall diagnostic yields of VCE and DBE were 64% and 66% respectively ($P = 0.72$). Diagnostic yield by lesion type showed a significantly higher detection rate for DBE in the detection of angioectasia and diverticula. Angioectasia detection by VCE was 25% compared to 35% for DBE ($P = 0.03$, Table 2). By location, 35% of angioectasias identified at VCE were in the first tertile, 43% in the second tertile and 22% in the third tertile. The vast majority of angioectasias (11/13) seen at DBE but not at VCE were in the proximal to mid-small bowel. Small bowel diverticula were seen in 1% of all VCE patients compared to 12% of DBE patients ($P = 0.002$). Diverticula were identified in the duodenum in 2 patients, jejunum in 7 patients and the ileum in 4 patients. Mass lesions were seen in two patients with VCE and both were confirmed at DBE. No additional mass lesions were discovered by DBE. Small bowel polyps were seen in 22% of VCE patients compared to 20% of DBE patients ($P = 0.62$). Small bowel ulcers were seen in 17% of VCE patients compared to 14% of DBE patients ($P = 0.44$) (Table 2).

Test characteristics of VCE

Comparison of VCE and DBE findings by lesion type: (1) Angioectasia: Angioectasias were found by both VCE and DBE in 18 patients. They were found only in VCE in 4 patients and in DBE alone in 13 patients; and (2) Diverticula: Small bowel diverticula were seen in both VCE and DBE in only 1 patient but were seen at DBE in 10 additional patients (Figure 1).

Two masses were seen by both VCE and DBE. Polyps were found by both VCE and DBE in eleven patients, at VCE and not DBE in 9 patients, and were seen at DBE and not VCE in 7 patients. Ulcers were found in both VCE and DBE in 6 patients, at VCE but not DBE in 9 patients, and were seen at DBE and not VCE in 6 patients (Table 3).

The sensitivity and specificity of VCE using DBE as the criterion standard varied by lesion type (Figure 2). Overall, the sensitivity of VCE was 65% and the specificity was 66%. VCE was most sensitive and specific for masses (100%). It was moderately sensitive (58%) but highly specific (93%) for angioectasia. The sensitivity for

**Figure 1** Small bowel diverticula.

ulcers/erosions was 50% and the specificity was 88%. For polyps, the sensitivity and specificity was 61% and 87%. Importantly, VCE had very low sensitivity for detecting diverticulosis (9%) (Figure 2, Table 3).

The positive and NPV of VCE by lesion were; Angioectasia 82% and 81% respectively; Diverticula 100% and 89% respectively; Mass 100% positive and NPV; Polyps 55.0% and 90% respectively; Ulcers/erosions 40% and 92% respectively (Figure 3, Table 3).

DISCUSSION

In our study of patients undergoing sequential VCE and DBE, the overall diagnostic yield of these two procedures was equivalent. This is consistent with prior studies^[1,2]. However, when diagnostic yield was compared by lesion type, we found significant differences between VCE and DBE. DBE had a higher diagnostic yield for both diverticula and angioectasia.

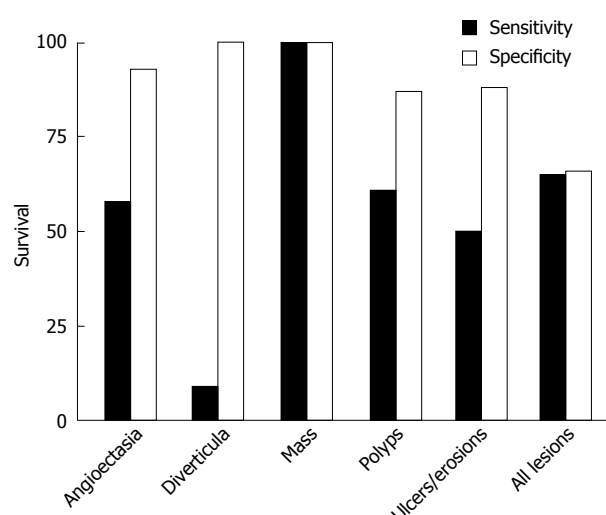
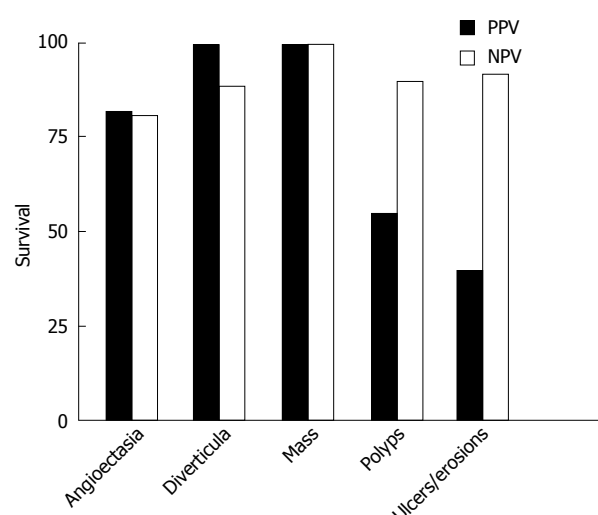
Duodenal diverticula are reported in 5% of upper abdominal radiographs and up to 25% in patients undergoing ERCP or at autopsy^[14]. Small bowel diverticula are less common but have been found in 0.5% to 5% of radiographs and autopsies^[15,16]. In our study, 11 patients (12%) who were referred for DBE were found to have diverticula. However, only 1 of 11 was detected on VCE. The failure of VCE to diagnose small bowel diverticula has been noted previously. In 2008, Hussain *et al*^[17] reported finding multiple diverticula in a patient undergoing DBE, which was not detected by VCE. In 2009, Fukumoto *et al*^[18] reported finding an ileal diverticulum on DBE that was missed by VCE. Marmo *et al*^[19] reported two missed jejunal diverticula that were later seen on subsequent DBE. Similarly, Arakawa *et al*^[20] reported 2 cases of diverticulosis of the small bowel that were missed at previous VCE. In this larger series, the sensitivity of VCE for detecting diverticula was only 9%, confirming that VCE cannot be relied upon to make this diagnosis.

The diagnostic yield for angioectasia at DBE was significantly higher than VCE (35% *vs* 25%). Differences in angioectasia detection by VCE and DBE have been reported. Some studies found a higher detection rate at VCE while others found a higher rate at DBE. Fukumoto

Table 3 Test characteristics of video capsule endoscopy using double balloon enteroscopy as the Criterion Standard

Lesions	VCE+/DBE+	VCE+/DBE+	VCE+/DBE+	VCE+/DBE+	Sensitivity of VCE	Specificity of VCE	PPV	NPV
Angioectasia	18	4	13	54	58%	93%	82%	81%
Diverticula	1	0	10	78	9%	100%	100%	89%
Mass	2	0	0	87	100%	100%	100%	100%
Polyps	11	9	7	62	61%	87%	55%	90%
Ulcers/erosions	6	9	6	68	50%	88%	40%	92%

VCE: Video capsule endoscopy; DBE: Double balloon enteroscopy; PPV: Positive predictive value; NPV: Negative predictive value.

**Figure 2** Sensitivity and specificity of video capsule endoscopy.**Figure 3** Positive and negative predictive value of capsule. PPV: Positive predictive value; NPV: Negative predictive value.

et al.^[18] described 2 patients that had angioectasia at VCE that were missed at subsequent DBE. Similarly, Arakawa reported 3 cases with missed angioectasia at DBE. Both studies attributed the missed lesions to incomplete DBE^[18,20]. Angioectasia detected at DBE but not at VCE has also been described. Arakawa and Marmo each reported 2 VCE-negative DBE-positive cases^[19,20]. None of these studies, however, assessed the test characteristics of VCE using DBE as the criterion standard. In our study, we found that VCE is highly specific but only moderately sensitive for detecting angioectasia (93% and 58% respectively). Since DBE detects a greater number of angioectasia, a negative capsule should not be viewed as conclusive. However, since not all red spots identified at DBE are true angioectasia, the clinical significance of the detection rate differences between VCE and DBE remains uncertain.

The diagnostic yield for polyp detection at VCE and DBE was statistically equivalent (22% and 20% respectively). However, using DBE as the criterion standard, the actual sensitivity of VCE was only 61% and the specificity was 87%. The low sensitivity implies that a significant number of lesions were missed at VCE. Alternatively some lesions thought to be polyps at VCE that were not confirmed at DBE may have been due to over interpretation of bulges and folds at VCE. The limitation of DBE however, was a lack of complete enteroscopy in all patients. Our approach of VCE directed deep enteroscopy

is consistent with standard practice^[3]. Nevertheless, these findings illustrate the limitation of relying on diagnostic yield as an overall measure of test accuracy. The same findings holds true for ulcers and erosions.

The limitations of our study include its retrospective design, interobserver variability in community based VCE interpretation^[21], reliance on capsule directed deep enteroscopy rather than attempting complete enteroscopy in all patients and the likelihood of false positive and false negative results at DBE. Correlation of VCE findings with pre-procedure preparation was not assessed since the effect of preparation on diagnostic yield remains controversial^[10-12]. Despite these limitations, we believe this data is significant and reflects the actual clinical practice of referring patients to specialized centers for deep enteroscopy based on the findings of community read VCE studies. Thus, the test characteristics described in this study may be unique to patients undergoing community based VCE followed by expert DBE and may not reflect the test characteristics of VCE in patients undergoing both studies at a tertiary care referral center. However, our study is reflective of real world practice and adds to our understanding of the benefits and limitations of these modalities.

In summary, our results suggest that comparing the diagnostic yield of VCE and DBE as a measure of test accuracy is misleading. By assessing the test characteris-

tics of VCE utilizing deep enteroscopy as the criterion standard, we have demonstrated that VCE is moderately sensitive and specific in the diagnosis of patients with small bowel disease. VCE cannot, however, be relied upon to rule out small bowel diverticula. Furthermore, based on our findings, the currently accepted algorithm for the evaluation of patients with obscure bleeding^[22] which currently recommends observation alone in patients with a negative VCE should be reconsidered.

COMMENTS

Background

Studies comparing video capsule endoscopy (VCE) and deep enteroscopy have shown equivalent diagnostic yields. Although both procedures yield similar numbers of abnormalities, the accuracy of VCE by lesion type utilizing double balloon enteroscopy (DBE) as the criterion standard has not been well defined.

Research frontiers

The aim of this study is to determine the test characteristics of community based VCE in patients undergoing subsequent DBE and define the accuracy of VCE by individual lesion type.

Innovations and breakthroughs

The results of this study show that the detection rates for DBE and VCE were equivalent overall (66% vs 64%). However, detection rates were not equivalent when comparing individual lesions. DBE had a significantly greater detection rate for AVM's (35% vs 25%, $P = 0.03$) and diverticulosis (12% vs 1%, $P = 0.002$). The sensitivity and specificity of VCE varies by lesion type.

Applications

VCE and DBE are complimentary procedures. In the community setting, VCE is typically performed initially in patients with obscure gastrointestinal bleeding and will help guide subsequent DBE. However, VCE has a low sensitivity for certain lesions, especially small bowel diverticula. Therefore, patients with negative VCE and obscure bleeding should undergo subsequent deep enteroscopy.

Terminology

Diagnostic yield refers to the number of positive findings in each exam.

Peer review

The manuscript is very valuable presenting a comparison of VCE with DBE in real life setting. Although the review is retrospective it offers a lot of new information mostly for the daily endoscopy practice.

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Endoscopic retrograde cholangiopancreatography under moderate sedation and factors predicting need for anesthesiologist directed sedation: A county hospital experience

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Abstract

AIM: To evaluate variables associated with failure of gastroenterologist directed moderate sedation (GDS) during endoscopic retrograde cholangiopancreatography (ERCP) and derive a predictive model for use of anesthesiologist directed sedation (ADS) in selected patients.

METHODS: With institutional review board approval, we retrospectively analyzed consecutive records of all patients who underwent ERCPs between July 1, 2009 to October 1, 2011 to identify patient related and procedure related factors which could predict failure of GDS. For patient related factors, we abstracted and analyzed

data regarding the age, gender, ethnicity, alcohol and illicit drug use habits. For procedure related factors, we abstracted data regarding initial or repeat procedures, indication for performing ERCP, the interventions performed during ERCP, and the grade of difficulty of cannulation as defined in the American Society for Gastrointestinal Endoscopy guidelines. Our outcome of interest was procedural success. If the procedure was not successful, the reasons for failure of procedures were recorded along with immediate post procedure complications. Multivariate analysis was then performed to define factors associated with failure of GDS and a model constructed to predict requirement of ADS.

RESULTS: Fourteen percent of patients undergoing GDS could not complete the procedure due to intolerance and 2% due to cardiovascular complications. Substance abuse, male gender, black race and alcohol use were significant predictors of failure of GDS on univariate analysis and substance abuse and higher grade of procedure remained significant on multivariate analysis. Using our predictive model where the presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3, only 12% patients with a score of 1 would require ADS due to failure of GDS, compared to 50% with a score of 3 or higher.

CONCLUSION: We conclude that ERCP under GDS is safe and effective for low grade procedures, and ADS should be judiciously reserved for procedures which have a higher risk of failure with moderate sedation.

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Key words: Cholangiopancreatography; Endoscopic retrograde/methods; Conscious sedation/utilization; Deep sedation/utilization; Adult; Endoscopy

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INTRODUCTION

Endoscopic procedures have routinely been performed under moderate sedation administered by the gastroenterologist in the United States^[1]. In recent years there has been an increasing trend towards using deep sedation or general anesthesia provided by a trained anesthesia professional. Given the high volume of endoscopic procedures and the high volume performed under anesthesia guidance, the spending on such procedures is estimated to increase into the billions of dollars over the next few years^[2]. Endoscopic retrograde cholangiopancreatography (ERCP) is considered an advanced endoscopic procedure which has evolved from a diagnostic procedure to a predominantly therapeutic one of increasing duration and complexity. No guidelines specifically recommend the use of deep sedation or general anesthesia for ERCPs though the American Society of Gastrointestinal Endoscopy (ASGE) suggests considering deep sedation for increasing length or complexity of procedure^[1]. Over the years, the spectrum of interventions performed during ERCPs have also increased tremendously, requiring various societies to grade the ERCP procedure into different grades of complexity (Grade 1-3 by ASGE)^[3]. The more challenging and higher grade of ERCPs are now performed at tertiary centers by dedicated advanced endoscopists, while lower grade interventions are routinely performed in various community hospitals and practices.

Increasingly, high volume centers are now routinely performing ERCPs with anesthesiologist directed sedation (ADS) while moderate to low volume centers usually perform ERCPs under gastroenterologist directed moderate sedation (GDS). Anesthesia support is usually sought if prior attempts with GDS have failed.

In this era of increasing health care costs and resource limitations, it is important to establish the role of ADS in ERCP.

The objective of our study was to evaluate variables associated with failure of moderate sedation administered by gastroenterologists (GDS) during ERCP and derive a predictive model for use of ADS in selected patients.

MATERIALS AND METHODS

The study was approved by the local institutional review board of our hospital. We retrospectively analyzed consecutive records of all patients who underwent ERCPs between July 1, 2009 to October 1, 2011 to identify patient related and procedure related factors which could

Table 1 Endoscopic retrograde cholangiopancreatography-degree of difficulty

Grade	Diagnostic	Therapeutic
Grade 1: standard	Deep cannulation, diagnostic sampling	Biliary sphincterotomy, stones < 10 mm, stents for leaks and low tumors.
Grade 2: advanced	Billroth II diagnostics, minor papilla cannulation	Stones > 10 mm, hilar tumor stent placement, benign biliary strictures
Grade 3: tertiary	Manometry, Whipple, Roux en Y, intraductal endoscopy	Billroth II therapeutics, intrahepatic stones, pancreatic therapies

The date was quoted by the reference of 3.

predict failure of GDS. The type of sedation use was documented as GDS which is administered with an opioid (meperidine or fentanyl) and a benzodiazepine (midazolam); or ADS which was administered as monitored anesthesia care with propofol or general anesthesia requiring intubation. If the ADS was administered after failure of GDS, it was abstracted as secondary ADS and if it was administered because the patient did not meet our institution's criteria for administration of GDS it was abstracted as elective or primary ADS. The exclusion criteria for administering GDS in our institution include patients who are American Society of Anesthesiologists (ASA) Grade 3 or more, history of anesthesia or sedation complication/difficulty, history of difficulty with tracheal intubation, compromised airway, morbid obesity, hemodynamic instability and pregnant patients. For patient related factors, we abstracted and analyzed data regarding the age, gender, ethnicity, alcohol and illicit drug use habits. For procedure related factors, we abstracted data regarding initial or repeat procedures, indication for performing ERCP, the interventions performed during ERCP, and the one word-graded difficulty of procedure as defined in the ASGE guidelines Table 1^[3].

Outcome measures

Our outcome of interest was procedural success. A procedure was deemed successful if deep cannulation had been obtained and the objective of the procedure accomplished. If the procedure was not successful, the reasons for failure of procedures were recorded along with immediate post procedure complications. In order to limit selection bias in patients who elected for primary ADS, we compared the cannulation rates of patients receiving primary ADS to the rest of the patients.

Statistical analysis

The results were expressed as mean plus or minus standard deviation and range. Univariate analysis was performed using logistic regression. To evaluate the association between related factors and intolerance to sedation, multivariable models were constructed that included terms to adjust for age, race, gender, alcohol and substance use and included in the final model if they

Table 2 Patient demographics

Demographic	<i>n</i> (%)
Gender	
Males	234 (48)
Females	252 (52)
Race	
Hispanic	189 (39)
Non hispanic black	179 (37)
White	91 (19)
Asian	20 (4)
Unspecified	7 (1.5)
Alcohol use	225 (46)
Other illicit substance use	79 (16)

significantly contributed to the outcome variable ($P < 0.05$). From these multivariable models, odds ratios were estimated using the logistic regression. All data was analyzed using STATA version 10.1 (College Station, TX).

RESULTS

Five hundred ninety-one ERCP procedures done in 392 patients were reviewed. One hundred and five of 591 procedures (18%) were performed electively with primary ADS and were excluded. Four hundred eighty-six procedures were included for our analysis. One hundred thirty-nine patients had more than 1 procedure during the study period. Patient demographics are presented in Table 2. Substance abuse was documented in 14% patients (24% of men, 4% of women). The mean dose of medications administered were 5.9 milligrams of midazolam, and 115 micrograms of fentanyl or 100 milligrams of meperidine. Most common indication for performing ERCP was choledocholithiasis (40%) followed by strictures (26%). The majority of procedures were Grade 1, with one fifth of the procedures Grade 2 or 3. The cannulation rates were similar in the patients with primary ADS (91%) to the rest of the patients (92%). Reasons for failure with GDS are presented in Table 3.

In our univariate analysis, substance abuse, male gender, black race and alcohol use were significant predictors of failure of GDS. However, after adjusting for substance abuse, these variables were no longer significant predictors. Hispanic race was a significant predictor for success of GDS after adjusting for substance abuse (Table 4) although most of the procedures were grade 1 procedures. ERCPs for strictures and pancreatic interventions were the most likely procedures to convert to ADS (Table 5). On multivariate analysis, substance abuse and higher grade of intervention remained the most significant predictors of need for monitored/general anesthesia (Table 6). A predictive model for requirement of monitored anesthesia for ERCP was derived. Presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3 as according to the grade of the procedure. Using this model, 12% of procedures with a score of 1, 25% with score of 2 and 50% with score of 3 or higher required monitored anesthesia.

Table 3 Causes of endoscopic retrograde cholangiopancreatography failure with gastroenterologist directed sedation *n* (%)

Cause	<i>n</i> (%)
Total number of patients undergoing GDS	486
Patient intolerance	68 (14)
Cardiopulmonary complications	10 (2)
Hypertension	6 (1.2)
Hypoxia, hypotension, bradycardia or tachycardia	4 (0.8)
Failure to cannulate	40 (8)
Food/contrast in lumen	8 (1.6)
Roux en Y anatomy	2 (0.4)
Esophageal bleeding on entry	1 (0.2)

GDS: Gastroenterologist directed sedation.

DISCUSSION

Based on our analysis, most patients at moderate volume ERCP centers do not require anesthesia service use for ERCPs. Our results indicate that less than 20% of patients failed moderate sedation provided as GDS. On multivariate analysis, the most important predictors of failure of gastroenterologist directed moderate sedation included substance abuse and the grade of the procedure. Using our predictive model where the presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3 as according to the grade of the procedure, less than one in eight procedures with a score of 1 would require monitored anesthesia compared to half of patients with a score of 3 or higher.

To our knowledge, this is the first study that has attempted to define factors predicting the failure of GDS for ERCPs. Our study population is unique in that most of our low risk patients undergo GDS for ERCPs. Since anesthesia resources are limited, only those patients who meet strict criteria for monitored anesthesia based on their ASA scores or other co-morbidities are scheduled for elective anesthesia service use.

Most of the previously published studies evaluating the use of anesthesia in ERCP conclude that ERCPs with gastroenterologist directed sedation have similar cannulation and complication rates to those with ADS^[4-6]. However none of these studies was designed to specifically study the factors predicting the failure of GDS.

In some studies, ADS has been associated with higher physician satisfaction and slightly higher completion rates^[7,8]. These studies have been uncontrolled or limited by lack of blinding. Furthermore, routine anesthesia service use for ERCP has other limitations. Aside from increasing the cost of the procedure, it may also increase the peri-procedure time. Additionally, it may make the procedure more difficult to schedule if anesthesia support outside the operating rooms is not readily available.

Our study may have several limitations. First, as a retrospective study, we cannot be certain that our results are confirmed from chance alone (verification bias). Care was taken to a priori assess only the variable thought to be directly related to success of GDS. Further prospective studies are needed to determine if these two variables

Table 4 Patient variables predicting failure with gastroenterologist directed sedation for endoscopic retrograde cholangiopancreatographies

Patient variables	MS	MS failure	P value	Patient variables ¹	MS	MS failure	P value
Substance abuse	31	13	0.003				
Male	131	25	0.01	Male ¹	104	14	0.09
Female	157	12		Female ¹	153	10	
Race				Race ¹			
AA	79	22	0.001	AA	61	10	0.06
White	42	6	0.8	White	38	6	0.2
Hispanic	142	8	0.001	Hispanic	134	7	0.04
Asian	15	1	0.5	Asian	15	1	0.7
> 65 yr	37	2	0.15	> 65 yr ¹	33	1	0.16
≤ 65 yr	251	35		≤ 65 yr ¹	224	23	
Alcohol use	113	21	0.04	Alcohol use ¹	87	11	0.24
No alcohol use	175	16		No alcohol use ¹	170	13	
Bilirubin-elevated	252	44	0.03	Bilirubin-elevated ¹	222	34	0.45
Bilirubin-normal	146	43		Bilirubin-normal ¹	126	24	

¹Adjusted for substance abuse. MS: Moderate sedation.**Table 5 Odds ratios for failure with gastroenterologist directed sedation by indication of the procedure**

Indication	n (%)	OR (95%CI)	Adjusted OR (95%CI) ¹
Gallstones/cholangitis	231 (38)	0.6 (0.4, 1.0)	0.7 (0.4, 1.3)
All strictures	125 (20)	1.5 (0.9, 2.4)	1.6 (0.9, 2.9)
Benign strictures	53 (9)	2.2 (1.2, 4.2)	2.7 (1.2, 5.7)
Suspected malignancy	72 (12)	0.9 (0.5, 1.8)	0.9 (0.4, 2.0)
Abn LFTs	36 (6)	0.6 (0.2, 1.6)	0.5 (0.12, 2.3)
Pancreatic	11 (2)	2.7 (0.8, 9.4)	3.7 (0.9, 16)
Other	7 (1)	1.8 (0.4, 9.7)	2.5 (0.5, 12.9)
Post cholecystectomy stone/leak	24 (4)	0.4 (0.1, 1.7)	0.3 (0.0, 2.0)
Exchange/incomplete	51 (8)	2.1 (1.1, 4.0)	0.9 (0.3, 2.5)
	485		

¹Adjusted to substance abuse. OR: Odds ratio.

(substance use and procedure grade) can determine the likelihood of GDS success. Second, while the procedures were deemed successful, we did not identify delayed complications which may have occurred after the patient left the endoscopy unit. Third, our ERCPs are initially attempted by gastroenterology trainees and only later taken over by the supervising physician. This may increase the procedure time and lead to patient intolerance especially in patients under gastroenterologist directed moderate sedation. High dose of benzodiazepines and opioids may convert moderate sedation to deep sedation, which has been demonstrated in previous studies that advocated the use of capnography during sedation^[9]. While we did not use capnography to gauge the respiratory depression, our mean doses of sedating agents used was 6 mg of midazolam and 115 mg of fentanyl suggesting a reasonably conservative approach with medication administration.

Recent data suggests an increased utilization of anesthesia services for low risk endoscopic significantly increases the cost of the procedures and may potentially affect the cost effectiveness of procedures like screening colonoscopies^[2].

Although, no cost benefit analysis have been done for

Table 6 Multivariate analysis of predictors of failure with gastroenterologist directed sedation

Variable	β coefficient	P value	OR (95%CI)
Grade of procedure (1-3) ¹	0.75	0.002	2.1 (1.3, 3.4)
Substance abuse ¹	1.03	0.001	2.8 (1.5, 5)
Indication			
Strictures	0.13	0.687	1.1 (0.6, 2.1)
Gallstone	-0.18	0.563	0.8 (0.5, 1.5)
Alcohol use	0.33	0.267	1.4 (0.8, 2.5)
Female gender	-0.29	0.33	0.7 (0.4, 1.3)

¹Significant variables in the multivariate model.

use of anesthetist administered sedation or anesthesia for ERCPs, our study suggests that most of the ERCPs can be safely performed and completed under gastroenterologist directed sedation.

We conclude that ERCP under GDS is safe and effective for low grade procedures, and anesthesia service use should be judiciously reserved for procedures which have a higher risk of failure with moderate sedation.

COMMENTS

Background

In recent years there has been an increasing trend towards utilizing anesthesiologist directed sedation (ADS) in patients undergoing endoscopic procedures. Factors predicting failure of gastroenterologist directed moderate sedation (GDS) during endoscopic retrograde cholangiopancreatography (ERCP) have not been well studied.

Research frontiers

Evaluate variables associated with failure of GDS during ERCP and derive a predictive model for use of ADS in selected patients.

Innovations and breakthroughs

Gastroenterologist directed sedation is safe and effective for low grade ERCP procedures. Higher grade ERCPs and/or those performed in patients with substance abuse have a higher risk of failure with moderate sedation and therefore anesthesiologist directed deep sedation should be considered for these procedures. A predictive model for requirement of monitored anesthesia for ERCP was derived. Presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3 as according to the grade of the pro-

cedure. Using this model, 12% of procedures with a score of 1, 25% with score of 2 and 50% with score of 3 or higher required monitored anesthesia.

Applications

Based on the analysis, most patients at moderate volume ERCP centers do not require anesthesia service use for ERCPs. The results indicate that less than 20% of patients failed moderate sedation provided as GDS. On multivariate analysis, the most important predictors of failure of gastroenterologist directed moderate sedation included substance abuse and the grade of the procedure. Using the predictive model where the presence of substance abuse was given 1 point and planned grade of intervention was scored from 1-3 as according to the grade of the procedure, less than one in eight procedures with a score of 1 would require monitored anesthesia compared to half of patients with a score of 3 or higher.

Terminology

The type of sedation use was documented as GDS which is administered with an opioid (meperidine or fentanyl) and a benzodiazepine (midazolam); or ADS which may be administered as general anesthesia or intravenous anesthesia administered with propofol.

Peer review

With this study, the authors conclude that that ERCP under GDS is safe and effective for low grade procedures, and anesthesia service use should be judiciously reserved for procedures which have a higher risk of failure with moderate sedation.

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Polyethylene glycol 3350 based colon cleaning protocol: 2 d vs 4 d head to head comparison

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Abstract

AIM: To compare between 2 and 4 d colon cleansing protocols.

METHODS: Children who were scheduled for colonoscopy procedure (2010-2012) for various medical reasons, were recruited from the pediatric gastroenterology clinic at Marshall University School of Medicine, Huntington, WV. Exclusion criteria were patients who were allergic to the medication used in the protocols [polyethylene glycol (PEG) 3350, Bisacodyl], or children with metabolic or renal diseases. Two PEG 3350 protocols for 4 d (A) and 2 d (B) were prescribed as previously described. A questionnaire describing the volume of PEG consumed, clinical data, and side effects were recorded. Colon preparation was graded by two observers according to previously described method. Main outcome measurements: Rate of adequate colon preparation.

RESULTS: A total of 78 patients were considered for final calculation (group A: 40, group B: 38). Age and stool consistency at the last day was comparable in both groups, but the number of stools/day was significantly higher in group B ($P = 0.001$). Adequate colon

preparation was reached in 57.5% (A) and 73.6% (B), respectively ($P = 0.206$). Side effects were minimal and comparable in both groups. There was no difference in children's age, stool characteristics, or side effects between the children with adequate or inadequate colon preparation. Correlation and agreement between observers was excellent (Pearson correlation = 0.972, kappa = 1.0).

CONCLUSION: No difference between protocols was observed, but the 2 d protocol was superior for its shorter time. Direct comparison between different colon cleansing protocols is crucial in order to establish the "gold standard" protocol for children.

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Key words: Colonoscopy; Polyethylene glycol 3350; Cleansing protocol; Children

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INTRODUCTION

Colon cleansing protocols have been one of the limiting factors in preparing children for diagnostic colonoscopy procedures needed for various medical reasons. Due to bad palatability and the quantity needed, the commonly used liquids in adult patients are not accepted by children and compliance is unacceptable^[1-3]. In the last decade, polyethylene glycol (PEG) 3350 has been introduced to children and was found to be palatable and acceptable by children for the treatment of various medical conditions, mainly constipation. Several studies have shown that children will accept this PEG based solution and the compli-

ance rate was very good even for long term therapy^[4-7]. In the past, we showed that PEG 3350 is an excellent solution for colon cleansing protocol in children reaching adequate colon preparation in up to 92% of the children examined^[8]. Moreover, we reported that following the number of defecation and stool consistency in the last days of preparation may be used as indicators for the colon condition, and would reduce the number of failed procedures due to an unprepared colon. In recent years a similar PEG 3350 based protocol was reported that suggested similar results with a shorter preparation^[9]. In that protocol, a higher dose of PEG 3350 with daily dose of 5 mg Bisacodyl resulted in an excellent colon condition for colonoscopy reaching up to 92%^[9].

An unprepared colon in adults is considered one of the limiting factors for achieving an adequate rate of polyp detection during colonoscopy procedures^[10,11]. In children, the rate of the unprepared colon during colonoscopy is high and was reported between 5%-30%^[12-15]. The different colon cleansing protocols used by different centers was never standardized and the "optimal" protocol has never been established. We believe that a head to head comparison between protocols in children is needed in order to standardize clinical practice and to find the best available protocol. Such protocol would limit the rate of the unprepared colon and established the gold standard protocol for colonoscopy procedures in children.

In the present study, in a head to head analysis, we prospectively compare two different PEG 3350 based protocols in order to establish the better cleansing protocol in children.

MATERIALS AND METHODS

Children who were scheduled for colonoscopy procedure (2010-2012) for various medical reasons, were recruited from the pediatric gastroenterology clinic at Marshall University School of Medicine, Huntington, WV. Exclusion criteria were patients who were allergic to the medication used in the protocols (PEG 3350, Bisacodyl), or children with metabolic or renal diseases. One of the two different colon protocols was prescribed to the participating patients. A computer generated random list assigned the children to each protocol. The parents/caregivers (or child when appropriate) were asked to complete a clinical questionnaire during the colon preparation as previously described^[8]. Briefly, the questionnaire included the amount of PEG 3350 consumed per day, number of stools per day, consistency of stool (scale: 1-5), and various side effects (abdominal pain, vomiting). Informed consent was obtained from all participants and the study was approved by the IRB Committee at Marshall University School of Medicine, Huntington, WV.

Colon cleansing protocols

Two PEG 3350 protocols for 4 and 2 d were prescribed as previously described^[8,9]. The 4 dy protocol (protocol A) included PEG 3350 at 1.5 g/kg per day (up to a limit

of 100 g/d) for 4 d. Patients were allowed to eat regular food until the day before procedure and clears only at the last day of protocol. The 2 d protocol (protocol B) included PEG 3350 at 2 g/kg per day (up to a limit of 136 g/d) plus 5 mg/d Bisacodyl for 2 d. Patients were allowed to eat regular food on day 1 and clears on day 2. No adjunct medication or enema was allowed in any of the protocols. The parents/caregivers were required to complete a simple questionnaire as previously described^[8]. The questionnaires were returned to the physicians on the day of procedure and reviewed with the parents to ensure compliance and accuracy. Patients who did not follow the protocol for various reasons including: inadequate PEG 3350 dose, missed clinical data on the questionnaire, or other protocol violations, were excluded from the final calculation.

Colon preparation assessment

Colonoscopy procedure was performed under propofol sedation given by certified anesthesiologists. The colon was assessed according to previous methodology as previously described^[8]. Briefly, the colon preparation was graded according to 5 different levels (Grade 1 to 5) as follows: G1: unacceptable (large amount of solid stool covering the mucosa); G2: poor preparation (enough stool that much of intra-procedural cleaning was required); G3: fair preparation (some liquid stool, easily removed); G4: good preparation (successful visualization of the colon mucosa); G5: Excellent preparation (Crystal clear colonic mucosa). For the current study, colon preparation at grade ≥ 4 was considered as adequate colon preparation. The investigators were allowed to incorporate 0.5 grade per their discretion. Grading of colon preparation was performed within 5-10 min of procedure completion. To reduce bias, the grading was performed simultaneously and separately by the endoscopist (Elitsur Y), and the assisting endoscopy nurse who participate in the procedure (Butcher L). The grading was documented on a separate page where both persons were blinded to the documentation of the other. Once documentation was done, both grades became final and no change of grading was allowed. A correlation between physician's grade and the nurse's grade was calculated.

Statistical analysis

Comparison between the two protocols was performed using two-tailed χ^2 analysis, and nonparametric analysis (Wilcoxon Signed Rank Test) using the IBM-SPSS statistics 19 program. Correlation analysis was performed using Pearson correlation. Significant analysis was set at P value < 0.05 .

RESULTS

A total of 93 children enrolled (period 2010-2012), of whom 48 were assigned to protocol A and 45 to protocol B. A total of 15 patients were not included in the study due to a protocol violation, 8 in protocol A and 7 in pro-

Table 1 Clinical data

Protocol	4 d	2 d	P value ¹
No patients	40	38	
Age (yr, mean \pm SD)	10.10 \pm 4.6	9.91 \pm 4.7	0.792
Male/female ration	1.0:1.0	0.8:1.0	0.811 ⁴
No stools/d (mean \pm SD) ²	5.15 \pm 2.6	7.88 \pm 4.1	0.001
Consistency (mean \pm SD) ²	5.65 \pm 0.8	5.49 \pm 0.9	0.904
Colon grade (mean \pm SD)	3.50 \pm 1.1	4.01 \pm 1.0	0.140
Colon grade (\geq 4) ³	23 (57.5%)	28 (73.6%)	0.206 ⁴

¹P value: wilcoxon signed rank test; ²At the last day of protocol; ³Grade \geq 4 considered adequate preparation; ⁴P value: χ^2 analysis.

tolocol B. The major clinical diagnoses were gastrointestinal bleeding of unknown origin, and follow up colonoscopy in inflammatory bowel disease patients. Overall, a total of 78 patients were considered for final calculation, 40 in protocol A and 38 in protocol B. In both protocols, the number of stools per day increased from the first day to the last day of protocol (data not shown). The age, male/female ratio, and stool consistency at the last day in either protocol was comparable for both groups, but the number of stools per day was significantly higher in group B compared to group A (Table 1). Adequate colon preparation (defined as grade \geq 4) was reach in 57.5% and 73.6% of children from protocol A and protocol B, respectively ($P = 0.206$, Table 1). Side effects were minimal and comparable in both groups (abdominal pain: 26%-32%, vomiting: 2%). None of the children discontinued his protocol due to side effects. The cecum was successfully reached in 76 (98%) children, and when attempted, the terminal ileum was visualized in 68 (87%) children (32 children in protocol A and 36 children in protocol B). There was no difference in children's age, stool frequency, stool consistency, or side effect between the children who had adequate colon preparation (grade > 4.0) and those with inadequate colons (grade < 4.0) (data not shown). The correlation and agreement between colonoscopy grading between physician and the endoscopy nurse for both groups was excellent ($P = 0.972$, kappa = 1.0).

DISCUSSION

Preparing the colon for colonoscopy procedure for children has been a difficult task for many years, and various colon cleansing protocols have been suggested and used. In fact, there is no one pediatric protocol that has been accepted as the "gold standard" and different medical centers are using different protocols. In some centers, the adult protocol is used for teenage children and young adults. After we confirmed the excellent results with a 4 d PEG 3350 protocol, it became the preferred colon cleansing protocol in our clinic^[8]. In 2011, Phatak *et al*^[9] presented a similar PEG 3350 based colon preparation protocol that was shorter. In the present study, we present for the first time a true head to head comparison between 2 different colon cleansing protocols in order to

establish the better protocol for children. Results showed that both protocols were comparable with regard to the rate of adequate colon preparation, stool characteristics, side effects, or patients' compliance. The number of stools per day at the last day of the shorter protocol (protocol B) was significantly higher compared to protocol A ($P = 0.001$), but no difference in the colon grading was noted between the groups. In fact, the adequate colon preparation, as defined in our study (grade ≥ 4), was higher in protocol B but did not reach a statistical significance (57.5% *vs* 73.6%, $P = 0.206$). We believe that the addition of a stimulant laxative (Bisacodyl), and the higher dose of PEG 3350 prescribed in protocol B (1.5 g/kg *vs* 2.0 g/kg) were the reasons for those results. We suggest that the 2 d protocol is at least as good as the 4 d protocols while having the advantage of being a shorter protocol.

We acknowledge the few differences existed in our study. (1) When compared with previous reports, our study showed a lower rate of adequate colons in both groups (57.5% and 73.6% for protocols A and B, respectively). In the present study we followed a stricter definition for adequate colon preparation (grade ≥ 4.0) that may reduce the rate of success in our population. When the definition of adequate preparation dropped to grade ≥ 3.5 , our success rate increased to 63% and 79%, respectively ($P = 0.17$). Similarly, when a higher degree of preparation (excellent preparation) was considered in Phatak's study^[9], a comparable rate of adequate colon was achieved between both studies; (2) Compared with previous study^[9], a second observer (gastrointestinal nurse), blinded to the grading of the first observer, was utilized to grade the colons. The agreement between both observers was excellent (Spearman correlation = 0.972, kappa = 1.0); and (3) The number of participants in our study was lower than in previous studies, a fact that could explained the lack of statistical significance noted between the protocols^[8,9]. We suggest that those methodological differences may explain the lower rate of adequate colon preparation reported in our study.

In conclusion, we prospectively compared two PEG 3350 based cleansing protocol for children who were scheduled for diagnostic colonoscopy. Our results showed that both protocol were acceptable to children, but the 2 d protocol is superior to the 4 d protocol at least for its shorter course. Further comparison between different cleansing protocols in children is needed in order to establish the best protocol for colonoscopy procedure in children.

COMMENTS

Background

Colon cleansing protocols have been the major obstacle in successful colonoscopy in children. Of the polyethylene glycol (PEG) 3350 protocols published, none has been recommended as the best protocol.

Research frontiers

In the last decade, PEG 3350 has been introduced to children and was found to be palatable and acceptable by children for the treatment of various medical

conditions, mainly constipation. Several studies have shown that children will accept this PEG based solution and the compliance rate was very good even for long term therapy.

Innovations and breakthroughs

In recent years a similar PEG 3350 based protocol was reported that suggested similar results with a shorter preparation. In that protocol, a higher dose of PEG 3350 with daily dose of 5 mg Bisacodyl resulted in an excellent colon condition for colonoscopy reaching up to 92%.

Applications

In the present study, in a head to head analysis, the authors prospectively compare two different PEG 3350 based protocols in order to establish the better cleansing protocol in children.

Peer review

The number of stools per day at the last day in each protocol, and the mean colon grading was significantly higher in the shorter protocol (protocol B). This is a randomized controlled trial and an interesting and important paper for colonoscopy procedures in children.

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Malpractice claims for endoscopy

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Abstract

AIM: To summarize the magnitude and time trends of endoscopy-related claims and to compare total malpractice indemnity according to specialty and procedure.

METHODS: We obtained data from a comprehensive database of closed claims from a trade association of professional liability insurance carriers, representing over 60% of practicing United States physicians. Total payments by procedure and year were calculated, and were adjusted for inflation (using the Consumer Price Index) to 2008 dollars. Time series analysis was performed to assess changes in the total value of claims for each type of procedure over time.

RESULTS: There were 1901 endoscopy-related closed claims against all providers from 1985 to 2008. The specialties include: internal medicine ($n = 766$), gastroenterology ($n = 562$), general surgery ($n = 231$), general and family practice ($n = 101$), colorectal surgery ($n = 87$), other specialties ($n = 132$), and unknown ($n = 22$). Colonoscopy represented the highest frequen-

cies of closed claims ($n = 788$) and the highest total indemnities (\$54 093 000). In terms of mean claims payment, endoscopic retrograde cholangiopancreatography (ERCP) ranked the highest (\$374 794) per claim. Internists had the highest number of total claims ($n = 766$) and total claim payment (\$70 730 101). Only total claim payments for colonoscopy and ERCP seem to have increased over time. Indeed, there was an average increase of 15.5% per year for colonoscopy and 21.9% per year for ERCP after adjusting for inflation.

CONCLUSION: There appear to be differences in malpractice coverage costs among specialties and the type of endoscopic procedure. There is also evidence for secular trend in total claim payments, with colonoscopy and ERCP costs rising yearly even after adjusting for inflation.

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Key words: Complications; Endoscopy; Colonoscopy; Endoscopic retrograde cholangiopancreatogram; Medical malpractice

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INTRODUCTION

Endoscopies are being performed at an increasing rate for the last decade^[1]. Endoscopic procedures are also becoming more complicated as interventional techniques are used more widely. Despite increasing national awareness of medical errors, and the high costs of associated malpractice, there is a lack of data sources from which to understand the incidence and trends of errors resulting in major injuries during endoscopic procedures.

Traditionally, the main source of information on endoscopy-related errors comes from institutional morbidity and mortality conferences. However, this and other

self-reporting methods are known to underestimate the true incidence of complications^[2]. In general and vascular surgery, the National Surgical Quality Improvement Program has become a platform for validated, risk-adjusted outcome comparisons between institutions, however, only a select minority of hospitals have implemented the program, and similar registries have not been as widely accepted in other interventional subspecialties.

Aligned with value-based purchasing by the Centers for Medicare and Medicaid Services, the American College of Gastroenterology and the American Society of Gastrointestinal Endoscopy have advocated for measuring endoscopy quality indicators. As preventing errors is linked to quality, endoscopists increasingly are recognizing the importance of understanding and benchmarking endoscopic errors at a national level.

Claims in malpractice litigation offer an opportunity to study major iatrogenic injuries. In a study by Studdert *et al*^[3], trained reviewers examined 1500 closed claims of alleged medical injuries from negligence and found that 97% of closed claims involved injury, of which 63% resulted from error. In another study of surgical claims^[4], technical errors accounted for about half of the cases. A study by Conklin *et al*^[5] focusing on gastroenterologists showed that 25% of claims were due to improper performance of an endoscopic procedure, but further information such as type of endoscopies were not described. In addition, endoscopies in the United States are also performed by non-gastroenterologists, and there have been no studies to our knowledge that have looked into malpractice information in this population.

Our aim is to provide a synopsis of the magnitude and time trends of endoscopy-related claims and to compare total malpractice indemnity according to specialty and procedure.

MATERIALS AND METHODS

We obtained summary-level data from a comprehensive database of closed claims against physicians who are members of the Physicians Insurers Association of America (PIAA), which is a trade association of professional liability companies owned by physicians, hospitals, and other health care providers. PIAA, which has the largest database of malpractice claims in the nation, insures over 300 000 doctors and 1300 hospitals, representing over 60% of United States doctors and underwrites 46% or \$5.2 billion of the total medical liability industry premium. The closed claims represented data from all 50 states from January 1985 up to December 2008.

Due to confidentiality agreements with member companies, the PIAA is unable to provide specific geographic information. The de-identified data is therefore not traceable to the provider. PIAA collects data based on information provided by the member liability insurance company which covered the physician. The professional coder from the liability insurance company codes the condition, care rendered, and outcome by complying with PIAA guidelines. Inclusion criteria were all endoscopic

procedures (esophagogastroduodenoscopy, EGD; colonoscopy, flexible sigmoidoscopy; rigid proctosigmoidoscopy; endoscopic retrograde cholangiopancreatography, ERCP; and percutaneous endoscopic gastrostomy, PEG) that resulted in closed claims during the study period. There was no identifiable code available for endoscopic ultrasound at the time of the study.

Etiologies of claims were categorized by PIAA coders according to a priori definition of errors. Improper performance is defined as an endoscopic procedure that was done incorrectly. An example is an ERCP with improperly placed stent that led to a fatal complication. Diagnosis error is resulted from failure to diagnose or providing an incorrect diagnosis. Data on total and average payment to plaintiffs for claims were provided according to specialty but not to type of procedure.

A claim is a written demand for compensation for medical injury within the statute of limitations of a jurisdiction. A claim can be closed in one of four possible ways: (1) at the end of a trial by final judgment; (2) at any point before the end of the trial when the case is settled with a payment; (3) when the case is voluntarily dropped by the plaintiff; or (4) if the defendant successfully files a motion to dismiss the case when there is a valid legal basis to do so. Thus, a claim may be closed with or without indemnity payment, which is defined as the sum of money paid in compensation for injury.

Statistical analysis

Total payments by procedure and year were calculated, and were adjusted for inflation (using the consumer price index) to 2008 dollars. We then focused on time series analysis to see how the total value of claims for each type of procedure changed over time. Two models were used: a linear least-squares regression model, which will show the average absolute growth in total claims (in adjusted dollars) per year; and an exponential least-squares regression model, which will derive the average percent growth. The ability of these models to describe the data is captured in the value of R^2 . A value of zero means that the model has no explanatory power, while a value of one indicates that the total claim value can be perfectly deduced from the year.

RESULTS

There were 1901 endoscopy-related closed claims against all providers from 1985 to 2008. The specialties include: internal medicine ($n = 766$), gastroenterology ($n = 562$), general surgery ($n = 231$), general and family practice ($n = 101$), colorectal surgery ($n = 87$), other specialties ($n = 132$), and unknown ($n = 22$). Over 98% resulted in physical injury, which was generally severe (25.8% resulted in deaths and 40.7% resulted in significant or major disability). Close to 70% of all cases were dropped by the plaintiff or dismissed by the court before the trial was concluded. An additional 5% of cases were won by the defendant at trial.

Closed claims against gastroenterologists from 1985

Table 1 Endoscopy claims against gastroenterologists (1985 to 2006) *n* (%)

Etiology of claims	Frequency (<i>n</i> = 341)
Improper performance	175 (51.3)
Diagnosis error (failure, incorrect)	59 (17.3)
Meritless (no clear evidence)	35 (10.3)
Failure to supervise or monitor	17 (4.9)
Not indicated/contraindicated	14 (4.1)
Failure to recognize complication	12 (3.5)
Failure to communicate with patient	6 (1.8)
Delay in performance	4 (1.2)
Others	19 (5.6)

to 2006 that involve endoscopies are shown in Table 1. The majority resulted from improper performance of an endoscopic procedure, followed by diagnosis error. Right and left-sided colon cancers were almost equally represented. Closed claims involving colon cancer according to location were as follows: cecum (*n* = 3), hepatic flexure (*n* = 2), transverse colon (*n* = 2), rectosigmoid junction (*n* = 6), rectum (*n* = 3), and unspecified location (*n* = 5).

Colonoscopy, followed by sigmoidoscopy (flexible and rigid) represented the highest frequencies of closed claims and the highest total indemnities (Table 2). In terms of average cost per claim, ERCP ranked the highest.

Table 2 shows the average and total indemnity comparing the various specialties that perform endoscopies. Internists had the highest number of total claims and total claim payment. Figure 1 shows the total claim payments over time according to procedure. For procedures such as EGD which sometimes have only one or two closed claims per year, one very large payment can skew these averages. Colonoscopy and ERCP have had many more paid claims, and for these procedures there is a clear increase in average claim payment. Indeed, there appears to have been an average increase of 15.5% per year for colonoscopy and 21.9% per year for ERCP after adjusting for inflation.

In the time period covered, closed claims for PEG procedures were recorded during only six of the years studied, thus there was insufficient data for analysis. For the other procedures, an exponential model fit the data better than a linear model in three of the four cases. Table 3 shows both the absolute and percentage increase (in real dollars) of the average value of claims. Of note, the total sigmoidoscopy claims have been declining on average since 1985. The data from which these regression figures were calculated is shown in Figure 1.

DISCUSSION

Our study shows that from the standpoint of insurers, internists who perform endoscopies had the highest total claim payment, costing over twice than gastroenterologists in terms of compensation for negligence. The largest total indemnities resulted from colonoscopies and sigmoidoscopies, but only colonoscopy and ERCP have

Table 2 Endoscopy claims by specialty against all providers according to procedure, ranked according to total claims payment to plaintiffs (1985-2008) (*n* = 1901)

Procedure	Closed claims	Total paid claims	Total claim payments (\$)	Mean claim payments (\$)
Colonoscopy	788	216	54 093 000	250 430.56
Flexible sigmoidoscopy	513	182	28 674 000	157 549.45
ERCP	217	67	25 207 000	376 223.88
Rigid proctoscopy	125	51	15 726 000	308 352.94
EGD	209	47	9 666 000	205 659.57
PEG	49	7	2 598 000	371 142.86
Internal medicine	766	-	70 730 101	261 963
Gastroenterology	562	-	30 841 008	250 740
General surgery	231	-	13 305 060	187 395
General/family practice	101	-	7 288 674	186 889
Colorectal surgery	87	-	6 593 000	286 652
Other specialties	154	-	7 206 157	163 776

ERCP: Endoscopic retrograde cholangiopancreatography; EGD: Esophago gastroduodenoscopy; PEG: Percutaneous endoscopic gastrostomy.

been increasing over time. This could reflect the increasing number of colonoscopies performed per year and the increasing number of endoscopists who perform ERCPs.

The annual cost of the United States medical liability system is estimated to be \$55.6 billion^[6]. According to the United States Government Accountability Office, the primary driver in medical liability insurance industry economics is the rising average cost of indemnity, which leads to rising premiums that has affected gastroenterologists and non-gastroenterologists alike. Although the specialty of gastroenterology has always been viewed as low-risk for medical malpractice lawsuit, a recent seminal study^[7] has shown that gastroenterology ranks six out of 25, before obstetrics and gynecology, in terms of proportion of physicians facing malpractice claims.

Our data have several limitations. PIAA produces summary data making us unable to cross-reference variables and to assess inter-relationships between any predictors. There is no information on individuals who do not sue. However, these claims represent the most significant injuries that merit attention. Also, no chart validation studies were performed to confirm robustness of findings. The denominator, or the total number of physicians per specialty who perform endoscopies is unknown, so our data reflect frequencies and not proportions. Internists had higher cost per claim, but we do not know if there is higher cost per insured internist because the denominator is not available. It is possible that gastroenterologists were misclassified as internists, but sued doctors self-classified themselves, of which the PIAA coders used in data collecting. Thus, we believe a gastroenterologist would have no incentive to classify him or herself as an internist.

There are also several factors other than legal merit that determines whether claims are paid in litigation, such as severity of injury. Thus, we realize that the legal definition of negligence (or failure to use reasonable care) is not necessarily synonymous with genuine error in all instances. Typically, there is a hierarchy as to what people

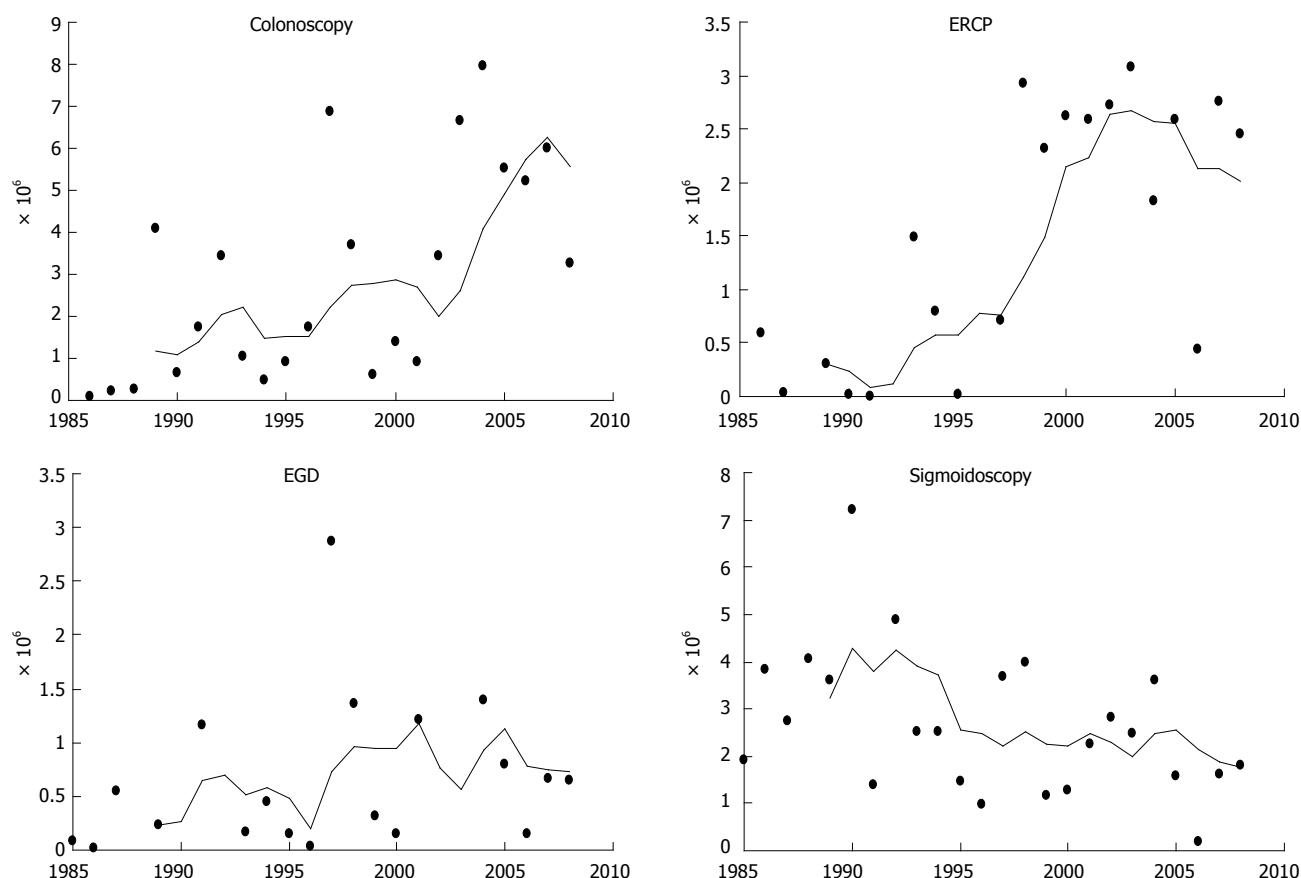


Figure 1 Total claim payments by procedure type, adjusted to 2008 dollars, together with 5-year moving averages (y-axis, total claim payments in dollars; X-axis, years), showing an increasing temporal trend for colonoscopy and endoscopic retrograde cholangiopancreatography. EGD: Esophagogastroduodenoscopy; ERCP: Endoscopic retrograde cholangiopancreatography.

Table 3 Absolute percentage increase of average closed claims

	Linear increase/ yr (\$)	Model R^2	Expon increase/ yr, %	Model R^2
Colonoscopy	229 000	0.3976	12.59	0.4874
ERCP	122 000	0.5098	19.06	0.4076
EGD	23 000	0.0567	7.53	0.1697
Sigmoidoscopy	-93 000	0.1873	-4.6	0.1938

ERCP: Endoscopic retrograde cholangiopancreatography; EGD: Esophago gastroduodenoscopy.

consider preventable injury—there are those caused by error, of which some involved negligence, but usually all negligence involves error.

However despite our limited data resource, our study provides useful, unprecedented information on litigations related to endoscopy. All closed claims are likely captured by the collaborative PIAA database. Because of the economics of litigation, these cases typically represent those involving serious injuries.

In summary, closed malpractice claims data yielded important information on alleged injuries resulting from endoscopy. We found discrepancies in malpractice costs among specialties and the type of procedure. There is also evidence for secular trend in total claim payments,

with colonoscopy and ERCP costs rising yearly after adjusting for inflation.

Malpractice insurers might use this information to scale their premiums according to both specialty and type of endoscopy performed, allowing a risk differential payment structure. They may also incentivize simulation training, credentialing, or other regulatory strategies, and to sponsor safety improvement efforts to reduce their exposure. Gastroenterologists are to be held accountable for managing risks of errors^[8] in endoscopy by adhering to standards of practice, especially when performing ERCP^[9,10] (adequate training and yearly volume) or colonoscopy^[11] (minimize colon cancer miss rates and ensure proper documentation). The limitations of our retrospective data highlight the need for a comprehensive, perhaps even a prospective, nationwide database at an individual level to capture the incidence rates of major adverse events and errors, and to design interventions that can reduce iatrogenic injuries resulting from substandard endoscopy.

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COMMENTS

Background

Little is known about major endoscopy-related errors categorized by procedure and specialty, and time trends.

Research frontiers

In general and vascular surgery, the National Surgical Quality Improvement Program has become a platform for validated, risk-adjusted outcome comparisons between institutions, however only a select minority of hospitals have implemented the program, and it has not been highly developed for other fields that involve procedures.

Innovations and breakthroughs

Authors obtained summary-level data from a comprehensive database of closed claims against physicians who are members of the Physicians Insurers Association of America (PIAA), which is a trade association of professional liability companies owned by physicians, hospitals, and other health care providers.

Applications

Their study provides useful, unprecedented information on litigations related to endoscopy. All closed claims are likely captured by the collaborative PIAA database. Because of the economics of litigation, these cases typically represent those involving serious injuries.

Peer review

In this study the investigators compare and contrast major endoscopy-related errors for which insurance claims were filed, categorized by procedure and specialty, and time trends. They also compared total malpractice indemnity by specialty and procedure. The data was acquired from a database of closed claims from a trade association of professional liability insurance carriers, and covers approximately 60% of United States physicians in all 50 states. A total of 1901 endoscopy-related closed claims were found against all providers from 1985 to 2008. Colonoscopy and endoscopic retrograde cholangiopancreatography (ERCP) had highest dollar value per claim. Internists had the highest number of total claims and total claim payment. Corrected for inflation, only total claim payments for colonoscopy and ERCP seem to have increased over time. The study was retrospective and showed rates, not proportions.

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Endocytoscopic visualization of squamous cell islands within Barrett's epithelium

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Abstract

AIM: To study the endocytoscopic visualization of squamous cell islands within Barrett's epithelium.

METHODS: Endocytoscopy (ECS) has been studied in the surveillance of Barrett's esophagus, with controversial results. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for the staining of Barrett's mucosa. Integrated type endocytoscopes (GIF-Q260 EC, Olympus Corp, Tokyo, Japan) have been recently developed, with the incorporation of a high-power magnifying endocytoscope into a standard endoscope together with narrow-band imaging (NBI). Moreover, double staining with a mixture of 0.05% crystal violet and 0.1% of methylene blue (CM) during ECS enables higher quality images comparable to conventional hematoxylin eosin histopathological images.

RESULTS: *In vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported. Conventional white light endoscopy showed typical long-segment Barrett's esophagus, with small squamous cell islands within normal Barrett's mucosa, which were better visualized by NBI endoscopy. ECS after double CM staining showed regular Barrett's esophagus, while higher magnification ($\times 480$) revealed the orifices of glandular structures better. Furthermore, typical squamous cell papillary protrusion, classified as endocytoscopic atypia classification (ECA) 2 according to ECA, was identified within regular glandular Barrett's mucosa. Histological examination of biopsies taken from the same area showed squamous epithelium within glandular Barrett's mucosa, corresponding well to endocytoscopic findings.

CONCLUSION: To our knowledge, this is the first report of *in vivo* visualization of esophageal papillary squamous cell islands surrounded by glandular Barrett's epithelium.

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Key words: Endocytoscopy; Barrett's esophagus; Surveillance; Endocytoscopic atypia classification; Crystal violet; Methylene blue; Hematoxylin eosin stain

Core tip: Endocytoscopy has been also studied in surveillance of Barrett's esophagus, with controversial results. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for staining of Barrett's mucosa. In the present study, *in vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported.

Eleftheriadis N, Inoue H, Ikeda H, Onimaru M, Yoshida A, Hosoya T, Maselli R, Kudo S. Endocytoscopic visualization of squamous cell islands within Barrett's epithelium. *World J Gastrointest Endosc* 2013; 5(4): 174-179 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i4/174.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i4.174>

INTRODUCTION

Endocytoscopy (ECS) with ultra-high magnification ($\times 400$ -1100) represents the most recent innovation in endoscopic imaging, permitting *in vivo* cellular imaging of gastrointestinal (GI) mucosa and visualization of nuclear atypia in neoplastic lesions during routine endoscopic examination^[1-5]. Not only structural atypia, but also cellular atypia, with observation of lumens and nuclei, is achieved by recent advances in ECS^[5-9].

Two different integrated type endocytoscopes (GIF-Q260, Olympus Medical Systems Corp, Tokyo, Japan) have been recently developed^[2,6]. The first is a dual charged couple device (CCD) integrated type (CIF-Y0001, EC1 Olympus, Tokyo, Japan) and the other is a single CCD integrated type (CIF-Y0002, EC2 Olympus).

The dual CCD prototype carries both conventional magnification ($\times 80$) and ultra-high magnification ($\times 480$) abilities, which can be easily interchanged by pushing a button on the endocytoscope^[2,6].

The single CCD prototype endocytoscope (CIF-Y0002, EC2 Olympus) has only one lens that can consecutively increase the magnification power from the conventional magnification power to $\times 380$ using a hand lever. The video processor (prototype, Olympus CV-260X) with a light source (Olympus CLV-260) allows narrow-band imaging (NBI)^[2].

Methylene blue or toluidine blue single staining was initially used for endocytoscopic evaluation of esophageal lesions^[6,10,11]. Recently, however double staining with a mixture of 0.05% crystal violet and 0.1% methylene blue (CM) has been also proposed during ECS^[2,3]. Crystal violet alone effectively stains the cytoplasm, while methylene blue single staining dyes both nuclei and cytoplasm, revealing details of cell structure^[11,12]. Double CM staining enables well balanced staining of both cytoplasm and nuclei, resulting in improved endocytoscopic visualization of GI lesions, comparable to conventional hematoxylin eosin histopathological images^[1].

Minami *et al*^[2] has recently described a five type endocytoscopic atypia classification (ECA) of esophageal squamous cell lesions based on size and uniformity of nuclei, number of cells and regularity of cellular arrangement. ECA-1 to ECA-3 lesions correspond to histological categories 1 to 3, according to the revised Vienna^[13,14] histological classification of gastrointestinal epithelial neoplasia, while ECA-4 to ECA-5 lesions correspond to Vienna categories 4 to 5 (Table 1). According to the results of Minami *et al*^[2], overall accuracy of ECS in evaluation of esophageal squamous cell lesions was 91.3%,

providing images similar to conventional hematoxylin and eosin staining^[2]. Other endocytoscopic atypia classification systems of esophageal lesions based on "nuclear density" and "nuclear abnormality" have also been studied, with promising results^[15].

Endocytoscopy has also been studied in surveillance of Barrett's esophagus, with controversial results^[16,17]. In initial studies, however, a soft catheter type endocytoscope was used, while only methylene blue dye was used for staining of Barrett's mucosa^[16,17]. Although a standardized endocytoscopic atypia classification system for Barrett's esophageal glandular lesions has not been yet described, endocytoscopically, dysplasia was diagnosed on the basis of polarity of cells and nuclei (spacing, orientation); size, shape and uniformity of nuclei; chromatin; nucleoli; and nucleus to cytoplasm ratio^[17].

In the present study, *in vivo* endocytoscopic visualization of papillary squamous cell islands within glandular Barrett's epithelium in a patient with long-segment Barrett's esophagus is reported.

MATERIALS AND METHODS

The dual CCD integrated prototype endocytoscope (CIF-Y0001, EC1 Olympus, Tokyo, Japan) was used for evaluation of long-segment Barrett's esophagus in the present study. In order to compare endocytoscopic images to histological images, biopsies were taken from the same area of ECS by an experienced endoscopist.

Conventional magnifying endoscopy and ECS was performed under conscious sedation with intravenous pethidine hydrochloride (35 mg; Opystan, Mitsubishi Tanabe Pharma Corporation, Osaka, Japan), supplemented with diazepam (5-10 mg, Takeda Pharmaceutical Co., Osaka, Japan). In order to suppress esophageal peristalsis, scopolamine butylbromide (20 mg; Buscopan, Boeringer Ingelhei, GmbH, Ingelheim, Germany) was also administered intravenously. Conventional and ultra-high magnification examination was performed simultaneously. Flushing with water containing a small amount of simethicone was carried out to eliminate gas and foamy mucus from the esophagus before the procedure.

Conventional white light endoscopy (WLE) showed typical long-segment Barrett's esophagus, without visible lesions (Figure 1A). NBI clearly visualized small squamous cell islands within normal Barrett's mucosa, which were also identified by WLE with difficulty (Figure 1B).

After double CM staining, ECS with gradual magnification followed. A total amount of 10 mL CM mixture was directly injected through the working channel with a 5 mL syringe to esophageal Barrett's mucosa. No catheter spray was necessary. The CM mixture is routinely prepared for ECS use, from 0.05% crystal violet and 0.1% methylene blue due solutions. After waiting 60 s to stain nuclei and cytoplasm, ECS followed.

RESULTS

Initially, detailed endocytoscopic observation on the back-

Table 1 Revised Vienna classification of gastrointestinal epithelial neoplasia

Category	Diagnosis
Group 1	Negative for neoplasia
Group 2	Indefinite for neoplasia
Group 3	Mucosal low grade neoplasia Low grade adenoma Low grade dysplasia
Group 4	Mucosal high grade neoplasia
Subgroup 4.1	High grade adenoma/dysplasia
Subgroup 4.2	Non-invasive carcinoma (carcinoma <i>in situ</i>)
Subgroup 4.3	Suspicious for invasive carcinoma
Subgroup 4.4	Intramucosal carcinoma
Group 5	Submucosal invasion by carcinoma

The Endocytoscopic Atypia (ECA) Classification^[10] for superficial esophageal squamous cell lesions is as follow: ECA 1: Large, cytoplasm-rich cells with a rhomboid shape are found in a regular arrangement. Small nuclei are located at their center. This appearance corresponds to healthy squamous epithelium in the esophagus; ECA 2: The cell margin often becomes round. Different-sized small nuclei are observed. The image often shows inflammatory or reactive changes; ECA 3: The cell becomes smaller in size but the nuclei are still compact. This appearance is often observed in borderline lesions; ECA 4: The number of cells increases with an increased nucleus-cytoplasm ratio. This appearance strongly suggests a malignant lesion; ECA 5: Cells of various sizes are arranged irregularly with a high nucleus-cytoplasm ratio. This appearance is recognized endoscopically as a definitely malignant lesion. All images were categorized according to size and uniformity of nuclei, number of cells and regularity of cellular arrangement. Higher ECA category is associated with stronger atypia. ECA 1 to ECA 3 corresponds to Vienna categories 1 to 3; ECA 4 to ECA 5 corresponds to Vienna categories 4 to 5. The data was quoted from the references of 13, 14.

ground mucosa showed regular Barrett's esophagus, without endocytoscopic signs of dysplasia (Figure 1C), while with higher magnification the adenomatous Barrett's glandular orifices were better visualized (Figure 1D). Particularly, high quality endocytoscopic images revealed normal cellular structures, with cells similar in size and shape, without crowding or overlapping and an equal uptake of methylene blue, uniformly oriented in a glandular structure. Furthermore, nuclei were uniform, regular in shape, small in size with normal nucleus/cytoplasm ratio.

Subsequently, ECS focused on the largest squamous cell island surrounded by regular Barrett's epithelium, which was previous identified by NBI. A typical squamous papillary protrusion was clearly identified within regular glandular Barrett's mucosa (Figure 2A). Endocytoscopic findings revealed combined round-shaped cytoplasm-rich cells in an almost regular arrangement, while different sized small nuclei were observed, corresponding to ECA2 according to endocytoscopic atypia classification^[2] (Figure 2A). These findings were suggestive of mild inflammatory changes of esophageal squamous epithelium (DVD).

After detailed observation, biopsies were taken from the same area in order to obtain a pathological diagnosis. The location of endocytoscopic images were matched to histological images and complete correspondence of endocytoscopic images with histopathological images was obtained (Figure 2) based on the records of endocyto-

scopic examination (DVD).

Histological examination showed squamous epithelium within non-dysplastic columnar Barrett's epithelium (Figure 2B). No dysplasia or atypia was found in histopathology of both squamous cell islands and adenomatous Barrett's epithelium, which was in accordance with endocytoscopic images.

DISCUSSION

Barrett's esophagus is the transformation of the normal squamous esophageal mucosa into columnar epithelium and is considered a premalignant condition with high risk of esophageal adenocarcinoma^[18-21]. Traditionally, the diagnosis of Barrett's esophagus is based on histology of biopsy specimens and hematoxylin eosin stain, revealing glandular structures combined with goblet cells^[22,23]. The presence of goblet cells is the sine qua non of Barrett's esophagus^[24,25].

Long-term endoscopic surveillance with multiple and repeated sets of biopsies are the standard recommended practice in Barrett's esophagus in an attempt to detect dysplasia or carcinoma at an early and potentially curable stage^[26-29]. The Seattle multiple biopsy protocol (4 quadrant jumbo biopsies every 1 cm with additional biopsies of mucosal abnormalities), is considered to be the optimal method for surveillance of Barrett's esophagus, although it has never been validated^[27,30]. However, even the most intensive biopsy protocols are associated with significant sampling errors^[31,32].

By convention, there are four broad categories used by pathologists to describe the dysplastic process in Barrett's: (1) no dysplasia; (2) indefinite for dysplasia; (3) low-grade dysplasia; and (4) high-grade dysplasia; which corresponds to groups 1 to 4 according to the revised Vienna^[14] classification for gastrointestinal epithelial neoplasia. The most significant category, high-grade dysplasia, is characterized by carcinoma *in situ* with malignant cells that do not invade the lamina propria. Category (5) corresponds to submucosal invasion by carcinoma^[14,18].

However, the ability to grade dysplasia remains a subjective endeavor, particularly outside specialized centers with expert gastrointestinal pathologists^[33]. Even among focused gastrointestinal pathologists there is discordance, particularly with regard to the presence of low-grade dysplasia^[34]. This lack of precision inherent in histopathological grading has stimulated efforts to identify alternative methods of surveillance in patients with Barrett's esophagus, including more objective molecular and biochemical indicators of an increased risk for progression^[18].

ECS is a revolutionized endoscopic imaging technique aiming to replace the histological examination of biopsy specimens, making "optical biopsy" possible while facilitating real time decision-making^[8].

ECS after double CM staining using modern integrated type endoscopes enables *in vivo* visualization of living cells and evaluation of tissue atypia by approximating the tip of the endoscope onto the mucosal surface^[10].

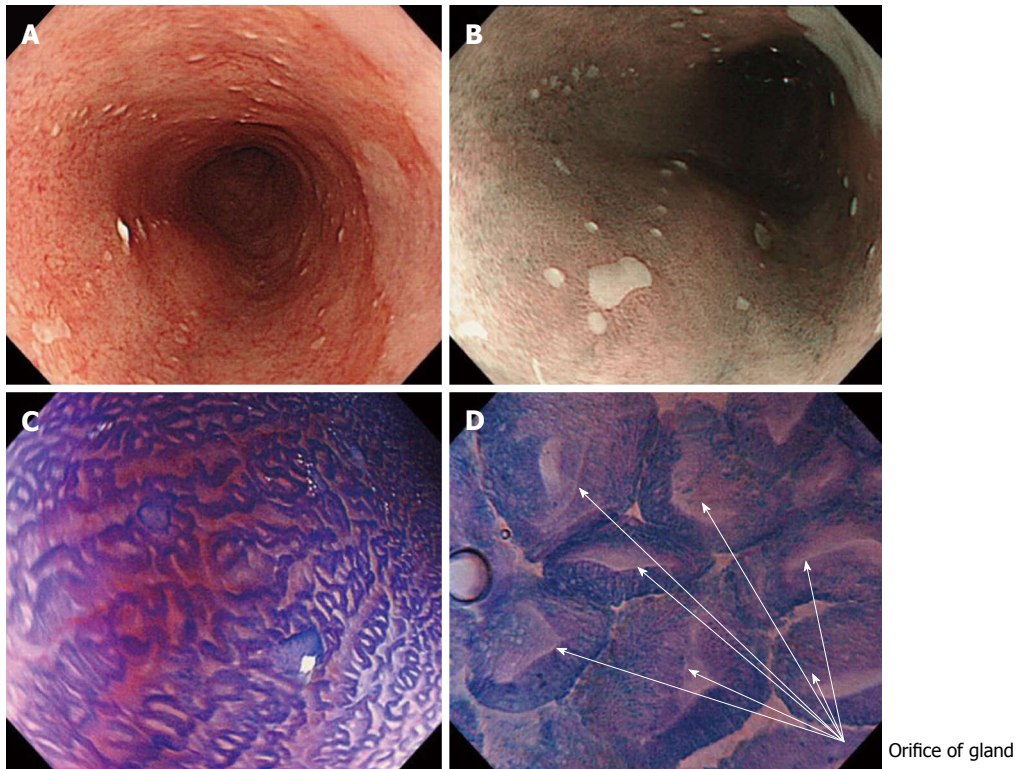


Figure 1 White light endoscopy, narrow-band imaging and endocytoscopy examination of long segment Barrett's esophagus. A: Long segment Barrett's esophagus under white light endoscopy (WLE); B: Narrow-band imaging with low magnification clearly visualized small squamous cell islands within regular columnar Barrett's epithelium, which are also identified by WLE with difficulty; C: Endocytoscopy (ECS) examination after crystal violet and methylene blue (CM) double staining; D: ECS examination under higher magnification ($\times 480$) shows the glandular orifices of regular Barrett's epithelium.

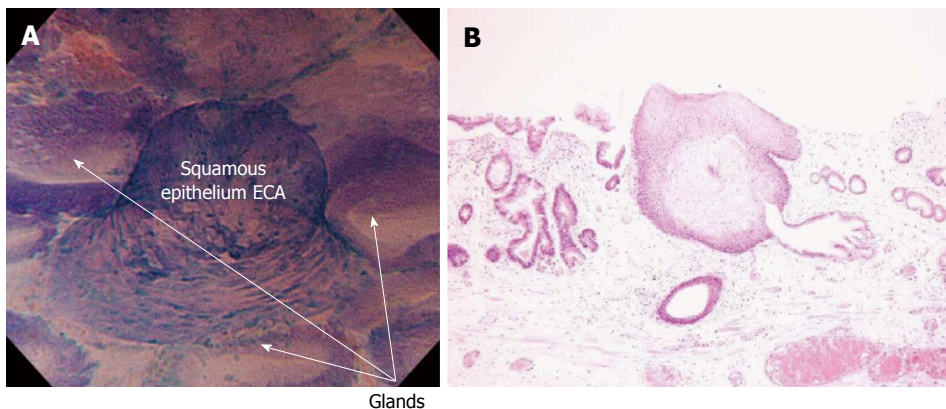


Figure 2 Endocytoscopy examination of histologically confirmed squamous cell islands within Barrett's esophagus. A: Endocytoscopy (ECS) examination shows squamous cell islands, within regular glandular structures of Barrett's esophagus. According to ECS examination, squamous papillary structure is classified as ECA2, (round-shaped cells with different-sized small nuclei, suggestive of inflammatory changes); B: Histological examination (hematoxylin and eosin stain magnification) of biopsies from the same area as in Figure (A) confirmed the presence of a squamous papillary structure surrounded by Barrett's glandular epithelium.

No serious complications of ECS have been reported yet^[6].

At present, a standardized endocytoscopic atypia classification system has been described for esophageal squamous cell lesions^[2] and colorectal^[5] adenomatous lesions. ECS has been also applied for Barrett's esophagus^[16,17,35,36], with controversial results, however, and without a standardized endocytoscopic classification system.

In contrast to previous endocytoscopic studies in Barrett's esophagus^[16,17] where a soft catheter type endo-

cytoscope was used, endocytoscopic evaluation of long-segment Barrett's esophagus in the present study was performed by a dual CCD integrated endocytoscope^[2]. This scope has the advantage of gradual magnification at the center of the monitor, ensuring biopsies from the same area of ECS. This is important to compare endocytoscopic images to histological images. Standard endoscopy, supplemented by NBI and conventional magnification endoscopy was also performed by the same endoscope^[2].

Another interesting finding of the present study is the

use of the double CM staining technique, which provided higher quality endocytoscopic images of both Barrett's metaplastic epithelium and esophageal squamous cell islands. Although double CM staining has been used in ECS of esophageal squamous cell lesions, to our knowledge, it has not been previously reported in endocytoscopic evaluation of Barrett's esophagus.

ECS may further allow target biopsy, as in the presented case, which is extremely important in surveillance of Barrett's esophagus where random biopsy protocols are currently in use. In the present case, ECS permitted *in vivo* high quality images of squamous cell islands within long-segment Barrett's epithelium comparable to histology. To our knowledge, this is the first report of *in vivo* visualization of typical esophageal squamous cell islands surrounded by glandular Barrett's epithelium. According to the positive results of the present study, although from only one case, endocytoscopic evaluation of Barrett's mucosa is promising. However, further studies and expertise are necessary.

COMMENTS

Background

Barrett's esophagus is the transformation of the normal squamous esophageal mucosa into columnar epithelium and is considered a premalignant condition with high risk of esophageal adenocarcinoma. Multiple biopsy protocols are currently the optimal practice in surveillance of Barrett's esophagus, with significant sampling errors, however. Moreover, there is discordance regarding the ability to grade dysplasia in Barrett's esophagus even among focused gastrointestinal pathologists. This lack of precision inherent in histopathological grading has stimulated efforts to identify alternative methods of surveillance in patients with Barrett's esophagus.

Research frontiers

Endocytoscopy (ECS) has emerged as a novel method of *in vivo* diagnosis of gastrointestinal mucosal lesions aimed at replacing the histological examination of biopsy specimens while facilitating real time decision-making.

Innovations and breakthroughs

ECS has been studied in surveillance of Barrett's esophagus, with controversial results. In contrast to previous studies in which a soft catheter type endocytoscope was used after single methylene blue dye for staining of Barrett's mucosa, in the present study, a novel integrated type endocytoscope after double crystal violet and methylene blue (CM) staining resulted in higher quality endocytoscopic images, corresponding to hematoxylin eosin histopathological images. To the knowledge, this is the first report of *in vivo* endocytoscopic visualization of typical esophageal squamous cell islands within regular glandular Barrett's epithelium.

Applications

Based on the encouraging results of the present study, ECS, according to the technique described in this article, would be reliably used for real time, *in vivo* diagnosis of Barrett's esophagus as an alternative to histological examination of biopsy specimens. ECS may allow target biopsy, as in the presented case, which is extremely important in surveillance of Barrett's esophagus where random biopsy protocols are currently in use. However, further studies and expertise are necessary, while a standardized endocytoscopic atypia classification system, similar to that described for esophageal squamous cell lesions and colorectal adenomatous lesions, is necessary and awaited.

Terminology

CCD: charged couple device; ECS is a novel endoscopic imaging of gastrointestinal mucosa, with ultra-high magnification ($\times 400$ -1100), permitting *in vivo* cellular imaging and observation of lumens and nuclei during routine endoscopic examination; The dual CCD integrated prototype (CIF-Y0001, EC1, Olympus, Tokyo, Japan) endocytoscope ($\times 480$) carries both conventional magnification ($\times 80$) and ultra-high magnification ($\times 480$) abilities, which can be

easily interchanged by pushing a button on the endocytoscope; The single CCD prototype (CIF-Y0002, EC2 Olympus) endocytoscope ($\times 380$) has only one lens that can consecutively increase the magnification power from the conventional magnification power to $\times 380$ using a hand lever; The revised Vienna classification of gastrointestinal epithelial neoplasia, which is based on the severity of cytological and architectural changes and on invasion status, has to some extent, resolved the differences between Western and Japanese pathologists in the diagnostic classification of gastrointestinal epithelial neoplastic lesions, especially in the use of the terminology of dysplasia, adenoma, early cancer and advanced cancer.

Peer review

It is very interesting brief report. Superb images and careful description of the technique are the strong points of the paper.

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Ischemic colitis induced by the newly reformulated multicomponent weight-loss supplement Hydroxycut[®]

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do not disclose their use voluntarily to their physicians. Hydroxycut has to be considered as a potential trigger for otherwise unexplained ischemic colitis.

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Key words: Hydroxycut; Weight-loss supplement; Herbal; Ischemic colitis; Gastrointestinal bleeding; Colonoscopy

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Abstract

Ischemic colitis accounts for 6%-18% of causes of acute lower gastrointestinal bleeding. It is more often multifactorial and more common in elderly. Drugs are considered important causative agents of this disease with different mechanisms. In this paper, we describe a 37-year-old otherwise healthy female presented with sudden onset diffuse abdominal pain and bloody stool. Radiologic, colonoscopic and histopathologic findings were all consistent with ischemic colitis. Her only suspected factor was hydroxycut which she had been taking for a period of 1 mo prior to her presentation. Her condition improved uneventfully after cessation of hydroxycut, bowel rest, intravenous hydration, and antibiotics. This is a first case of ischemic colitis with clear relationship with hydroxycut use (Naranjo score of 7). Our case demonstrates the importance of questioning patients regarding the usage of dietary supplements; especially since many patients consider them safe and

INTRODUCTION

Ischemic colitis results from a sudden decrease of splanchnic blood flow to the colon. It occurs more often in the splenic flexure and rectosigmoid junction, which are also known as watershed areas of the colon. These two areas have limited collateralization between superior mesenteric artery and inferior mesenteric artery, and inferior mesenteric artery and internal iliac artery which supply splenic flexure and rectosigmoid junction of the colon, respectively. Therefore, these two areas are more prone to ischemic colitis^[1].

The mechanisms of developing ischemic colitis include hypoperfusion due to systemic hypotension secondary to sepsis, hemorrhage, cardiac failure or any other conditions that might cause hypotension. Vasoconstriction in the colonic vessels due to hypotension or certain substances such as cocaine and other sympathomimetic agents is another mechanism. The third mechanism is thromboembolism due to inherited or acquired hypercoagulable conditions such as antiphospholipid antibody syndrome. Also increased intracolonic pressure is another mechanism for ischemic colitis by causing decrease of the

blood flow into the colon which can occur after screening colonoscopy. Final mechanism is vasculitis involving colonic vessels such as polyarteritis nodosa^[1,2].

Advanced age, aortic surgery, diabetes mellitus, hypertension, and peripheral vascular disease have been also suggested to be predisposing factors for ischemic colitis^[1]. Hydroxycut is an over-the-counter herbal product that has been used for purpose of the weight loss, body building and as an energy enhancer. It is a multicomponent dietary supplement which has been reformulated twice after warnings from the food and drug administration (FDA). It has been linked to serious medical conditions, mostly acute liver toxicity. We describe here a case of ischemic colitis developed in a healthy young female after a month of hydroxycut consumption for purpose of weight loss in the absence of any other risk factors for ischemic colitis.

CASE REPORT

A 37-year-old otherwise healthy female presented with severe crampy abdominal pain. Pain was diffuse but more pronounce in left lower quadrant of her abdomen. The pain was also associated with nausea and one episode of non-bloody, non-bilious emesis. She had two bloody bowel movements at home and later on she had another two with blood clots in the stool at the emergency room. She denied fever, chills, urinary symptoms, similar symptoms in the past, recent travel, sick contact, or recent use of antibiotics or non-steroidal anti-inflammatory drugs (NSAIDs). She had no significant past medical history. She had hysterectomy 4 years ago for repeated abnormal Pap smears. She was not on any prescribed medications. She denied smoking or using illicit drugs, but was drinking alcohol occasionally. She had no family history of major medical problems including gastrointestinal diseases or blood disorders.

The patient was afebrile with temperature of 98.2 F°, blood pressure of 106/63 without orthostatic hypotension, heart rate of 65 bpm, weight of 181 pounds, and body mass index of 29.2 kg/m². Her physical exam was remarkable for diffuse generalized abdominal tenderness, especially in left upper and left lower quadrants without guarding or rebound tenderness. Rectal exam was remarkable for blood on digital exam. The rest of exam including cardiopulmonary, skin, and extremities were unremarkable. Laboratory studies were unremarkable including complete blood count (hemoglobin of 15.9 g/dL), basic metabolic panel, liver function tests, urinalysis, urine toxicology, stool studies (except for positive blood), lipase, amylase, cholesterol profile, hemoglobin A1c, and thyroid function tests. Computed tomography (CT) scan showed a moderately severe colonic wall thickening in the descending colon extending into rectosigmoid area (Figure 1A, B).

Colonoscopy revealed erythematous and edematous colonic mucosa with multiple superficial erosions and ulcerations from the distal descending colon up to the mid-transverse colon which was consistent with moderately

severe ischemic colitis (Figure 2). Multiple biopsies were taken which were consistent also with ischemic colitis (Figure 1C, D). CT angiogram was performed and did not identify any stenosis, occlusion, or thrombosis in the intra-abdominal vessels.

On further questioning to determine the etiology of ischemic colitis in our patient, she reported taking hydroxycut in a recommended dose by the manufacturer for weight loss purposes for a period of one month prior to her presentation.

This temporal relationship between hydroxycut exposure and her symptoms, in the light of absence of other causes of ischemic colitis strongly raises the probability of hydroxycut as the potential trigger of ischemic colitis. This case scored a 7 on the Naranjo Nomogram for adverse drug reactions, indicating a probable association between hydroxycut exposure and the development of ischemic colitis (Probable: 5-8).

She was treated with intravenous fluids, bowel rest, intravenous antibiotics, and discontinuation of hydroxycut. Her hospitalization course was uneventful and she was discharged home 3 d later. She was counseled to stop hydroxycut consumption.

DISCUSSION

This case illustrates the importance of investigation for potential triggers for ischemic colitis when the classical risk factors are absent. The causes of ischemic colitis vary from systemic hypotension, aortoiliac surgery, atherosclerosis, thromboembolic events, vasculitis, to varieties of drugs^[3].

Drugs have been implicated in the development of ischemic colitis by different mechanisms including decreasing blood flow *via* systemic hypotension such as angiotensin-converting enzyme inhibitors, causing vasospasm such as pseudoephedrine, promoting thromboembolism such as oral contraceptives, causing vasculitis such as gold salts, and increasing intracolic pressure such as alosetron^[4]. The mechanism of some drugs reported to cause ischemic colitis has not yet determined. The Table 1 below shows a list of medications and their mechanisms for causing ischemic colitis^[4].

Many case reports have linked ischemic colitis and some commonly used medications such as NSAIDs and triptans, chemotherapy such as bevacizumab and irinotecan, hepatitis C therapy with pegylated interferon and ribavirin, following screening colonoscopy, scuba diving, flying, snake bite, acute carbonic monoxide poisoning, electrical muscle stimulation of the abdominal wall, following long distance running, herbal remedies such as ma huang (ephedra), and weight loss medications such as phentermine^[4].

A significant proportion of Americans and people all over the world are using herbal supplements for different purposes based on geographic, race, and cultural backgrounds. In a survey in 2007, 17.7% of adults in the United States and 3.9% of children were using some kind

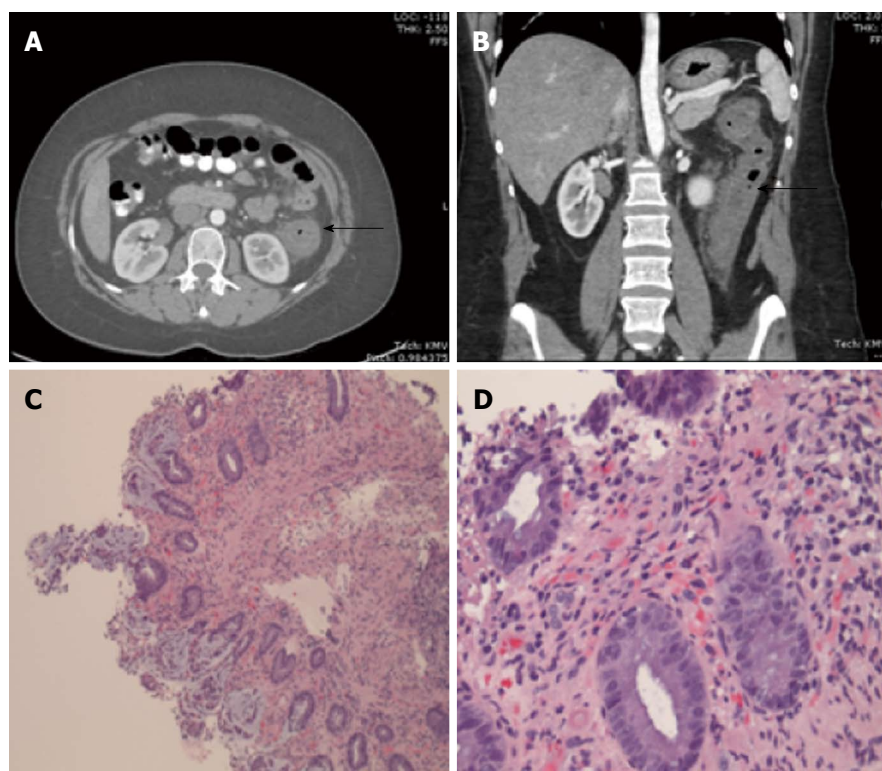


Figure 1 Computed tomography scan and histopathology. A, B: Computed tomography scan shows thickening of the colonic wall involving the descending colon (arrows); C, D: Histopathology shows: the overlying surface mucosa is eroded, the lamina propria is partially hyalinized with fibropurulent exudate and acute inflammation, consistent with ischemic colitis.

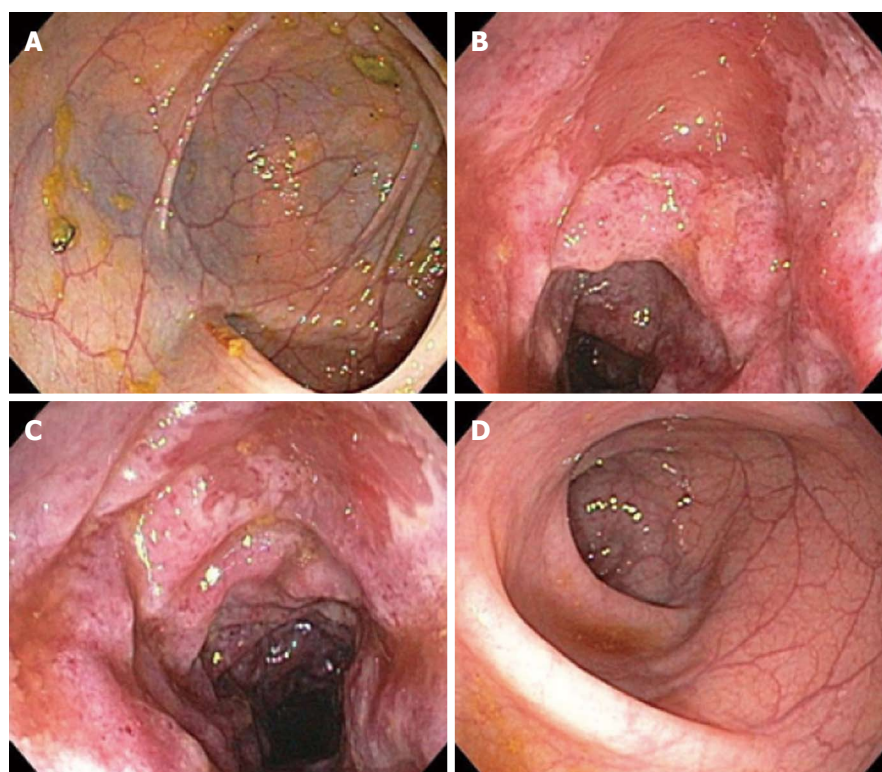


Figure 2 Colonoscopy shows. A: Normal mucosa of the right colon (hepatic flexure); B, C: Erythematous, edematous, erosive, and ulcerated mucosa of the splenic flexure of the colon, consistent with ischemic colitis; D: Normal mucosa of the sigmoid colon.

Table 1 Medications associated with ischemic colitis

Agent	Mechanism
Amphetamines	Vasoconstriction
Alosetron	
Catecholamines (epinephrine, norepinephrine)	
Cocaine	
Cyclosporine	
Digitalis	
Dopamine	
Ergot derivatives	
Nonsteroidal anti-inflammatory drugs	
Pseudoephedrine	
Triptans (Naratriptan, Rizatriptan, Sumatriptan)	
Vasopressin and vasopressin analogues	
Glycerin enema	Local vasospasm effect
Phosphosoda solution	
Angiotensin-converting enzyme inhibitors	
Antipsychotic (chlorpromazine)	Systemic hypotension
Beta blockers	
Barbiturates	
Diuretics	Vasculitis
Interleukin-2	
Tricyclic antidepressants	
Amphetamines	Thrombotic lesion induction
Gold compounds	
Estrogens	
Progestational agents	Increased intracolic pressure
Alosetron	
Danazol	
Glycerin enema	Undetermined
Carboplatin	
Flutamide	
Glutaraldehyde	
Hyperosmotic saline laxatives	
Interferon- α	
Mycophenolate mofetil	
Paclitaxel	
Simvastatin	
Tegaserod	

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of “non-vitamin, non-mineral, natural products” within the last 12 mo^[5]. Factors associated with herbal supplements use are middle age, female gender, uninsured persons, and higher education^[6]. Fifty eight percent of users do not disclose their use to their physicians^[6].

Among the most popular herbal supplements used in the United States are weight-loss products as obesity is becoming epidemic in the United States affecting more than one-third of population^[7]. These products are considered dietary supplements and are not regulated by the FDA^[8]. Dietary supplement manufacturers only need low-level of evidence for their efficacy and safety to get market approval, with most studies of small sample size for a short duration^[9]. In a systematic review of 19 human studies in 2009, the average number of participants was 64.4 (range: 24-153), and the average study duration was 15 wk (range: 2-36 wk)^[9,10]. Under Dietary Supplement Health and Education Act, once a product is marketed, it is the FDA's responsibility to prove it unsafe before with-

drawing or restricting its use, as opposed to conventional medications, for which pharmaceutical companies have to prove the safety of drug before marketing.

Hydroxycut is one of the most sold products among all weight-loss supplements. It is claimed to be a weight-loss aid, fat burner, and energy enhancer. Hydroxycut was introduced first containing ephedra as one of its components; however, after banning ephedra containing products by FDA in February 2004 for severe cardiovascular and neurologic toxicity, hydroxycut was withdrawn from the market and reformulated to exclude ephedra^[4,11]. In May 2009, FDA warned consumers to stop taking any hydroxycut products due to 23 reported cases of severe serious health events related to Hydroxycut, especially liver toxicity resulting in one death^[12].

The safety of hydroxycut (as well as its efficacy) is unstudied extensively and it is based on post-marketing case reports. Since 2004, after ephedra was withdrawn from hydroxycut, it has been reported 30 cases of serious medical conditions associated with hydroxycut ingestion including hepatotoxicity, in form of hepatocellular injury, immune-mediated hepatitis, or cholestasis patterns ($n = 26$), reversible cerebral vasoconstriction syndrome ($n = 1$), hypertensive retinopathy ($n = 1$), rhabdomyolysis ($n = 1$), atrial fibrillation ($n = 1$)^[13-24].

Prior to May 2009, its primary ingredients included *Gymnema sylvestre*, *Garcinia cambogia*, *Rhodiola rosea* extract, *Withania somnifera* extract, *Citrus Aurantium*, chromium, caffeine, and green tea extract (as *Camellia sinensis*), however; it has been reformulated again since then to have a variety of different herbal mixtures including Lady's mantle extract (as *Alchemilla vulgaris*), Wild olive extract (as *Alea europaea*), Komijn extract (as *Cuminum cyminum*), Wild mint extract (as *Mentha longifolia*), Acerola concentrate (as *Malpighia glabra*), Goji extract (as *Lycium barbarum*), blueberry (as *vaccinium corymbosum*), Pomegranate (as *Punica grantum*), Bilberry extract (as *Vaccinium myrtillus*), Brazilian acai concentrate (as *Euterpe oleracea*), Green coffee extract (as *Cunephora robusta*), Cayenne pepper (as *Capsicum annum*), Yohimbe extract (as *Pausinystalia yohimbe*), caffeine, many amino acids, vitamins and minerals^[25].

It has not determined clearly which substance(s) is responsible for reported toxicities. It has been suggested hydroxycitric acid, *Garcinia cambogia*, chromium, epigallocatechi-2-gallate (EGCG), green tea extract (as *Camellia sinensis*), and contaminated chemicals or bacteria as the cause of hepatotoxicity; however studies' results are conflicting^[13,16,20,26,27]. EGCG in Hydroxycut has been suggested as the suspected causative component for developing atrial fibrillation by blocking the atrial-specific *KCN45* potassium channel^[24].

The proposed mechanism for hydroxycut-induced ischemic colitis is the local vasoconstriction of vessels supplying the colon due to one or more substances. High dose of caffeine in hydroxycut has been suggested as a sympathomimetic agent causing vasoconstriction in the brain which might cause similar effects in other organs such as colon; however, it is unproven^[21,22,28]. Chromium

Table 2 Naranjo adverse drug reaction nomogram in our patient

	Yes	No	Our patient
1: Are there previous conclusive reports on this reaction?	1	0	0
2: Did the adverse event appear after the suspected drug was administered?	2	-1	2
3: Did the adverse reaction improve when the drug was discontinued or a specific antagonist was administered?	1	0	1
4: Did the adverse reaction reappear when the drug was readministered?	2	-1	0
5: Are there alternative causes (other than the drug) that could have, on their own, caused the reaction?	-1	2	2
6: Did the reaction appear when a placebo was given?	-1	1	1
7: Was the drug detected in the blood (or other fluids) in concentration known to be toxic?	1	0	0
8: Was the reaction more severe when the dose was increased or less severe when dose was decreased?	1	0	0
9: Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	1	0	0
10: Was the adverse event confirmed by any objective evidence?	1	0	1

Definite: Score ≥ 9 ; Probable: 5-8; Possible: 1-4; Doubtful: ≤ 0 .

in prior formulas is another suggested substance to cause vasoconstriction by activating sympathetic nervous system^[23]. Other components are also possible causes by causing direct or indirect vasoconstriction in susceptible subjects; especially hydroxycut has multiple ingredients with limited known information regarding their precise mechanisms of action. Hydroxycut may work in serotonergic or adrenergic systems as many conventional weight-loss medications, however, it is difficult to identify the exact ingredient or mechanism by which hydroxycut works or causes its side effects.

While causation is impossible to confirm, the temporal relationship between initiation of this product and development of ischemic colitis, in the light of absence of other etiologies, raises the suspicion of hydroxycut as a potential culprit in this case. When applying Naranjo nomogram in our patient, a score of 7 was granted indicating a probable likelihood (Table 2).

Naranjo nomogram for adverse drug reaction consists of 10 questions to assess the cause-effect relationship between any potential offending drug and any event. The likelihood of a drug-event relationship is defined as definitive if score is 9 or greater, probable if the score is 5-8, possible if the score is 1-4, and doubtful if the score is 0 or less^[29]. It is considered a useful tool for evaluating the causality of any potential drug-induced event.

In conclusion, this is the first case report of ischemic colitis associated with ephedra-free weight-loss supplement hydroxycut. Our case demonstrates the importance of questioning patients regarding the usage of these supplements; especially since many patients consider them safe and do not disclose their use voluntarily to their physicians. Hydroxycut has to be considered as the potential cause for otherwise unexplained ischemic colitis.

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Endoscopic retrieval of a duodenal perforating teaspoon

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Abstract

Foreign objects ingestion occur commonly in pediatric patients. The majority of ingested foreign bodies pass spontaneously the gastrointestinal tract and surgery is rarely required for extraction. Endoscopic removal of foreign bodies larger than 10 cm has not yet been described. We present the case of a 16 years old bulimic girl that swallowed a 12 cm long teaspoon in order to provoke vomiting. The teaspoon perforated the duodenum. However, it was removed during gastroscopy and the site of perforation was closed endoscopically. This particular case shows the importance of endoscopy for retrieval of large foreign bodies, and the possibility to endoscopically close a perforated duodenal wall.

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Key words: Foreign body ingestion; Upper endoscopy; Bowel perforation; Bulimia

Boškoski I, Tringali A, Landi R, Familiari P, Contini ACI, Pintus C, Costamagna G. Endoscopic retrieval of a duodenal perforating teaspoon. *World J Gastrointest Endosc* 2013; 5(4): 186-188
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INTRODUCTION

Foreign objects ingestion occur commonly in pediatric patients, psychiatric patients, and those suffering from bulimia or anorexia. Mostly 90% of the foreign bodies pass spontaneously the gastrointestinal tract, 10%-20% require endoscopic removal, and less than 1% require surgery^[1].

Ingestion of long, sharp and rigid foreign bodies is associated with an increased risk of impaction, perforation and bleeding. Foreign bodies may also impact or perforate the bowel wall. Symptoms are variable and mostly related to the site of impaction or perforation of the bowel wall. Foreign bodies can also be found incidentally on X-rays done for other reasons.

Anatomical sites where foreign bodies impact most commonly are pylorus, duodenal C-loop and ileo-cecal valve. Foreign bodies longer than 10 cm mostly impact in the duodenal C-loop because this part is fixed in the retroperitoneum^[2]. Endoscopic removal of these objects should be attempted in a way to avoid perforation and if this fails, surgery should be considered.

CASE REPORT

A 16-year-old bulimic girl swallowed a teaspoon in a way to induce vomiting. She informed the parents only 24 h later, when she had abdominal pain. On plain abdominal X-ray the teaspoon was in the right upper abdominal quadrant without evidence of intra-abdominal air (Figure 1A). On urgent upper endoscopy, there was a large amount of food in the stomach and in the duodenal bulb despite prolonged fasting. The tip of the teaspoon handle was found impacted into the duodenal mucosa at the level of the superior duodenal genu with suspected duodenal perforation (Figure 1B). With delicate maneuvers

using a rat-tooth forceps the impacted teaspoon handle was removed from the duodenal wall, brought into the stomach and then extracted. The spoon was 12 cm long, 2 cm large at the cup and 0.5 cm at the handle, which was sharp (Figure 1C). Control endoscopy was performed immediately after extraction of the teaspoon, and this confirmed perforation of the duodenal wall. The mucosal flaps on the site of perforation were closed by placing 5 clips (EZ clips long, Olympus, Tokyo, Japan), and by injection of 3 mL of fibrin glue (Beriplast, Nycomed, Germany) over the clips in a way to consolidate the closure. Air injection during endoscopy induced the onset of subcutaneous emphysema, which was diagnosed on palpation. On urgent computed tomography (CT) scan there was diffuse bilateral retro-pneumoperitoneum extending to the right inguinal region, with a small amount of fluid into the retro-duodenal region near the right kidney (Figure 1D).

White blood cells count was 12.240 (normal value 4.100-9.800), without fever. On physical examination there was abdominal tenderness without signs of peritonitis. The patient started *iv* therapy with broad spectrum antibiotics and proton pump inhibitors. Clinical course was uneventful during the following days, and white blood cells count normalized without occurrence of fever. Four days later upper gastrointestinal enema with water soluble contrast confirmed the absence of leaks at the site of perforation. On control CT scan after 7 d diffuse retro-peritoneum was still present without evidence of fluid collections and upper endoscopy confirmed complete closure of the perforation. One week later the patient started oral nutrition and was discharged in good clinical conditions.

DISCUSSION

Swallowing of large objects (> 10 cm) may occur, but these usually do not pass spontaneously through the gastrointestinal tract, and often require urgent surgery due to perforation^[2]. In the setting of intentional foreign body ingestion, the rate of endoscopic intervention may be much higher (63%-76%) and the need for surgical intervention ranges from 12% to 16%^[3,4]. This however depends on the size of the foreign body (usually < 10 cm). Mortality rate in these patients is extremely low^[5]. The technique of fibrin glue injection has already been described^[6]. Our patient developed diffuse subcutaneous emphysema during endoscopy. The use of carbon dioxide instead of air should be preferred in these circumstances because of much more rapid reabsorption. Timing of endoscopy in these patients is very important, in order to reduce the risk of bacterial contamination in case of perforation^[5].

This particular case shows the importance of endoscopy for retrieval of large foreign bodies, and the possibility to endoscopically close a perforated duodenal wall. The endoscopic approach was essential in this case and avoided surgery to this young patient.

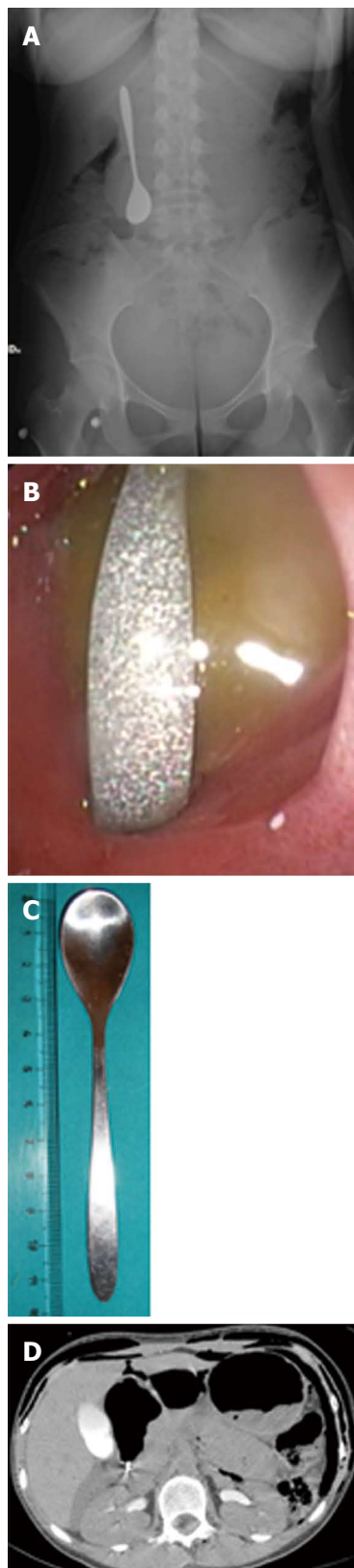


Figure 1 Endoscopic retrieval of a duodenal perforating teaspoon. A: Plain abdominal X-ray showing the teaspoon in the right upper abdominal quadrant. Note the absence of free intra-abdominal air; B: The tip of the teaspoon handle impacted into the duodenal mucosa at the level of the superior duodenal genu; C: The spoon after extraction: 12 cm long, 2 cm large at the cup and 0.5 cm at the handle; D: Urgent computed tomography scan showing diffuse bilateral retro-pneumoperitoneum extending to the right inguinal region, with a small amount of fluid into the retro-duodenal region near the right kidney.

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Diagnosis of *Ascaris lumbricoides* infection using capsule endoscopy

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for *A. lumbricoides* infection, especially when other diagnostic methods have failed to detect the parasite. We report a case of *A. lumbricoides* infection that resulted in intestinal obstruction at the level of the ileum. Both stool sample examination and open surgery failed to indicate the presence of *A. lumbricoides*, and the cause of the obstruction was only revealed by capsule endoscopy. The patient was treated with anthelmintics.

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Key words: Capsule endoscopy; *Ascaris lumbricoides*; Intestinal obstruction

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Abstract

Ascaris lumbricoides (*A. lumbricoides*) is the most common intestinal roundworm parasite, infecting approximately one quarter of the world's population. Infection can lead to various complications because it can spread along the gastrointestinal tract. Although *A. lumbricoides* infection is a serious healthcare issue in developing countries, it now also has a worldwide distribution as a result of increased immigration and travel. Intestinal obstruction is the most common complication of *A. lumbricoides* infection, potentially leading to even more serious consequences such as small bowel perforation and peritonitis. Diagnosis is based primarily on stool samples and the patient's history. Early diagnosis, aided in part by knowledge of the local prevalence, can result in early treatment, thereby preventing surgical complications associated with intestinal obstruction. Further, delay in diagnosis may have fatal consequences. Capsule endoscopy can serve as a crucial, non-invasive diagnostic tool

INTRODUCTION

Ascaris lumbricoides (*A. lumbricoides*) has a worldwide distribution, but occurs most frequently in underdeveloped regions where sanitation is poor^[1,2]. In most cases the infection remains asymptomatic until the number of worms in the intestines increases considerably. It can cause serious complications, the most common of which is intestinal obstruction, although pancreatitis, cholangitis, bleeding, and obstructive jaundice can also occur^[3,4]. The diagnosis of *A. lumbricoides* infection is based mainly on patient history and stool samples, but complementary exams such as abdominal radiography and computed tomography can also aid in the diagnosis^[5]. We report a case of *A. lumbricoides* infection that resulted in intestinal obstruction. Although the obstruction was apparent during open surgery and imaging, neither they, nor the stool

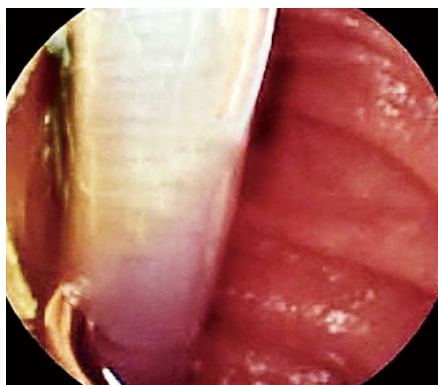


Figure 1 *Ascaris lumbricoides* roundworm physically blocking the small bowel.

samples analysis revealed the presence of *A. lumbricoides*. The presence of this parasite was however determined by video capsule endoscopy.

CASE REPORT

A 64-year-old Brazilian woman presented with abdominal discomfort and intermittent subocclusive episodes that had developed over the previous few weeks. The discomfort was relieved by evacuation. Physical examination indicated good health, and no abdominal tenderness was noted. The patient had undergone 2 previous exploratory laparoscopy procedures to examine the subocclusion, but the findings were normal. A stool sample was analyzed to detect the possible presence of a parasitic infection, but the findings were negative. However, contrast radiography and computed tomography revealed a partial obstruction with an undetermined tube-like structure at the level of the ileum, suggesting a parasitic infection. Capsule endoscopy (MiroCam capsule; Intromedic, Seoul, South Korea) was performed to determine the cause of the obstruction. A diagnosis of roundworm infection with partial obstruction of the ileum with live *A. lumbricoides* was confirmed (Figures 1 and 2). The first roundworm was seen 1 h 34 min after capsule ingestion (Figure 1) and the last one was seen 2 h later (Figure 2). Treatment with albendazole and piperazine was initiated, and the patient made a full recovery.

DISCUSSION

A. lumbricoides is the most common intestinal helminth parasite, infecting approximately one quarter of the world's population^[6]. It has long been endemic in devel-

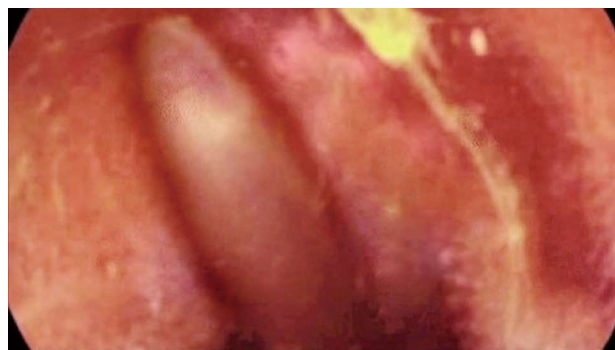


Figure 2 Infection of the ileum with live *Ascaris lumbricoides*.

oping countries, but it now has a worldwide distribution due to the increase in immigration and travel^[7]. Capsule endoscopy is an important tool for evaluation of small bowel disorders, allowing for non-invasive diagnosis of many diseases. In this case, it was used successfully to reveal the cause of intestinal obstruction as being due to *A. lumbricoides* infection. This was after stool sample analysis and open surgery, which are currently considered to be the gold standard for *A. lumbricoides*.

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Mucosal-incision assisted biopsy for suspected gastric gastrointestinal stromal tumors

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Abstract

To evaluate the diagnostic yield of the procedure, mucosal-incision assisted biopsy (MIAB), for the histological diagnosis of gastric gastrointestinal stromal tumor (GIST), we performed a retrospective review of the 27 patients with suspected gastric GIST who underwent MIAB in our hospitals. Tissue samples obtained by MIAB were sufficient to make a histological diagnosis (diagnostic MIAB) in 23 out of the 27 patients, where the lesions had intraluminal growth patterns. Alternatively, the samples were insufficient (non-diagnostic

MIAB) in remaining 4 patients, three of whom had gastric submucosal tumor with extraluminal growth patterns. Although endoscopic ultrasound and fine needle aspiration is the gold standard for obtaining tissue specimens for histological and cytological analysis of suspected gastric GISTs, MIAB can be used as an alternative method for obtaining biopsy specimens of lesions with an intraluminal growth pattern.

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Key words: Endoscopic ultrasound-guided fine-needle aspiration; Gastrointestinal stromal tumor; Mucosal-incision assisted biopsy; Submucosal tumor; Endoscopic submucosal dissection

Ihara E, Matsuzaka H, Honda K, Hata Y, Sumida Y, Akiho H, Misawa T, Toyoshima S, Chijiwa Y, Nakamura K, Takayanagi R. Mucosal-incision assisted biopsy for suspected gastric gastrointestinal stromal tumors. *World J Gastrointest Endosc* 2013; 5(4): 191-196 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i4/191.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i4.191>

INTRODUCTION

Gastric submucosal tumors (SMTs) are a wide range of diverse conditions including neoplastic lesions such as gastrointestinal stromal tumor (GIST), leiomyoma, leiomyosarcoma, schwannoma, granular cell tumor and non-neoplastic lesions such as inflammatory fibroid polyp, gastric varices, heterotopic pancreas and heterotopic gastric mucosa^[1,2]. Endoscopic ultrasonography (EUS) is one of the most useful modalities for diagnosing gastric SMTs^[3,4]. However, it is usually not possible to differentiate GIST from benign conditions such as leiomyoma or schwannoma by EUS. Tissue sampling is necessary for definitive diagnosis of GIST. Endoscopic ultrasound-

guided fine-needle aspiration (EUS-FNA) has been developed for tissue sampling of suspected GIST and is generally accepted to be a very useful for the diagnosis of this lesion^[5]. When considering the diagnostic yield of EUS-FNA for suspected gastric GIST, it is important to evaluate whether the samples obtained are adequate for both cytological and histological analysis, as immunohistological analysis is indispensable for a definitive diagnosis. In general, the success rate of EUS-FNA for tissue sampling for cytology has been reported to be relatively high (83%), but the success rate for histology does not seem to be satisfactory (62%)^[6]. Therefore, there has been an interest in exploring an alternative modality for tissue sampling in suspected GIST.

Endoscopic submucosal dissection (ESD) has been developed as an advanced endoscopic therapy for superficial gastric neoplasms^[7] and ESD has rapidly become widely used. In this situation we have become interested in using ESD-associated techniques for tissue sampling of suspected GIST instead of using EUS-FNA. More recently, Lee *et al*^[8] has shown the cases where the ESD-associated technique was useful for tissue sampling of suspected GISTs. It remains, however, to be determined whether the ESD-associated technique would be suitable for tissue sampling of any of suspected GISTs. Although an official term for this procedure has yet to be determined, we have named it mucosal-incision assisted biopsy (MIAB). We reviewed 27 cases with gastric SMTs in which MIAB was performed to obtain biopsy specimens. In the present study, we have shown that MIAB can be as an alternative diagnostic modality for tissue sampling of suspected GISTs when the lesions have an intraluminal growth pattern. MIAB may be contraindicated in suspected gastric GISTs with an extraluminal growth pattern.

CASE REPORT

We undertook a retrospective review of the 27 patients with gastric SMTs who underwent MIAB in our hospitals between May 2005 and August 2011 in order to distinguish GIST from benign causes of SMT. An extraluminal growth pattern was defined as growth in an extraluminal direction with little intraluminal growth. An intraluminal growth pattern was defined as growth in an intraluminal direction, regardless of any extraluminal growth. Informed consent was obtained from all patients before MIAB was undertaken. MIAB was performed as follows; In brief, a mucosal incision line was chosen which was usually not directly over the lesion, for easier closure with endoclips after the biopsy. Saline with 0.001% epinephrine was injected into the submucosa at the chosen incision line. A mucosal incision was made in the same way as the circumferential mucosal incision is made for ESD, using electrosurgical knives such as the flush knife or needle knife, followed by careful submucosal dissection until a portion of the SMT was exposed. When a single mucosal incision did not provide satisfactory exposure, a second incision was made perpendicular to the first

incision. Several biopsy specimens were taken under direct vision using conventional biopsy forceps. The mucosal incisions were then closed with endoclips to prevent post-procedure complications including bleeding and/or perforation. The biopsy samples obtained by MIAB were fixed in formalin solution and stained with hematoxylin and eosin (HE). If applicable, specimens underwent immunohistochemical analysis. Applicable data were expressed as the mean \pm SE.

Characteristics of patients who underwent MIAB

Individual patient characteristics are shown in Table 1 and a summary is shown in Table 2. Fourteen females and 13 males were included in the study, with a mean age of 58.9 ± 2.4 years. Gastric SMT lesions were 10-36 mm in diameter with a mean diameter of 21.2 ± 1.0 mm. In 23 of the 27 patients, tissue samples obtained by MIAB were sufficient to make a histological diagnosis (diagnostic MIAB). We diagnosed GIST in 16 patients, leiomyoma in 4 patients, aberrant pancreas in one patient, inflammatory granuloma in one patient, and glomus tumor in one patient. In 23 patients with diagnostic MIAB, all of the lesions had intraluminal growth patterns. Fourteen of sixteen patients underwent surgical resection based on a preoperative diagnosis of GIST; the other patients (Cases 5 and 15) did not accept surgical resection and is currently under close follow-up. The post-operative pathological findings in all fourteen cases of GIST were identical to those obtained with MIAB, including findings on HE staining and immunohistochemical analysis. On the other hand, four patients (Cases 17, 25-27) resulted in non-diagnostic MIAB. In three of them, the SMT lesions had extraluminal growth patterns. In one patient with non-diagnostic MIAB (Case 17), the samples obtained by MIAB suggested a spindle cell tumor on HE staining. We could not obtain the further pathological diagnosis. In this case, since the lesion was growing rapidly and suspected to be a GIST, a surgical resection was performed. As a result, the final pathological diagnosis after surgery was a GIST (Table 1). The mean procedure time was 32.0 ± 2.4 min and no procedure-related complications (including uncontrolled bleeding or perforation) were observed. We present two representative cases below.

Case 1

A 70-year-old man was referred to our hospital for evaluation of a suspected gastric SMT. EGD revealed a solid, round, protruding lesion covered with normal mucosa, measuring about 20 mm in diameter, at the middle of the lesser curvature of the body of the stomach (Figure 1A). EUS with a miniature probe showed a hypoechoic mass was observed, which originated from the 4th layer (muscularis propria) (Figure 1B), confirming that the lesion was an SMT. The lesion was thought to be a gastrointestinal mesenchymal tumor (GIMT) such as a GIST, leiomyoma or schwannoma. EUS findings showed an intraluminal growth pattern. MIAB was performed to obtain biopsy samples for histological diagnosis. Two mucosal incision

Table 1 Characteristics of the patients with submucosal tumor who underwent mucosal-incision assisted biopsy

Case	Age	Sex	Location of SMT	Size (mm)	Growth pattern	Diagnosis by MIAB	Post-operativediagnosis
1	70	M	Body, LC	21	Intraluminal	GIST	GIST
2	60	M	Body, LC	20	Intraluminal	GIST	GIST
3	55	F	Angulus, LC	36	Intraluminal	GIST	GIST
4	73	M	Body, LC	26	Intraluminal	GIST	GIST
5	72	F	Body, LC	20	Intraluminal	GIST	Not applicable
6	69	F	Fundus	19	Intraluminal	GIST	GIST
7	72	F	Body, LC	23	Intraluminal	GIST	GIST
8	53	M	Body, PW	23	Intraluminal	GIST	GIST
9	79	F	Body, GC	24	Intraluminal	GIST	GIST
10	66	F	Angulus, GC	22	Intraluminal	GIST	GIST
11	66	F	Body, PW	25	Intraluminal	GIST	GIST
12	39	M	Body, PW	15	Intraluminal	GIST	GIST
13	58	M	Body, GC	20	Intraluminal	GIST	GIST
14	24	M	Cardia, AW	30	Intraluminal	GIST	GIST
15	60	F	Body, PW	10	Intraluminal	GIST	Not applicable
16	57	M	Body, PW	20	Intraluminal	GIST	GIST
17	40	F	Body, PW	30	Intraluminal	IS	GIST
18	55	M	Cardia, LC	23	Intraluminal	Leiomyoma	Not applicable
19	36	F	Cardia, LC	19	Intraluminal	Leiomyoma	Not applicable
20	62	F	Cardia, LC	25	Intraluminal	Leiomyoma	Not applicable
21	57	F	Body, LC	15	Intraluminal	Leiomyoma	Not applicable
22	50	M	Antrum, AW	20	Intraluminal	Glomus tumor	Glomus tumor
23	63	M	Body, LC	20	Intraluminal	Aberrant pancreas	Not applicable
24	57	M	Body, GC	20	Intraluminal	Inflammatory change	Not applicable
25	66	M	Body, GC	15	Extraluminal	IS	Not applicable
26	71	F	Body, LC	15	Extraluminal	IS	Not applicable
27	61	F	Antrum, GC	17	Extraluminal	IS	Not applicable

IS: Insufficient samples for diagnosis; GIST: Gastrointestinal stromal tumor; MIAB: Mucosal-incision assisted biopsy; SMT: Submucosal tumor; PW: Posterior wall; LC: Lesser curvature; GC: Greater curvature; M: Male; F: Female.

Table 2 Summary of the cases which underwent mucosal-incision assisted biopsy

Age	58.9 ± 2.4 (27)
Sex	Female (13)/male (14)
Location of SMT	Fundus (1) Cardia (4) Body (18) Angulus (2) Antrum (2)
Size of the lesion (mm)	21.2 ± 1.0 (27)
Growth pattern	Intraluminal (24) Extraluminal (3)
Diagnosis by MIAB	GIST (16) Leiomyoma (4) Aberrant pancreas (1) Inflammatory changes (1) Glomus tumor (1) Not diagnosed (4)

GIST: Gastrointestinal stromal tumor; MIAB: Mucosal-incision assisted biopsy; SMT: Submucosal tumor.

lines were made perpendicular to each other to expose the surface of the SMT (Figure 1C) and tissue samples were successfully obtained (Figure 1D), followed by closure of the mucosal incisions with endoclips (Figure 1E). Pathological examination of the biopsy specimens showed a spindle cell mesenchymal tumor with abundant hyalinized fibrous stroma on HE staining. Immunohistochemical analysis was positive for c-Kit and CD34 and negative for desmin, which enabled us to make a diagno-

sis of GIST. The patient underwent surgical resection of the lesion. The final pathological diagnosis after surgery was GIST with a 21 mm diameter and mitotic index less than 5/50 HPFs, indicating a very low risk GIST according to Miettinen *et al*^[9] (Figure 1F).

Case 25

A 66-year-old man was referred to our hospital for evaluation of a suspected gastric SMT at the greater curvature of the lower body. EGD did not initially reveal any lesion (Figure 2A), but an SMT-like lesion was detected later during the examination (Figure 2B). As we were unable to detect the lesion by EUS with a miniature probe, conventional EUS was undertaken, revealing a hypoechoic, oval mass originating from the 4th layer (Figure 2C) which was suggestive of a GIST such as a GIST, leiomyoma or schwannoma. The lesion had an extraluminal growth pattern. MIAB was undertaken to obtain biopsy specimens for a histological diagnosis. In this case we were unable to expose the lesion clearly due to risk of perforation (Figure 2D and E). The lesion appeared to be covered with normal smooth muscle of the muscularis propria. Some tissue samples were obtained, followed by closure of the incision with endoclips (Figure 2F). Pathological examination of the biopsy specimens with HE staining showed fascicles of smooth muscle cells accompanied by small fragments of spindle-shaped cells. Immunohistochemical analysis showed that the spindle-shaped cells were probably positive for c-Kit and CD34. These findings

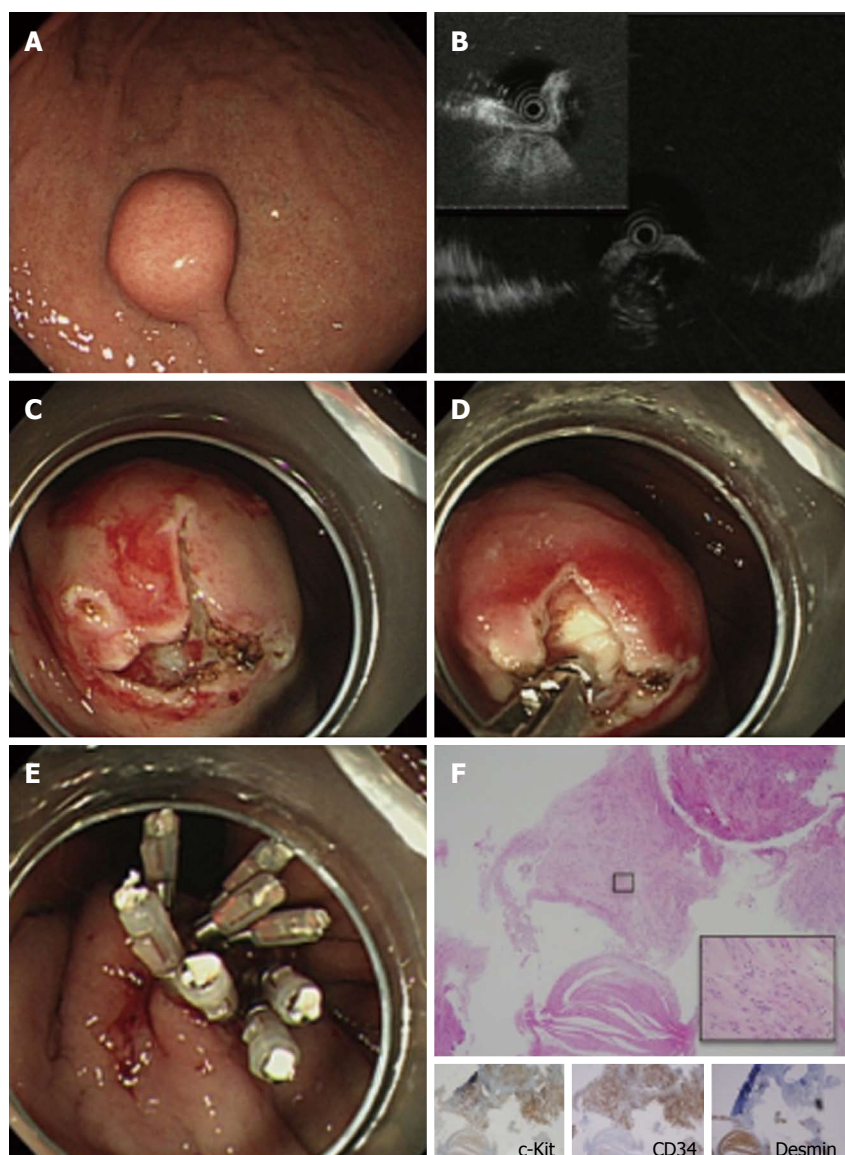


Figure 1 Case 1 of gastrointestinal stromal tumor which underwent mucosal incision assisted biopsy. A: Endoscopic image of the lesion. The lesion was covered by normal mucosa with a bridging fold; B: Endoscopic ultrasonography imaging of the lesion with a miniature probe. The lesion was located in the 4th layer (muscularis propria); C: Two mucosal incisions were made to expose a portion of the lesion; D: Tissue samples were obtained using biopsy forceps; E: Closure of the mucosal incisions with endoclips; F: Pathological examination of the biopsied specimen. Immunohistochemical analysis showed that the lesion was positive for c-Kit and CD34 and negative for desmin. The biopsy samples also contained normal smooth muscle tissue, which was negative for c-Kit and CD34 and positive for desmin.

were suggestive of GIST, but not conclusive. In this case, MIAB was considered a non-diagnostic procedure.

DISCUSSION

In the present study, we retrospectively reviewed 27 cases with suspected GIST, in which MIAB was undertaken to obtain tissue samples for histological diagnosis. A definitive histological diagnosis was obtained in 23 of the 27 patients (85.2 %) who had gastric SMTs with intraluminal growth pattern. MIAB resulted in insufficient tissue sampling in the other four patients. In three of them, the SMT lesions had extraluminal growth patterns. We have shown that MIAB can be as an alternative diagnostic modality for tissue sampling of suspected GISTs when the lesions have an intraluminal growth pattern. MIAB may

be contraindicated in suspected gastric GISTs with an extraluminal growth pattern^[10,11].

EUS-FNA has been developed for tissue sampling and analysis of suspected GIST and plays an important role in making a histological diagnosis of this lesion^[5]. Even though EUS-FNA has become the gold standard for obtaining biopsy samples for cytological and histological analysis of suspected gastric GIST, the procedure does not seem satisfactory. Mekky *et al*^[6] recently reported the diagnostic yield from EUS-FNA for a total of 141 patients with gastric SMTs. They reported adequate samples in 117 of 141 cases (83%). In 29 cases of the 117 cases, however, the samples were sufficient for suggestion of a diagnosis based on cytological examination, but were inadequate for immunohistochemical analysis. Adequate samples for histological diagnosis were there-

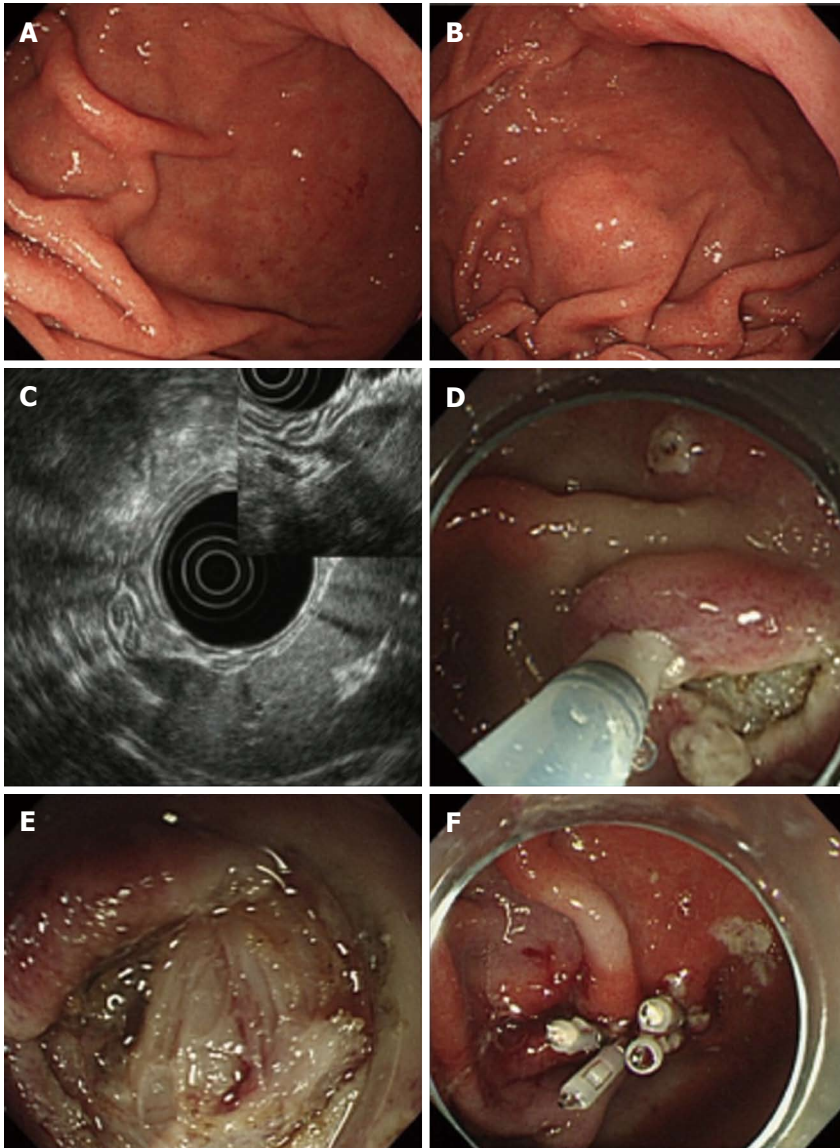


Figure 2 Case 25 of submucosal tumor with an extraluminal growth pattern in which mucosal incision assisted biopsy was non-diagnostic. A: No submucosal tumor (SMT)-like lesion was initially detectable; B: Later during the procedure, the SMT-like lesion was detectable; C: Conventional endoscopic ultrasonography showed that the lesion was located in the 4th layer (muscularis propria) and had an extraluminal growth pattern; D, E: Due to the risk of perforation, the lesion could not be clearly exposed. The lesion appeared to be covered with the normal smooth muscle of the muscularis propria; F: Closure of the mucosal incision with endoclips. Pathological examination of the biopsy samples suggested gastrointestinal stromal tumor, but was not conclusive.

fore obtained in only 88 of 141 cases (62%). Since immunohistochemical analysis is indispensable for a definitive diagnosis of GIST, the diagnostic yield of EUS-FNA for suspected GIST was not satisfactory. Therefore, there has been an interest in developing an alternative modality for tissue sampling of suspected GIST. Reasonably, we have become interested in using ESD-associated techniques for tissue sampling of suspected GIST instead of using EUS-FNA as recently shown by Lee *et al*^[8].

MIAB has the following advantages over EUS-FNA. First, MIAB would be less costly than EUS-FNA. Although both ESD and EUS-FNA require a high skill level, ESD only needs an electrosurgical generator and electrosurgical knives (such as the flush knife, insulation-tipped electrosurgical knife, or grasping-type scissors forceps^[12]), and does not need expensive equipment such

as the linear echoendoscopy used for EUS-FNA. Second, on-site cytologists are not required for MIAB, whereas they need to be scheduled for successful EUS-FNA. Third, when the gastric SMT proves to be a GIST, tissue samples obtained by MIAB are large enough for pathologists to calculate or estimate the Ki-67 labeling index, which gives information about the relative risk of malignant behavior. Calculation of the Ki-67 labeling index is not possible with EUS-FNA biopsy samples. It is very advantageous to have an indication of the risk of malignant behavior of a GIST before surgical resection.

There are, however, some disadvantages and limitations to MIAB. First, MIAB does not seem to be appropriate for tissue sampling of gastric SMTs with an extraluminal growth pattern. In our study, MIAB was non-diagnostic in cases 25-27 in which the gastric SMTs

had an extraluminal growth pattern. In contrast, EUS-FNA is generally considered to be useful for obtaining tissue samples of gastric SMTs regardless of growth patterns. Other possible disadvantages are procedure-related complications including bleeding and perforation. MIAB may have a higher rate of procedure-related bleeding than EUS-FNA, but all bleeding was easily controlled by endoscopic hemostatic procedures in our cases. No perforation occurred in our cases, but extra care should be taken to prevent perforation in cases with an extraluminal growth pattern. It is not known whether procedure-related dissemination will be a possible late complication, but this has not been reported to date. It is important to close the mucosal incisions appropriately with endoclips after tissue sampling to prevent post-procedure complications.

In conclusion, although it is generally accepted that EUS-FNA is the gold standard for obtaining biopsies for histological and cytological analysis of suspected gastric GIST, MIAB may be chosen as an alternative diagnostic modality only when the lesion has an intraluminal growth pattern. Further studies will be required to further assess MIAB, including randomized controlled trials to compare MIAB with EUS-FNA.

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Endoscopic mucosal resection with circumferential mucosal incision of duodenal carcinoid tumors

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Abstract

Duodenal carcinoids are a rare form of neuroendocrine tumors, and tend to invade the submucosa during the early stage. Endoscopic treatment is generally recommended for duodenal carcinoids less than 10 mm in diameter. Although a few reports have described the use of endoscopic resection of duodenal carcinoids, there are no published studies on endoscopic mucosal resection with circumferential mucosal incision (EMR-CMI). We performed EMR-CMI for 5 cases of duodenal carcinoids in the duodenal bulb. The mean tumor diameter was 4.6 ± 1.8 mm. Although all of the tumors were located in the submucosa, R0 resection was performed without complication in each case. EMR-CMI may thus be a safe and effective treatment for duodenal carcinoids less than 10 mm in diameter.

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Key words: Case study; Digestive system endoscopic

surgery; Duodenal neoplasms; Submucosa; Neuroendocrine tumor

Core tip: Endoscopic treatment for duodenal carcinoids is generally recommended less than 10 mm in diameter. Although a few reports have described endoscopic resection of duodenal carcinoids, there are no published studies on endoscopic mucosal resection with circumferential mucosal incision (EMR-CMI). We performed EMR-CMI for 5 cases of duodenal carcinoids in the duodenal bulb. The mean tumor diameter was 4.6 mm. Although all of the tumors were located in the submucosa, R0 resection was performed without complication in each case. EMR-CMI may thus be a safe and effective treatment for duodenal carcinoids less than 10 mm in diameter.

Otaki Y, Homma K, Nawata Y, Imaizumi K, Arai S. Endoscopic mucosal resection with circumferential mucosal incision of duodenal carcinoid tumors. *World J Gastrointest Endosc* 2013; 5(4): 197-200 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i4/197.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i4.197>

INTRODUCTION

Carcinoid tumors are a rare neuroendocrine malignancies that are most frequently found in the gastrointestinal (GI) tract^[1]. Duodenal carcinoids account for 2%-5% of GI carcinoid tumors, and usually present as solitary small lesions confined to the duodenal submucosa^[2,3]. Endoscopic treatment is generally recommended for duodenal carcinoids less than 10 mm as it is associated with a low frequency of lymph node invasion and distant metastases^[3-5]. A few reports have described the use of endoscopic resection for the treatment of duodenal carcinoids. However, to our knowledge, no studies have been published to date on endoscopic mucosal resection with circumferential mucosal incision (EMR-CMI) for

these tumors. In this study, we described our experience of EMR-CMI for the treatment of 5 cases of duodenal carcinoids.

CASE REPORT

Between December 2006 and September 2012, 5 patients (4 men and 1 woman) with a duodenal carcinoid tumor underwent EMR-CMI at Nihonkai General Hospital. All patients were asymptomatic, and the tumors were incidentally detected during a screening esophago-gastro-duodenoscopy (EGD). All procedures were performed by a single endoscopist (Homma K), and all patients were examined by endoscopic ultrasonography (EUS) and abdominal computed tomography (CT) before EMR-CMI. The diagnosis of carcinoid tumor was confirmed by an endoscopic forceps biopsy. Indications for treatment by EMR-CMI were a tumor of diameter 10 mm or less that was confined to the submucosal layer with a clear separation between the tumor and the muscularis propria layer, as assessed by a 20-MHz EUS microprobe (UM2R, Olympus, Tokyo, Japan), and no lymph node invasion or distant metastases on abdominal CT.

After obtaining informed consent from the patient, EMR-CMI was performed under moderate sedation with a combination of pentazocine and flunitrazepam. A single-channel upper GI endoscope with a water-jet system (GIF-Q260J, Olympus) was used. The procedure began with a submucosal injection of hyaluronic acid solution (Mucoup, Johnson and Johnson, Japan) with a 0.1 mL mixture of 0.1% epinephrine and 0.4% indigocarmine dye in order to maintain prolonged elevation and good visibility. A circumferential mucosal incision was performed using a SB knife Jr (Sumitomo Bakelite, Tokyo, Japan) or Mantis Hook (Pentax, Tokyo, Japan), and an additional submucosal injection of hyaluronic acid solution was given beneath the lesion. The adequately raised lesion was then ensnared using a snare (B wave; Zeon Medical, Tokyo, Japan or K-snare; Pentax) in the same manner as the standard polypectomy technique. After EMR-CMI, the mucosal wound was closed with endoscopic clippings as much as possible in order to prevent postoperative bleeding and delayed perforation. To evaluate local recurrence at the resection site, periodic follow-up EGD was performed for all patients. The average age at the time of diagnosis was 64.2 ± 10.2 years (range 47-74 years). The tumors were located in the submucosa within the duodenal bulb in all cases, and the mean tumor size was 4.6 ± 1.8 mm (range 3-8 mm). *En bloc* resection was performed for all patients, and no complications were observed. The average resection time was 19.4 ± 3.6 min (Table 1) and the subsequent postoperative hospitalization period was 5 d in all patients. The median follow-up period was 13 ± 8.8 mo (range 2-29 mo).

In this study, we described one of the cases in greater detail in order to illustrate the typical endoscopic and histological findings associated with these tumors (Case 1). A 74-year-old woman presented with a carcinoid tumor located in the anterior wall of the duodenal bulb (Figure

1A). EUS revealed a hypoechoic mass measuring 3 mm in diameter, originating from the submucosal layer (Figure 1B). Abdominal CT revealed no lymph-node invasion or distant metastases. After local injection of hyaluronic acid solution with epinephrine and an indigocarmine dye to the submucosa around the lesion, a circumferential incision was performed using a SB knife Jr (Figure 2A). *En bloc* resection was then performed by using a standard polypectomy technique with K-snare (Figure 2B and C). The mucosal defect was closed with endoscopic clippings, and the entire procedure was completed in 26 min. A negative surgical margin was confirmed histologically (Figure 3).

DISCUSSION

Duodenal carcinoids are generally considered to be indolent tumors, but because of rarity, their natural history has not been adequately described to date^[6]. The metastatic potential of duodenal carcinoids is closely dependent on the size of the tumor. In a series of 99 duodenal carcinoids, Burke *et al*^[3] reported that the mean tumor diameter was 18 mm (range 2-50 mm) and that metastasis was presented in 21% of the cases. None of the patients with tumors less than 10 mm in diameter developed metastatic disease during a mean follow-up period of 65 mo. Zyromski *et al*^[6] also reported that 24 patients with duodenal carcinoid tumors less than 20 mm remained disease free after local excision during a mean follow-up of 46 mo. In another author described 14% of 201 patients with duodenal carcinoids less than 10 mm in diameter developed metastases, whereas this increased to 47% for patients with tumor diameters between 21 and 50 mm^[7].

In addition to the tumor size, involvement of the muscularis propria and the presence of mitotic figures have also been proposed as possible risk factors for metastases in duodenal carcinoids^[3]. Therefore, the accurate assessment of invasion depth is important for a successful treatment outcome. EUS has been reported to be an appropriate method for assessing carcinoid tumors including duodenal lesions^[8-10]. In a series of 36 GI carcinoid tumors including 7 duodenal lesions evaluated by EUS, Yoshikane *et al*^[8] reported that the tumors were generally visualized as hypoechoic and homogenous lesions, and the accuracy of determining the depth of invasion was 75%. Furthermore, when limiting this assessment to the lesions detectable on EUS, the accuracy was as high as 90%. In the present study, all cases were detectable on EUS and the accuracy of determining the depth of invasion was 100%, despite the relatively small number of cases.

European guidelines recommended that duodenal carcinoids less than 10 mm in diameter that are confined to the submucosa as seen on EUS should be treated by endoscopy in the absence of apparent lymph node invasion and distant metastases^[5]. However, the appropriate treatment for duodenal carcinoids larger than 10 mm is still controversial. Endoscopic treatment might be considered in patients with a high risk of perioperative complications because of old age or advanced comorbidity. If endos-

Table 1 Characteristics of five patients with a duodenal carcinoid tumor

No.	Age (yr)	Sex	Site	Size (mm)	Depth	Time (min)	<i>En bloc</i> resection	Complication
1	74	F	Bulb, anterior	3	Sm	20	Yes	No
2	67	M	Bulb, anterior	4	Sm	15	Yes	No
3	47	M	Bulb, anterior	5	Sm	21	Yes	No
4	74	M	Bulb, anterior	3	Sm	25	Yes	No
5	59	M	Bulb, anterior	8	Sm	16	Yes	No

F: Female; M: Male; Sm: Submucosa.

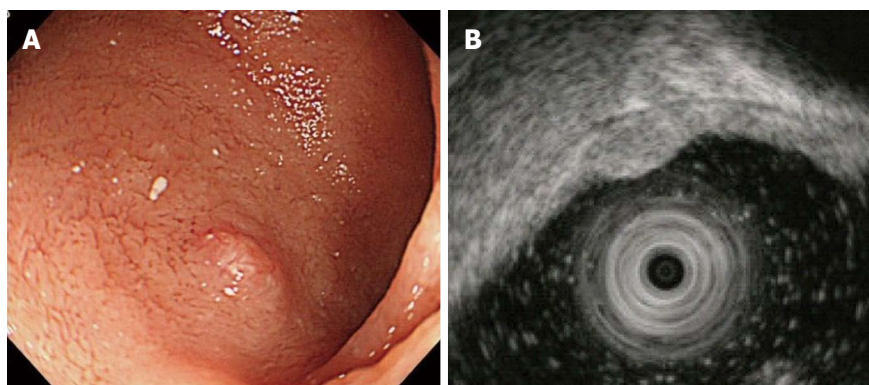


Figure 1 Endoscopic and endoscopic ultrasonography findings. A: Endoscopic image showing an elevated lesion in the anterior wall of duodenal bulb; B: Endoscopic ultrasonography image of the lesion, a 3 mm hypoechoic mass lesion that was located in the submucosal layer.

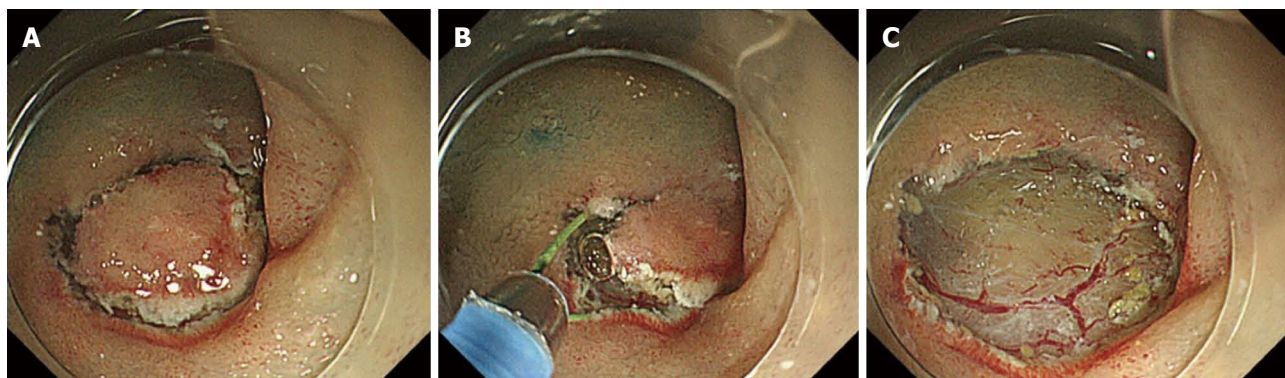


Figure 2 Endoscopic image showing the endoscopic mucosal resection with circumferential mucosal incision procedures. A-C: The entire lesion was removed *en bloc*.

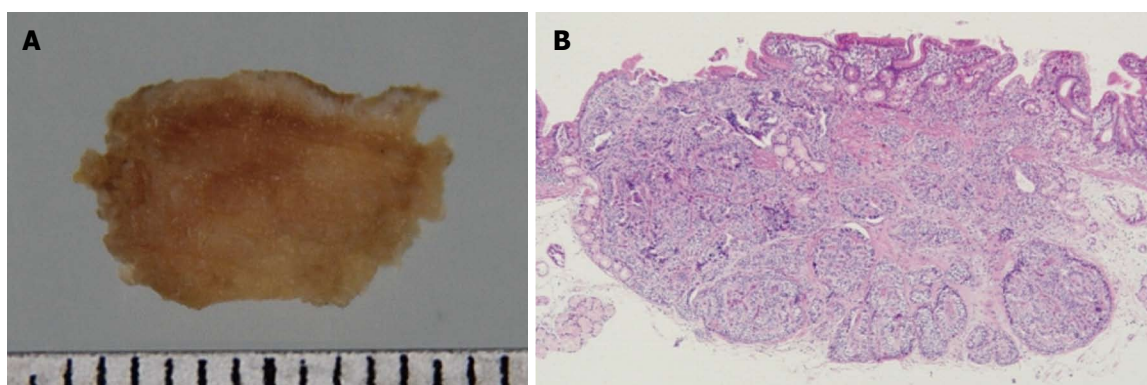


Figure 3 Histopathologic assessment of the resected specimen. A: Macroscopic view of the resected specimen; B: Well-differentiated neuroendocrine tumor was confined to the submucosa (hematoxylin and eosin, original magnification $\times 20$).

copy is deemed unsuitable, laparoscopic techniques could be a suitable alternative^[11].

Several endoscopic approaches have been reported for the treatment of carcinoid tumors. Endoscopic resection of carcinoid tumors with polypectomy or strip biopsy with grasping forceps is sometimes associated with margin involvement and crush injury of the resected specimens^[12-14]. EMR with band ligation, which is clinically accepted for R0 resection method for carcinoid tumors in the rectum, has been scarcely reported in the duodenal lesions, and its safety profile for the treatment of duodenal carcinoids is unknown^[15,16]. We believe that duodenal wall is thin, and band ligation of duodenal wall has a potential risk of muscular involvement. Endoscopic submucosal dissection, which is an emerging technique for the treatment of superficial GI lesion, has high perforation rates for the treatment of duodenal carcinoids (Suzuki *et al.*^[17]; 2/3 perforations, Matsumoto *et al.*^[18]; 2/5 perforations). Meanwhile, EMR-CMI was originally introduced as a preferred technique for large colonic lesions by Moss *et al.*^[19]. They reported that EMR-CMI resulted in deeper submucosal resections histologically compared to conventional EMR, which would be a preferred feature for the resection of duodenal carcinoids originating from the submucosa. In the present study, in which the tumors originated from the submucosa, R0 resection was successfully completed in all of the cases without any complications. We believe that adequate injection of hyaluronic acid solution into the submucosa and careful mucosal incision using a scissor-type knife was key to perform EMR-CMI safely. The average resection time, of nearly 20 min, was considered to be a safe even for older patients.

In conclusion, EMR-CMI may be a safe and effective approach for the treatment of duodenal carcinoids less than 10 mm in diameter in the absence of lymph node invasion or distant metastases. We hope that further clinical studies will help to verify these findings.

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Interference between pacemakers/implantable cardioverter defibrillators and video capsule endoscopy

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Abstract

Our Letter to the Editor, related to the article "Small bowel capsule endoscopy in patients with cardiac pacemakers and implantable cardioverter defibrillators: Outcome analysis using telemetry" by Cuschieri *et al*, comments on some small errors, that slipped into the authors discussions. The given informations concerning the pacemaker- and implantable cardioverter defibrillators modes were inaccurate and differ between the text and the table. Moreover, as 8 of 20 patient's pacemakers were programmed to VOO or DOO ("interference mode") and one patient was not monitored by telemetry during capsule endoscopy, 9 of 20 patients (45%) lack the informations of possible interference between capsule endoscopy their implanted device. Another objection refers to the interpretation of an electrocardiogram (figure 1, trace B) presented: in contrast to the author's opinion the marked spike should be interpreted as an artefact and not as "undersensing of a fibrillatory wave". Finally, three comments to cited reviews were

not complete respectively not quoted correctly.

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Key words: Capsule endoscopy; Small bowel capsule endoscopy; Interference; Cardiac pacemaker; Implantable cardioverter defibrillator; Telemetry

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TO THE EDITOR

In our perception, small errors crept in the interesting article by Cuschieri *et al*^[1] "Small bowel capsule endoscopy in patients with cardiac pacemakers and implantable cardioverter defibrillators: Outcome analysis telemetry review". Therefore it should be subject to the following comments.

First of all, the informations concerning the pacemaker-/implantable cardioverter defibrillators (ICD)-modes, the devices were programmed into during the small bowel capsule endoscopy (SBCE), given in table 1 differ from the informations in the text: whereas the text referring to table 1 contents the information, that "three were set to DDD, six to DDDR, one to DOO, four to VOO, one to VVIR, and one to AAI→DDD (table 1)", the presented table 1 shows three set to DOO, no one was set from AAI to DDD and five were set to VOO [Pacemaker-Code (North American Society of Pacing and Electrophysiology-NASPE and British Pacing and Electrophysiology Group-BPEG: the first letter identifies the chamber paced, the second letter identifies the chamber sensed: V - ventricular, A - atrial, D - dual; the third letter identifies the response to sensing: I - inhibited, T - triggered, D - dual; the fourth letter identifies

the response rate (R)]. The error may partially result from the fact, that the authors did not clearly understand the different meaning of the “→” and the “↔” arrows. “AAI ↔ DDD” does not mean a change in programming, but describes a novel pacemaker function, allowing to change from the AAI- to the DDD-mode automatically, if necessary, and it describes the “managed ventricular pacing” function in Medtronic-pacemakers.

As a second remark, the study included 20 patients, in 8 of whom the pacemaker were programmed to VOO or DOO. In these modes (“interference mode”), pacemakers revert to noise-mode function stimulating the ventricle (VOO) or atrium and ventricle (DOO) without sensing the native rhythm. Additionally, one patient (DDD-Mode, table 2) was not monitored during capsule endoscopy (CE). Consecutively, in 9 of 20 patients (45%) the question of the study, in how far SBCE would influence pacemakers, could not be answered, as the pacemakers cannot be influenced at all. Considering to our study^[2] without evidence of interference between CE and implantable cardioverter defibrillators (ICDs) it remains unclear, why the sensing function of the ICDs was turned off.

The third objection refers to the spike in figure 1, trace B, preceding the third (narrow) QRS-complex: QRS-complexes # 4, 5 and 6 are clearly stimulated, proving that ventricular stimulation works well in this patient. So the stimulus preceding QRS-complex 3 cannot be a ventricular one, because it should be able to capture the ventricle. There is no pacemaker-system available with mode switching to AAI or AOO. So if mode switch was the reason for this spike, it must stimulate the ventricle. Moreover: the orientation of this “spike” is exactly antipodal (positive in lead 1, negative in lead 2) compared with the orientation of the effective ventricular spikes (negative in lead 1, positive in lead 2), this is most unlikely in conventional holter/telemetry recordings, usually you find same polarities for atrial and ventricular spikes in surface electrodes. So this “spike” should be interpreted as an artefact.

In two patients, the authors assumed “inappropriate pacer spikes due to undersensing of very subtle atrial fibrillation”, and they mentioned, that similar episodes were documented before and after CE. In this context, it would be interesting, if those patients suffered from paroxysmal, persistent or permanent atrial fibrillation. In the opinion of the authors “the mostly likely possibility is that the thresholds for atrial pacing were set too high”. According to this presumption, further details to the programming of the pacemakers should have been presented.

Another concern against the study of Cuschieri *et al*^[1]

is that there is only a few number of patients left (11/20) for the (real) investigation of interference between CE and devices to be able to derive their conclusions from their data.

Finally, there are three comments to the cited references: (1) The radiated power of CE is mentioned with 50 nW. The reference cited in this connection is wrong. CE is not mentioned in this article^[3]; and (2) In our study for interference between CE and ICD^[4], we “electrically simulated the situation in a patient”. The pacemakers and CE were placed in a saline solution (resistivity corresponding to that of low frequency range of muscle tissue), not water, in analogy to a study, in which the interference behaviour of mobile phones with respect to pacemakers was investigated^[5]; and (3) The authors discuss that “it is conceivable that the site of entry for the noise signals is the unshielded part of the connector block which could occur, as the swallowed CE passes posterior to the heart while descending through the esophagus, consisting with studies on mobile phones”, as a possibility for interference between CE and devices. Cited references for this hypothesis are the study of Dubner *et al*^[6] and our study^[4]. In none of the cited studies mobile phones were used.

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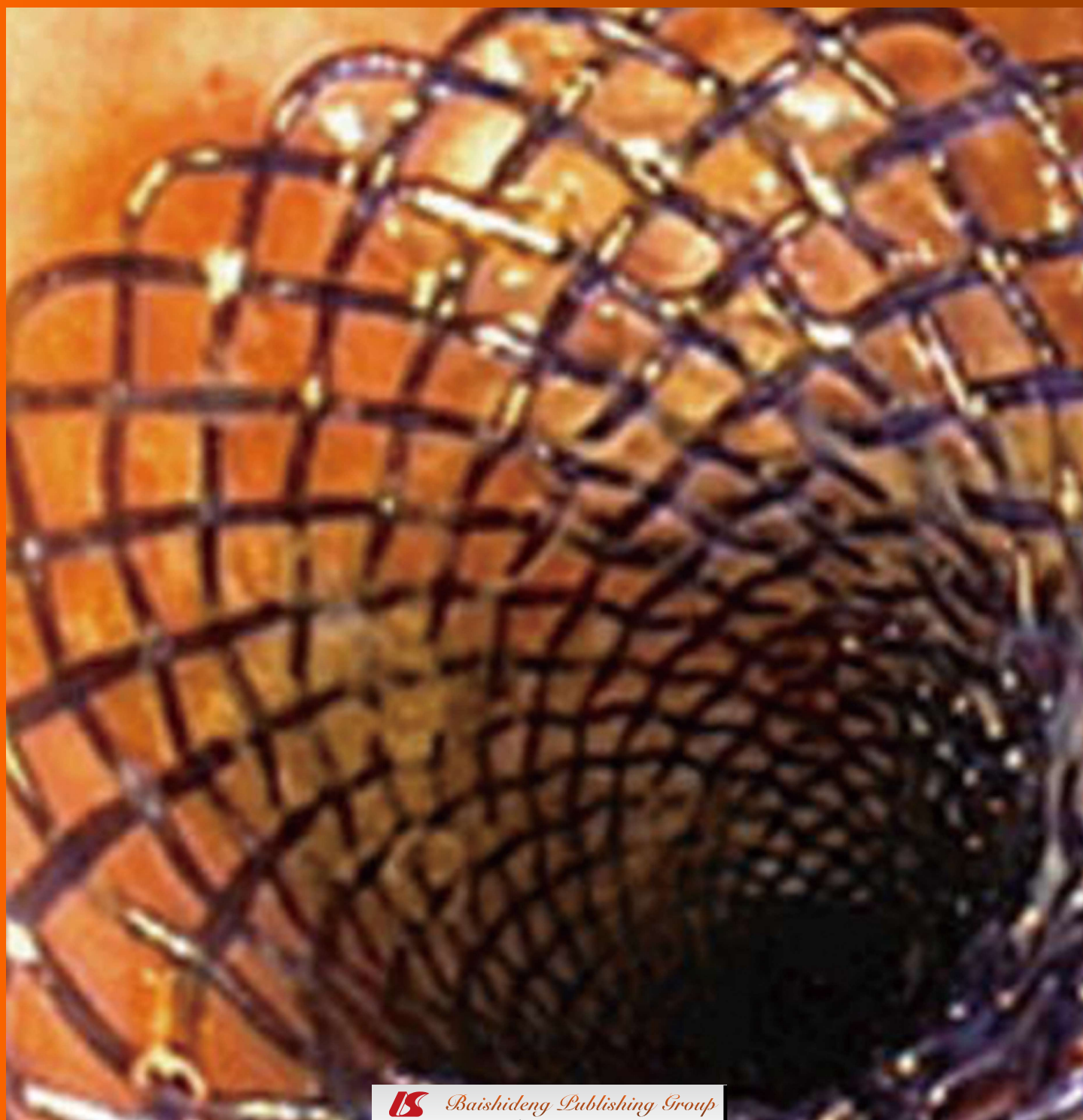
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Single operator choledochoscopy and its role in daily endoscopy routine

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Abstract

Different diagnostic procedures exist for the detection of bile duct lesions in clinical practice. However, neither retrograde contrast imaging of the bile duct endoscopic retrograde cholangiopancreatogram nor other imaging procedures allow a safe diagnosis of the lesions. Therefore choledochoscopy may be a useful diagnostic procedure in macroscopic assessing lesions of the bile duct. Even if the diagnostic sensitivity and specificity is not sufficient, first studies suggest an enhanced diagnostic accuracy for choledochoscopy. Since the progress of choledochoscopy has started in the 1970 different improvements were achieved. Meanwhile, the examination can be performed by an examiner and samples can be taken. Image and Resolution quality has improved over the past years, also. The SpyGlass system is a technically advanced cholangioscopic device to provide endoscopic diagnosis in case of inconclusive bile duct findings. Further more, two more lumina allow specific biopsy forceps and optical fibers for electrohydraulic or laser lithotripsy. The most frequent useful insert of SpyGlass in clinical practice are in complex gallstones and bile duct lesions of unclear dignity.

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Key words: Endoscopic retrograde cholangiography; Endoscopic choledochoscopy; SpyGlass Direct Visualization System™; "Mother-baby" endoscope technique; Gallstones; Bile duct lesions

Core tip: To date, technical restrictions of endoscopic retrograde cholangiopancreatogram may explain the insufficient sensitivity of diagnostics when biliary changes are suspected. Therefore choledochoscopy may be a direct diagnostic procedure to help. SpyGlass™ is a technically advanced cholangioscopy system facilitating diagnostics in the bile duct due to its single-operator feature. Different studies reported a clearly enhance diagnostic accuracy for this technique. However, the visualization of bile duct lesions itself is of great value since it offers precise dignity evaluation based on macroscopic criteria.

Hoffman A, Rey JW, Kiesslich R. Single operator choledochoscopy and its role in daily endoscopy routine. *World J Gastrointest Endosc* 2013; 5(5): 203-210 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/203.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.203>

INTRODUCTION

To date, the prediction of dignity for indistinct bile duct lesions in clinical practice are a difficult endeavour and mean a true diagnostic challenge to all disciplines involved. Neither retrograde contrast imaging of the bile duct endoscopic retrograde cholangiopancreatogram (ERCP) nor other imaging procedures allow for a safe diagnosis of the type if biliary duct findings are inconclusive like the ones experienced with strictures or intraluminal defects^[1]. Even with steadily improved endosonography and the use of microprobes enhancing bile duct lesion imaging, a number of limitations set by these investigation methods are still to overcome^[2]. Choledo-

choscopy may be a direct diagnostic procedure to help in macroscopically assessing inconclusive lesions inside the biliary duct system. However, technical means were limited so far as the “mother-baby” system had to be operated by two interventionalists, while confirming the results of malignancy-suspicious findings remained a true histological challenge^[3-5]. Technical restrictions of the above mentioned procedures may explain the insufficient sensitivity of diagnostics when it comes to biliary changes^[6].

SpyGlass is a technically advanced cholangioscopy system facilitating diagnostics in the bile duct due to its single-operator feature. First studies show that the use of SpyGlass may clearly enhance diagnostic accuracy. First of all, cholangioscopy-guided tissue acquisition in the biliary duct is much easier to perform even though diagnostic sensitivity and specificity require further improvement^[7].

PROGRESS IN CHOLEDOCHOSCOPY

Since the 1970s, choledochoscopy is used mainly in centers focussing on hepatobiliary diagnostics to macroscopically diagnose bile duct lesions^[8]. This procedure directly investigates the biliary tract endoscopically and benefits from directly assessing the mucous membrane so as to help evaluate the dignity of inconclusive lesions in the bile duct^[9]. For the first time, this offered diagnostic options superior to other imaging procedures in this region^[8,9].

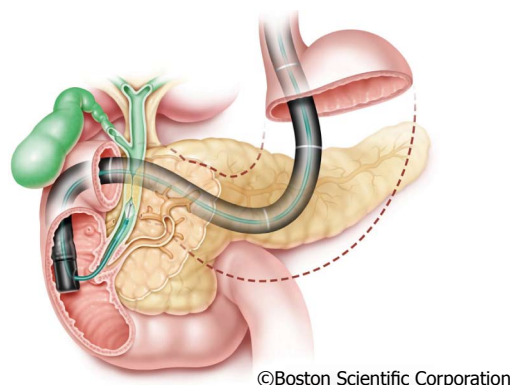
In choledochoscopy, a general distinction is made between percutaneous transhepatic and retrograde endoscopic access using the so-called “mother-baby” endoscope technique^[10,11].

With the frequently used and less invasive “mother-baby” endoscope technique, a thin choledochoscope (“baby scope”) is introduced in the bile duct for ERCP *via* instrument channel of a duodenoscope (“mother scope”) (Figure 1).

However, a number of limitations using the mother-baby choledochoscopy technique are still to cope with: The first fiber optic choledochoscopies provided a poor image quality with low resolution and poor illumination of the bile duct. The steerability of the microendoscope in only two planes considerably limited the maneuverability in the bile duct. Another clear disadvantage of the mother-baby endoscope technique was the need of two operators required to perform the procedure. However, the greatest detriment of all for a great many years was the fact that tissue acquisition was impossible which limited the use to diagnostic indications.

In the 1980s, a second generation of choledochoscopies was introduced providing a working channel and offering improved maneuverability.

In the late 1990s, first prototypes of video choledochoscopies were tested and first images of staining or virtual chromoendoscopy in the bile duct were presented, yet more to provide evidence of the possible and feasible than to introduce a serious means of routine endoscopy.



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Figure 1 Principle of “Mother-Baby” endoscope technique.



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Figure 2 Single-operator choledochoscopy system: “SpyGlass Direct Visualization System”.

To date, all available choledochoscopies on the market are fiber optic systems and all reports of high-resolution video choledochoscopies are based on a few prototype case reports only^[12-14].

The first single-operator choledochoscopy system was presented in 2005 by Boston Scientific under the name “SpyGlass Direct Visualization System”[®]. The system is a technically advanced cholangioscopic device to provide endoscopic diagnosis in case of inconclusive bile duct findings^[15].

The system does not only without the need of a second operator but also visualizes the bile duct lesions in a way to allow for effective assessment of their dignity (Figure 2). The targeted tissue acquisition performed by the same operator represented another novelty and allowed for further investigation of abnormalities^[15].

SPYGLASS DIRECT VISUALIZATION SYSTEM

The SpyGlass system consists of an integrated platform with a light source, camera, and monitor (Figure 3). Proven fiber optic technique is still used to illuminate the bile duct, yet with improved resolution to optimize bile duct visualization. An advanced steering system of the 10 Fr cholangioscopy catheter to be attached to the duodeno-



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Figure 3 SpyGlass system as integrated platform with light source, camera and monitor.

scope has been re-designed and eliminates the need for a second operator to handle the choledochoscope^[15,16]. This steering unit with its two steering wheels provides steering options in four planes, comparable to standard endoscopes (Figure 4).

The steering unit is positioned on top of the so-called 10-Fr guiding catheter or SpyScope equipped with four lumina (Figure 5). One lumen is intended for use of the fiber optic system to be advanced to the SpyScope's end. The fiber optic system consists of a coherent bundle of optical fibers surrounded by light fibers representing the system's most fragile component. Two more lumina are used for irrigation and a fourth one serves as the working channel for the specific biopsy forceps.

The SpyScope itself is advanced into the bile duct similar to the mother-baby technique *via* duodenoscope working channel. Due to the particular stability of the SpyScope offering optimum protection to the optical glass fibers the sometimes unavoidable angulation may be achieved during introduction into the bile duct when fully activating the Albarran lever. When in the bile duct, mucus or tough bile may be removed *via* the SpyScope's two dedicated irrigation channels by foot-activating the irrigation device. The most important access offers a 1.2 mm working channel. A specifically designed biopsy forceps (SpyBite) and also optical fibers for electrohydraulic or laser lithotripsy may thus be introduced into the biliary tract *via* working channel (Figure 6).

SpyGlass technique

First, the steering unit is attached to the duodenoscope handle. Normally, the guidewire already positioned in the bile duct at the distal end of the guiding catheter is now threaded in to the SpyScope *via* working channel to ease bile duct intubation using the guiding catheter (SpyScope) and the guidewire as a guide rail. Before advancing the guiding catheter (SpyScope) *via* duodenoscope working channel to intubate the bile duct the optical fiber should be advanced to the tip with care through a suitable working channel. Self-explanatory symbols pointing to the correct access support the process.

Having reached the papilla the Albarran lever is easily

used to achieve the required angulation facilitating intubation of the bile duct. With the SpyScope in the bile duct the optical fiber may be carefully advanced *via* catheter tip to directly inspect the bile duct lumen. Obstructive mucus or tough bile may be removed using the SpyScope's foot-activated dedicated irrigation device.

INDICATIONS

Among the most frequent clinical uses of the SpyGlass choledochoscopy are complex gallstones and bile duct lesions of unclear dignity (Figure 7).

Use of SpyGlass in bile duct lesions

Diseased bile ducts often are a clinical challenge since diagnostics have their limitations; on the other hand, quick and therapeutically relevant decisions for the patient may urgently be required^[17,18]. Sound assessment of the dignity is essential for therapy planning, however often difficult. Especially histological confirmation of malignity-suspicious findings is a key issue gastroenterologists have to cope with^[19-21]. Cholangiocarcinoma portend a dismal prognosis which makes an early decision for surgery based on timely diagnosis desirable^[17]. Limited diagnostic approaches hardly offer any solution, and patients may not be diagnosed properly until symptomatic with the tumor being in an advanced stage beyond any curative therapy^[19]. Brush cytology and endosonographically guided fine needle aspiration biopsy may be the preferred investigation methods to date, yet in almost all the studies the low sensitivity of the method is a serious issue^[21-26].

Cytology may provide good specificity which is why false positive cases are rarely found in literature but the low sensitivity of about 50% remains a key problem of this method^[21-26].

The golden standard when diagnosing bile duct diseases remains to be ERCP^[27]. Using ERCP provides good imaging of the bile duct anatomy including any pathological changes such as strictures and intraluminal filling defects. However, they might be insufficient, especially in early stages, to make definitive therapy decisions.

Special risk populations *e.g.*, patients with a primary sclerosing cholangitis (PSC), have an increased carcinoma risk due to years of chronic bile duct inflammation^[28].

Checks on a regular basis are supposed to detect in a timely manner carcinomatous prestages especially in such patient collective with multiple bile duct changes, yet the problem of safe differentiation between inflammatory/benign and dysplastic, potentially malign lesions remains unsolved.

Peroral choledochoscopy as the direct visualization of the bile duct therefore represents an important and interesting enhancement of ERCP^[7,29].

Since the introduction of the SpyGlass Direct Visualization System several studies and a number of publications describe a variety of clinical experiences^[15] (Table 1). A center point of the publications was the accessibility and macroscopic imaging of suspicious lesions. A cur-

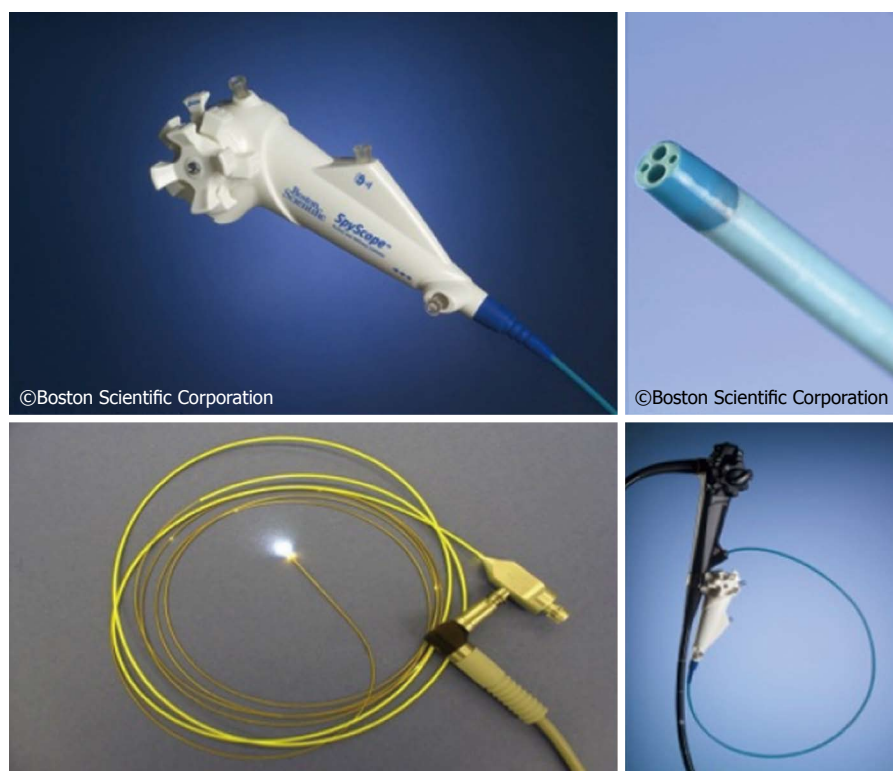
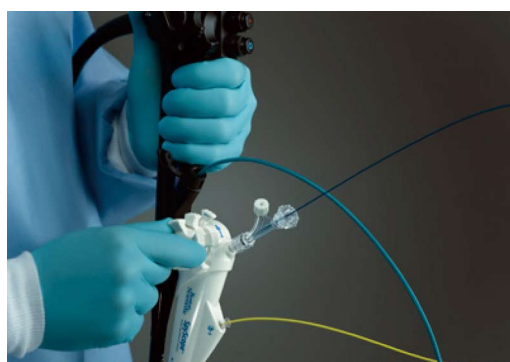


Figure 4 Components of the SpyGlass system.



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Figure 5 SpyScope.

rent study documents that the sensitivity of macroscopic evaluation using SpyGlass is significantly higher than with ERCP (81% *vs* 53%)^[29]. Another multi-center prospective study with nearly 300 enrolled patients investigated as a primary study endpoint whether there was success in reaching the suspicious lesion and acquiring tissue^[7].

Secondary study endpoints were the sensitivity and specificity of the cholangioscopically guided biopsies. A total of 96% of the biliary strictures were reached endoscopically using the cholangioscopic catheter and provided sufficient visualization. Additional tissue acquisition was possible in 88% of the cases^[7].

In his pilot study, researchers was able to clearly show in 35 patients that SpyGlass not only ensures reaching the lesions but also allows for sufficient macroscopic evaluation of findings with a sensitivity of 100% and specificity

of 77%. In an additional SpyGlass-guided biopsy a sensitivity of 71% and specificity of 100% were achieved, both significantly superior to brush cytology results^[30].

The most frequently expressed criticism with this method is that sensitivity of the cholangioscopically guided tissue acquisition is low; in some papers it even had to be adjusted downwards. To be stressed are quantity and quality of the acquired tissue frequently considered insufficient by pathologists. Grounds may be the too small a size of the tissue samples acquired using the SpyBite forceps offering no bigger option. To ensure sufficient amount of tissue for pathological investigation multiple tissue acquisitions (3 to 4 biopsies) from the lesion in question are recommended^[15,31]. But apart from the already mentioned histological criteria, macroscopic aspects should not be ignored. For effective differentiation of lesions, their macroscopic appearance in the bile duct is of great importance. It is in fact known that almost all malign changes in the hepatobiliary system are characterized by significant vascularization including tortuous and dilated vessels. In addition, exophytic growth, ulcerations, and being raised are considered further aspects of malignancy suspicion allowing for correct diagnosis^[32].

In a retrospective study including 129 patients, the initial working diagnosis was modified in 68% of the patients with biliary strictures based on the SpyGlass investigation^[33]. The significance of this result cannot be overestimated considering that in as many as 45% of the patients an initial tumor suspicion of the lesion was not confirmed when SpyGlass was used for diagnosis meaning for the individual patient a completely different thera-

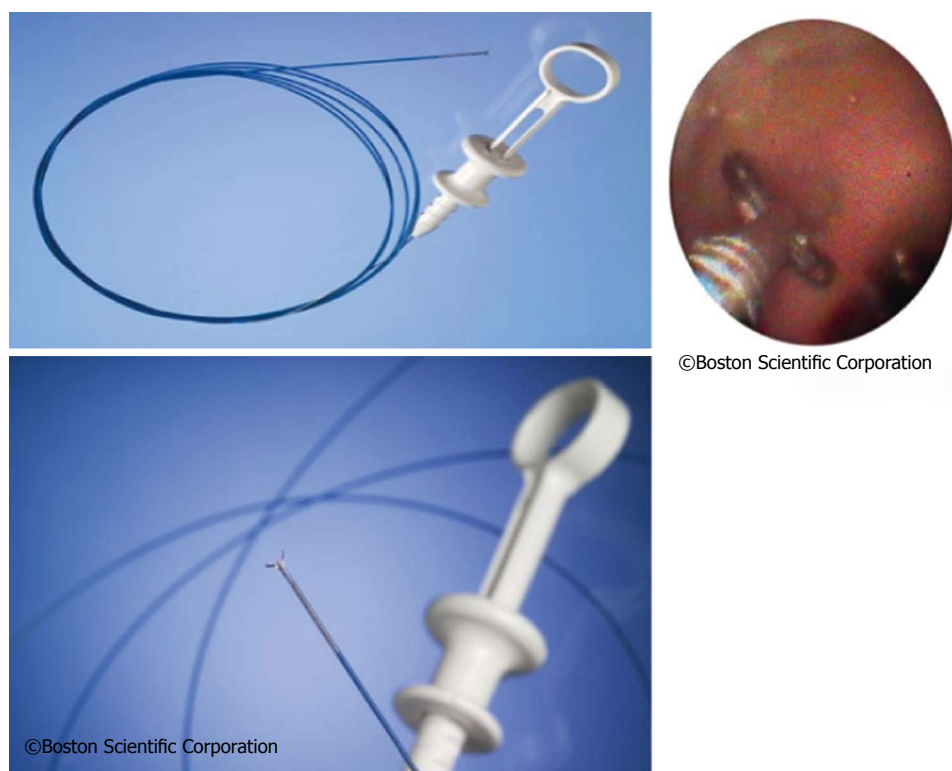


Figure 6 Re-designed biopsy forceps.

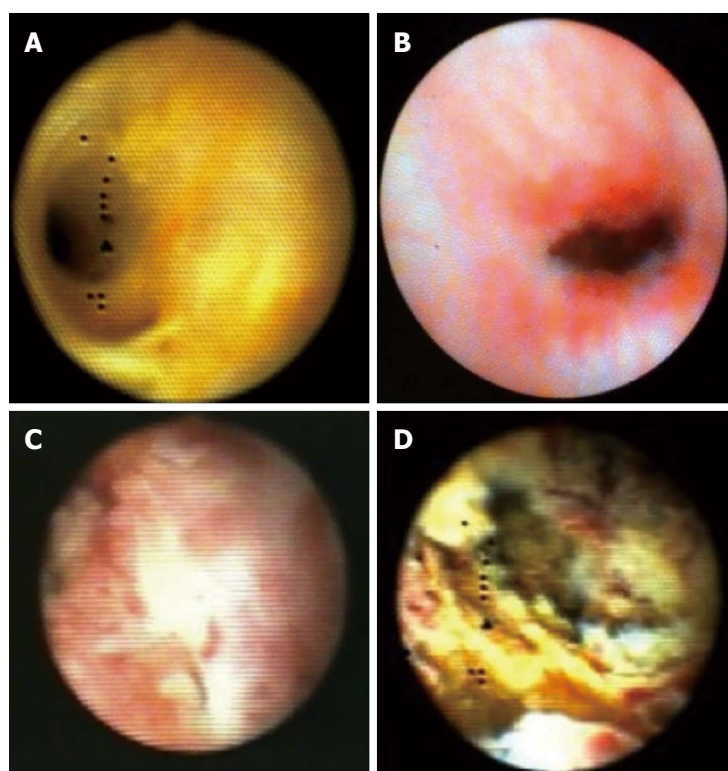


Figure 7 Typical cholangioscopic findings (source: A Hoffman). A: Normal bile duct; B: Inflammation with stricture; C: Cholangiocellular carcinoma with villous like appearance; D: Cholangiocellular carcinoma with ulcers and intraluminal growth.

peutic proceeding.

Use of SpyGlass in the treatment of gallstones

Cholecysto- and choledocholithiasis are an important issues in the Western industrialized countries and a main

reason for hospitalization due to gastrointestinal complaints.

An estimated 15%-20% of the Caucasian population is supposed to suffer from some sort of gallbladder disease, 15%-20% of which also have stones in their bili-

Table 1 Overview about the sensitivity and specificity of SpyGlass

First author, publication, year	Study design	Patient (n)	Sensitivity for visual diagnosis/biopsy	Specificity for visual diagnosis/biopsy	PPV for visual diagnosis/biopsy	NPV for visual diagnosis/biopsy	Accuracy for biopsy/visual diagnosis
Chen ^[15] , 2007	Prospective study	35	100%/71%	77%/100%	70%/100%	100%/87%	
Ramchandani <i>et al.</i> , 2012	Prospective study	36	95%/82%	79%/82%	88%/100%	92%/100%	89%/82%
Hartmann <i>et al.</i> , 2012	Retrospective analysis	89	/57%	/100%	/100%	/68%	/78%
Chen <i>et al.</i> , 2011	Prospective study	297	77.8%/48.9%	82%/98%	80%/100%	80%/72%	80%/75%
Kalaitzakis <i>et al.</i> , 2012	Retrospective analysis	141	72%	97%	93%	86%	88%

PPV: Positive predictive value; NPV: Negative predictive value.



Figure 8 Stone after direct probe-targeted fragmentation via short-pulsed laser waves (holmium laser) (Source: A Hoffman).

ary tracts. Normally, ERCP succeeds in removing these stones from the biliary duct system avoiding potential complications such as pancreatitis or cholangitis^[34,35]. In some cases, however, stones cannot be removed *via* traditional ERCP due to the large size of the calculi or their specific anatomy. Unfortunately, the success rate of extracorporeal shock wave lithotripsy with subsequent endoscopic extraction is also very low in these special cases^[33-35]. Using the SpyGlass system with its option of a full-fledged working channel in addition to dedicated irrigation, a probe may be advanced under direct visual control until it reaches the stone to perform lithotripsy using short-pulsed laser waves (Nd-YAG-2 laser or Holmium laser) or electrohydraulic waves^[36-38]. Direct advancement of the probe to the stone reduces the risk of bleeding or perforation of the bile duct and significantly increases the success rate of stone extraction versus extracorporeal shock wave lithotripsy^[39,40] (Figure 8).

Another important aspect is stones overlooked during ERCP. In two studies-one particularly with PSC patients, the other after routine ERCPs-an immediately following SpyGlass procedure diagnosed an initially overlooked 29% and 30% of stones^[41,42].

COMPLICATIONS

Based on published data for SpyGlass to date, only a few but not severe procedure related complications are to be assumed. But currently published complications do not differ from those of therapeutic ERCP without accom-

panying cholangioscopy. Apart from the complications associated with ERCP a complication rate of only 0.3% is assumed whereas it is difficult to differentiate whether the complication was caused by ERCP itself or by the cholangioscopy^[33].

The most common complication reported is cholangitis (3%). In some reports ascending cholangitis or cholangitis with intrahepatic abscess, especially after taking biopsies are reported. Some cases of ascending cholangitis, which were only marked by jaundice without fever, but white blood cell elevation or positive blood cultures, developed even some days after SpyGlass examination.

Irrigation should not be excessive when proximal of a stenosis especially with already existing cholangitis since it may significantly increase the risk of bacteremia. But all of the published studies are done by experts in ERCP with a low complication rate in all ERCP related therapeutic procedures. There is no published data about the complication rate during the learning curve of choledochoscopy or the complication rate of trainees in ERCP using SpyGlass.

Among other complications are: drop in blood pressure, abdominal pain, pancreatitis, and bile duct perforation caused by the guidewire.

CONCLUSION

The SpyGlass Direct Visualization System introduces a new type of cholangioscope for endoscopic use. Not only can cholangioscopy now be performed by a single operator but the optimized steering unit enables the user to exactly fix the biliary target lesion and acquire tissue providing true diagnostic benefit. The visualization of bile duct lesions itself is of great value since it offers precise dignity evaluation based on macroscopic criteria. Literature includes more and more reports on the safe and efficient use of the unit in clinical practice. Sceptics of the method mostly criticize the low sensitivity of cholangioscopically guided tissue acquisition. Standardization of the number of biopsies and further development of biopsy forceps may result in the desired enhancement of sensitivity.

Even if histological confirmation of the visual findings may remain difficult using SpyGlass-acquired tissue this new investigation method represents a valuable

complement in the diagnostic algorithm of inconclusive bile duct findings in terms of staged diagnostics.

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Endoscopic papillary balloon dilation after sphincterotomy for difficult choledocholithiasis: A case-controlled study

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Abstract

AIM: To evaluate the efficacy and safety of endoscopic sphincterotomy (EST) + endoscopic papillary large balloon dilation (EPLBD) *vs* isolated EST.

METHODS: We conducted a retrospective single center study over two years, from February 2010 to January 2012. Patients with large (≥ 10 mm), single or multiple bile duct stones (BDS), submitted to endoscopic retrograde cholangio-pancreatography (ERCP) were included. Patients in Group A underwent papillary large balloon dilation after limited sphincterotomy (EST+EPLBD), using a through-the-scope balloon catheter gradually inflated to 12-18 mm according to the size of the largest stone and the maximal diameter of the distal bile duct on the cholangiogram. Patients in Group B (control group) underwent isolated sphincterotomy. Stones were removed using a retrieval balloon catheter and/or a dormia basket. When necessary, mechanical lithotripsy was performed. Complete clearance of the bile duct was

documented with a balloon catheter cholangiogram at the end of the procedure. In case of residual lithiasis, a double pigtail plastic stent was placed and a second ERCP was planned within 4-6 wk. Some patients were sent for extracorporeal lithotripsy prior to subsequent ERCP. Outcomes of EST+EPLBD (Group A) *vs* isolated EST (Group B) were compared regarding efficacy (complete stone clearance, number of therapeutic sessions, mechanical and/or extracorporeal lithotripsy, biliary stent placement) and safety (frequency, type and grade of complications). Statistical analysis was performed using χ^2 or Fisher's exact tests for the analysis of categorical parameters and Student's *t* test for continuous variables. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS: One hundred and eleven patients were included, 68 (61.3%) in Group A and 43 (38.7%) in Group B. The mean diameter of the stones was similar in the two groups (16.8 ± 4.4 and 16.0 ± 6.7 in Groups A and B, respectively). Forty-eight (70.6%) patients in Group A and 21 (48.8%) in Group B had multiple BDS (*P* = 0.005). Overall, balloon dilation was performed up to 12 mm in 10 (14.7%) patients, 13.5 mm in 17 (25.0%), 15 mm in 33 (48.6%), 16.5 mm in 2 (2.9%) and 18 mm in 6 (8.8%) patients, taking into account the diameter of the largest stone and that of the bile duct. Complete stone clearance was achieved in sixty-five (95.6%) patients in Group A *vs* 30 (69.8%) patients in Group B, and was attained within the first therapeutic session in 82.4% of patients in Group A *vs* 44.2% in Group B (*P* < 0.001). Patients submitted to EST+EPLBD underwent fewer therapeutic sessions (1.1 ± 0.3 *vs* 1.8 ± 1.1 , *P* < 0.001), and fewer required mechanical (14.7% *vs* 37.2%, *P* = 0.007) or extracorporeal (0 *vs* 18.6%, *P* < 0.001) lithotripsy, as well as biliary stenting (17.6% *vs* 60.5%, *P* < 0.001). The rate of complications was not significantly different between the two groups.

CONCLUSION: EST+EPLBD is a safe and effective technique for treatment of difficult BDS, leading to high

rates of complete stone clearance and reducing the need for lithotripsy and biliary stenting.

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Key words: Endoscopic papillary large balloon dilation; Bile duct stones; Endoscopic sphincterotomy; Cholelithiasis

Core tip: The technique described by Ersoz comprises endoscopic limited sphincterotomy followed by papillary large balloon dilation. In theory, it increases efficacy on the extraction of large bile duct stones, while reducing the risk of bleeding that would occur if a larger sphincterotomy had to be performed, particularly in patients with coagulopathy or surgically modified anatomy, and simultaneously reduces the risk of post endoscopic retrograde cholangio-pancreatography acute pancreatitis that occurs when isolated papillary balloon dilation is performed. In this case-controlled study, the combined technique achieved higher rate of complete stone clearance than isolated endoscopic sphincterotomy, and reduced the need for lithotripsy and biliary stenting, with a similar safety profile.

Rosa B, Moutinho Ribeiro P, Rebelo A, Pinto Correia A, Cotter J. Endoscopic papillary balloon dilation after sphincterotomy for difficult choledocholithiasis: A case-controlled study. *World J Gastrointest Endosc* 2013; 5(5): 211-218 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/211.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.211>

INTRODUCTION

Endoscopic sphincterotomy (EST), first described by Classen *et al*^[1] in 1974, remains the standard procedure for the treatment of bile duct lithiasis. Some years later, in 1983, Staritz *et al*^[2] described endoscopic papillary balloon dilation (EPBD), which emerged as an alternative to EST, with comparable efficacy in patients with up to 3 bile duct stones (BDS) and ≤ 10 mm of diameter^[3]. EPBD is associated with a lower risk of bleeding than EST, although an increased risk of post endoscopic retrograde cholangio-pancreatography (ERCP) acute pancreatitis has been reported^[3-10]. When performed to a diameter that does not exceed 10 mm, EPBD may preserve the function of the sphincter of Oddi^[11,12], reducing late complications such as recurrence of biliary stones and papillary stenosis^[13-15]. However, both techniques have limitations in the setting of large (≥ 10 mm) BDS. Indeed, the completion of a large sphincterotomy may be limited by local anatomy and is associated with a higher risk of bleeding, while performing EPBD above 10 mm is associated with an increased risk of post-procedural acute pancreatitis^[3-9]. Because of these considerations, in the setting of large BDS the biliary orifice often cannot be safely opened wide enough to enable their extrac-

tion, and additional mechanical lithotripsy is often needed^[6,16-19]. To overcome these limitations, in 2003, Ersoz *et al*^[20] described the technique of endoscopic papillary large diameter (12-20 mm) balloon dilation after limited sphincterotomy (EST+EPLBD), for the treatment of large BDS. This combines the advantages of EST and EPBD by increasing the efficacy of stone extraction while minimizing complications of both EST and EPBD when used alone^[20,21]. This technique introduced a new concept that is different from isolated EPBD, as it actually results in the rupture of the orifice and permanent loss of the sphincter. It is progressively gaining widespread acceptance, with many authors reporting promising results regarding its efficacy and safety over the last few years^[10,11,18, 21-29]. In this study, we aimed to evaluate the efficacy and safety of EST+EPLBD in the treatment of difficult BDS, performing a comparative analysis with a control group of patients submitted to isolated EST.

MATERIALS AND METHODS

This was a retrospective single center study, covering a 2-year period, from February 2010 to January 2012. Patients meeting the following inclusion criteria were consecutively included: (1) referral for ERCP because of bile duct lithiasis; (2) 18 years of age or older; (3) informed consent obtained before ERCP; (4) large BDS identified at ERCP (≥ 10 mm in diameter, single or multiple); and (5) deep cannulation of the bile duct achieved without precut. Patients with previous ERCP, ongoing acute pancreatitis or cholecystitis, history of previous gastric or biliary surgery (except for cholecystectomy), severe haemostatic disorders, intrahepatic lithiasis and concomitant pancreatic or biliary malignant disorders were excluded. According to the study design, patients who underwent EST+EPLBD were included in Group A, while patients who were submitted to EST alone were allocated to a control group (Group B). Every ERCP was performed using Olympus® TJF 160 VR or TJF 145 side-viewing endoscopes. Patients were under propofol sedation assisted by an anaesthesiologist. Deep biliary cannulation was generally attained with a triple lumen sphincterotome (Papillotomy knife, wire-guided type, Olympus®). Stone size and number were documented on the initial diagnostic cholangiogram at ERCP. EST was performed over a 0.035 guide wire (Hydra Jagwire® guide wire, Boston Scientific Corp.®). Patients in Group A underwent papillary balloon dilation using a through-the-scope balloon catheter for oesophageal/pyloric dilation (CRE® wire-guided balloon dilatation catheter, Boston Scientific Microvasive®), gradually inflated to 12-18 mm according to the size of the largest stone and the maximal diameter of the distal bile duct on the cholangiogram. The biliary sphincter was considered adequately dilated when the waist of the balloon had completely disappeared in the fluoroscopic image. The fully expanded balloon was maintained in position for 60 s and then deflated and removed (Figure 1). Stones were removed using

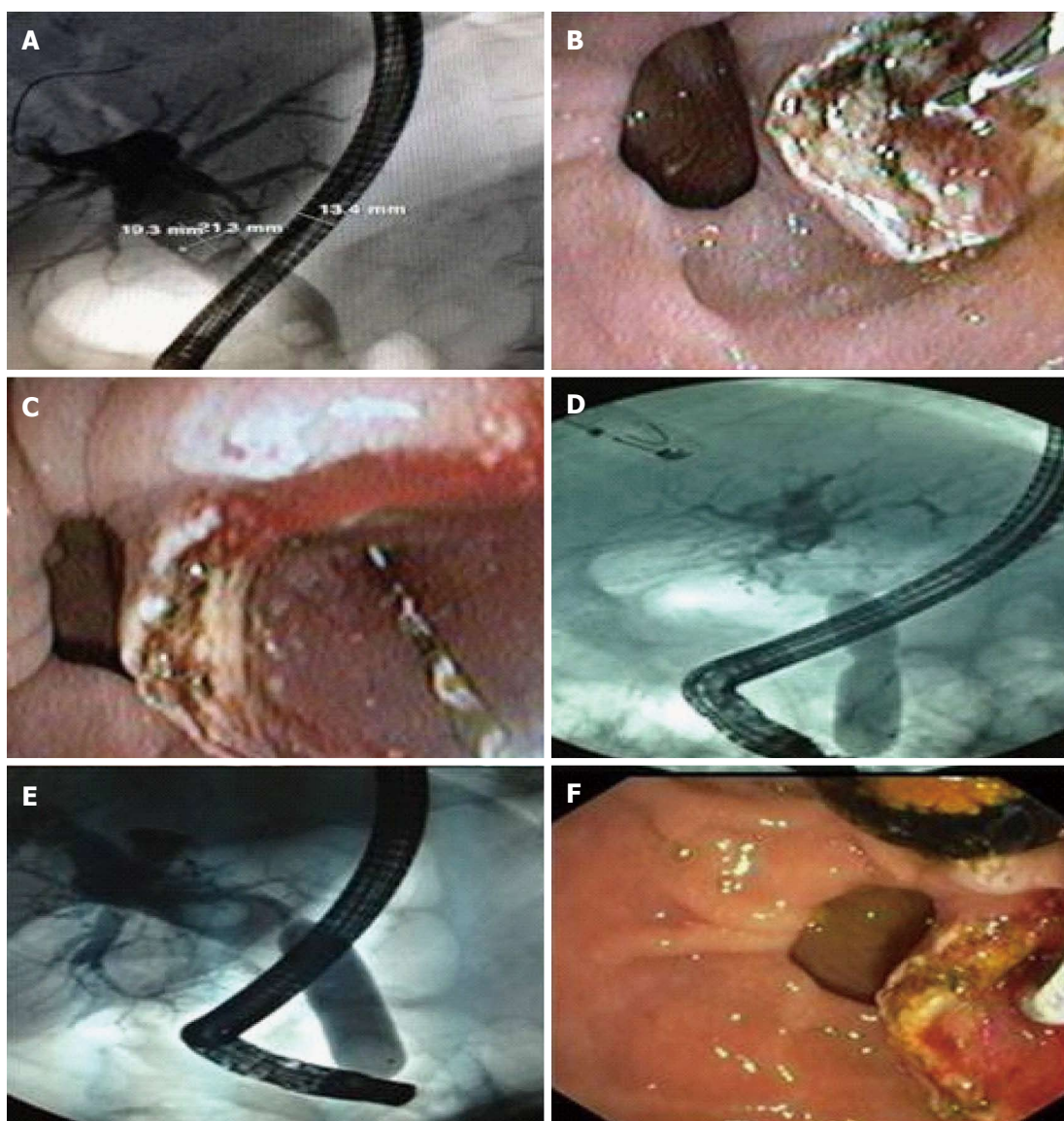


Figure 1 Combined endoscopic technique: Limited endoscopic sphincterotomy followed by endoscopic papillary large balloon dilation.

a retrieval balloon catheter (V-System single-use triple lumen stone extraction balloon, Olympus®) and/or a Dormia basket (Web® extraction basket, Wilson-Cook Medical Inc.®). When necessary, mechanical lithotripsy (BML 4Q, Olympus®; Fusion Lithotripsy Basket, Wilson-Cook Medical®) was performed to fragment the stones prior to removal. Complete clearance of the bile duct was documented with a balloon catheter cholangiogram at the end of the procedure. In the case of residual lithiasis, a biliary 7 Fr double pigtail plastic stent was placed and a second ERCP was planned within 4-6 wk. Some patients were sent for extracorporeal lithotripsy prior to subsequent ERCP. At the end of each ERCP, 100 mg rectal indomethacin was routinely given. Prophylactic antibiotics were not routinely administered. The primary efficacy endpoint was the success rate regarding complete clearance of the bile duct. Secondary endpoints included other efficacy criteria (number of ERCP until achievement of complete stone extraction, use of mechanical or

extracorporeal lithotripsy, biliary stenting) and assessment of the safety of the procedure (occurrence of complications such as bleeding, pancreatitis, cholangitis or perforation, which were classified and graded according to the 1991 consensus guidelines)^[30]. To assess complications, blood samples for complete blood count, liver function tests and serum levels of amylase, lipase and C-reactive protein were routinely obtained 24 h after the procedure.

Ethical considerations

This was a retrospective case-controlled study. All patients provided written consent to undergo ERCP and were informed of the risks and potential benefits of the procedures.

Statistical analysis

Statistical analysis was performed using SPSS version 16.0 (SPSS® Inc., Chicago, IL, United States). Categorical parameters were analyzed using χ^2 or Fisher's exact tests

Table 1 Population baseline characteristics

Characteristics	EST+EPLBD	EST	P value
n	68 (61.3%)	43 (38.7%)	
Age (yr)	70.8 ± 13.4	72.8 ± 12.4	NS
Female gender	45 (66.2%)	28 (65.1%)	NS
Multiple lithiasis	48 (70.6%)	21 (48.8%)	0.005
Largest stone diameter (mm)	16.8 ± 4.4 (12-30)	16.0 ± 6.7 (10-30)	NS
Bile duct diameter (mm)	17.1 ± 3.4 (8-35)	16.4 ± 7.2 (8-30)	NS
Presence of biliary stricture	4 (5.9%)	2 (4.7%)	NS
Balloon dilation diameter (mm)			
12	10 (14.7%)		
13.5	17 (25.0%)		
15	33 (48.6%)		
16.5	2 (2.9%)		
18	6 (8.8%)		

EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; NS: Not significantly.

and continuous variables were analysed by Student's *t* test. Quantitative data were summarized as the mean ± SD. A *P*-value of less than 0.05 was considered statistically significant.

RESULTS

From February 2010 to January 2012, 111 patients with large BDS meeting the inclusion criteria were enrolled in the study. Sixty-eight (61.3%) patients underwent EST+EPLBD and were included in Group A. Group B, the control group, included 43 (38.7%) patients who underwent isolated EST, with no subsequent papillary balloon dilation. Forty-eight (70.6%) patients in Group A and 21 (48.8%) in Group B had multiple BDS (*P* = 0.005). The mean diameter of the stones was 16.8 ± 4.4 and 16.0 ± 6.7 in Groups A and B, respectively (*P* = Not significant). Overall, balloon dilation was performed up to 12 mm in 10 (14.7%) patients, 13.5 mm in 17 (25.0%), 15 mm in 33 (48.6%), 16.5 mm in 2 (2.9%) and 18 mm in 6 (8.8%) patients, taking into account the diameter of the largest stone and that of the bile duct. Baseline characteristics of patients in both groups are summarized in Table 1.

Complete stone clearance was achieved in sixty-five (95.6%) patients in Group A *vs* 30 (69.8%) patients in Group B, and was attained within the first therapeutic session in 82.4% of patients in Group A *vs* 44.2% in Group B (*P* < 0.001). The mean number of ERCP sessions until complete clearance of the bile duct was 1.1 ± 0.3 in Group A *vs* 1.8 ± 1.1 (*P* < 0.001) in Group B. Failure to obtain bile duct clearance occurred in 3 (4.4%) patients in Group A *vs* 13 (30.2%) patients in Group B (*P* < 0.001). Mechanical lithotripsy was performed with a lithotripsy basket in 10 (14.7%) patients in Group A and in 16 (37.2%) in Group B (*P* = 0.007). Additionally, 8 (18.6%) patients in Group B were sent to extracorporeal lithotripsy, *vs* none of the patients in Group A (*P* < 0.001). A plastic biliary stent was placed in 12 (17.6%) patients

Table 2 Efficacy outcomes

Efficacy outcomes	EST + EPLBD	EST	P value
Complete stone removal	65 (95%)	30 (70%)	< 0.001
Complete stone removal in single session	56 (82.4%)	19 (44.2%)	< 0.001
Number of ERCP until complete stone removal	1.1 ± 0.3	1.8 ± 1.1	< 0.001
Mechanical lithotripsy	10 (14.7%)	16 (37.2%)	0.007
Extracorporeal lithotripsy	0	8 (18.6%)	< 0.001
Plastic biliary stenting	12 (17.6%)	26 (60.5%)	< 0.001
Failure	3 (4.4%)	13 (30.2%)	< 0.001

EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; ERCP: Endoscopic retrograde cholangio-pancreatography.

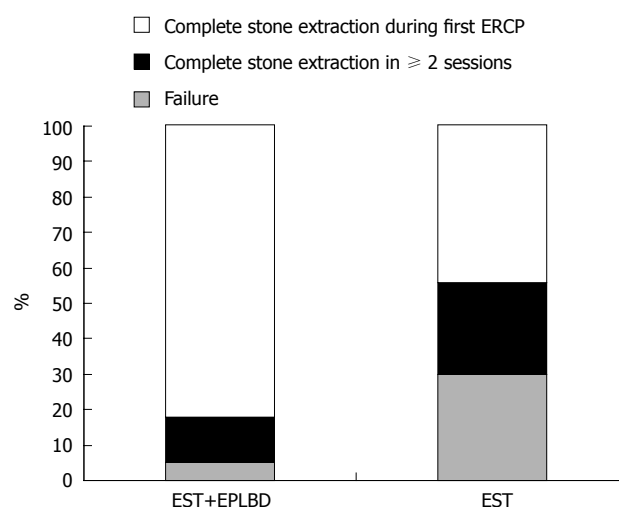


Figure 2 Efficacy of endoscopic sphincterotomy + endoscopic papillary large balloon dilation *vs* isolated endoscopic sphincterotomy for the treatment of difficult bile duct stones. EST: Endoscopic sphincterotomy; EPLBD: Endoscopic papillary large balloon dilation; ERCP: Endoscopic retrograde cholangio-pancreatography.

in Group A, *vs* 26 (60.5%) patients in Group B (*P* < 0.001), because of persistent BDS in all cases except for two patients in Group B, in whom the stents were placed because of ongoing cholangitis and delayed clearance of the contrast at the end of the procedure. Efficacy outcomes are summarized in Table 2 and Figure 2.

In a subanalysis of efficacy outcomes, taking into consideration the number and size of the stones, patients submitted to EST+EPLBD had a trend towards a higher rate of complete stone extraction at first ERCP session when a single stone was present (95.0% *vs* 77.1%, *P* = 0.072), and a higher use of plastic stents when multiple stones were present (22.9% *vs* 5.0%, *P* = 0.072), while none of the efficacy outcomes was influenced by the size of the stones in this group of patients. Conversely, in Group B, the number of stones did not seem to influence any of the efficacy outcomes, while the size of the stones seemed to be the key factor for their successful removal. Indeed, patients with smaller stones had significantly higher rates of complete bile duct clearance at first session (13 ± 4 mm *vs* 18 ± 8 mm, *P* = 0.029) and lower

rates of biliary stenting (18 ± 8 mm *vs* 13 ± 3 mm, $P = 0.042$). Moreover, patients with larger stones were more frequently referenced to extracorporeal lithotripsy (20 ± 8 mm *vs* 15 ± 6 mm, $P = 0.065$).

Regarding procedural-related complications, in our series 9/68 (13.2%) patients in Group A and 2/43 (4.7%) in Group B developed mild to moderate post-ERCP pancreatitis. This resolved with conservative treatment in less than 72 h, apart from two cases in Group A who required up to 10 d of hospitalization. In Group A, 7 (77.8%) patients who developed post-ERCP acute pancreatitis had been dilated up to 15 mm, and in the other 2 patients (22.2%) the papilla had been dilated to 13.5 mm. Significant bleeding did not occur in any of the patients in Group A, but in 2 (4.7%) patients from Group B. One patient in Group A (1.5%) and 1 patient in Group B (2.3%) developed acute cholangitis, both with good clinical evolution and short hospitalizations under conservative management. No cases of perforation or mortality occurred in our series. Overall, in Group A, the size of the stones did not influence the prevalence of complications (15 ± 1 mm in patients with complications *vs* 17 ± 5 mm in patients without complications, $P = 0.086$), although more complications occurred in the case of multiple BDS (9/48, 18.8% *vs* 1/20, 5.0%, $P = 0.138$). In patients from Group B, the rate of complications did not seem to be influenced either by the size (16 ± 7 mm in patients with complications *vs* 18 ± 8 mm in patients without complications, $P = 0.582$) or the number of stones (single stone: 2/24, 8.3% *vs* multiple stones: 3/19, 15.8%, $P = 0.019$).

DISCUSSION

Over the last few years, the technique of using EPLBD after limited EST has been increasingly recognized as an important therapeutic option for patients with large BDS^[10,11,18,21-29]. In our series, this approach proved to be highly effective in patients with large BDS when compared to the performance of EST alone, with no significant increase of complications. Indeed, patients who underwent EST+EPLBD had significantly higher rates of complete stone clearance (95.6% *vs* 69.8%), and this was achieved more often within the first therapeutic session (82.4% *vs* 44.2%). Moreover, the need for mechanical or extracorporeal lithotripsy was significantly lower (14.7% *vs* 37.2% and 0 *vs* 18.6%, respectively), as was the use of plastic biliary stents (17.6% *vs* 60.5%). These outcomes did not seem to be influenced by the size of the stones, but there was a trend towards higher rates of complete stone clearance at first ERCP (95.0% *vs* 77.1%) and reduced biliary stenting (5.0% *vs* 22.9%) in patients with a single bile duct stone. Conversely, in patients submitted to isolated EST, efficacy outcomes were mainly influenced by the size of the stones, rather than by its number. It must be stated, however, that this was a non-randomized retrospective case-controlled study, where the decision to perform isolated EST or EST+EPLBD was made on an

individual basis at the time of each examination. Thus, a possible selection bias influencing the results could be considered, particularly concerning the relatively low overall successful clearance rates (69.8%) and stone clearance in the first ERCP session of isolated EST (44.2%). In this group of patients, the size of the largest stone was the key factor influencing incomplete clearance, biliary stenting or referral for extracorporeal lithotripsy. Nonetheless, the mean diameter of the stones was comparable between Group A (16.8 ± 4.4 mm) and Group B (16.0 ± 6.7 mm), and also the prevalence of larger stones, up to 30 mm, was similar in both groups of patients. In our experience, EST+EPLBD was the preferred technique when multiple large BDS were detected in the initial cholangiogram, being chosen as first-line approach in this particular setting significantly more often than EST alone. The presence of bile duct strictures, such as papillary stenosis, has been reported to be manageable by papillary balloon dilation, although the safety of this approach has not been fully elucidated for EPLBD, and may constitute a limiting factor. In our series, 4 patients with biliary strictures were submitted to EPLBD up to 12 mm, allowing for stone removal with no complications. Overall, failure to obtain a complete clearance of the bile duct occurred in only 3 (4.4%) patients in Group A, as compared to nearly one third of patients in Group B (30.2%). Some authors had reported that by reducing the need for mechanical lithotripsy (5.7% *vs* 25.0%, $P < 0.01$), EST+EPLBD additionally reduced the total procedure time and radiation exposure^[11,31], however these outcomes were not evaluated in our study.

Our results challenge the conclusions of a recent meta-analysis of 7 randomized controlled trials that included 790 patients, comparing EST+EPLBD with EST^[32]. The authors reported that both techniques resulted in similar outcomes for overall successful clearance rates of BDS (97.4% *vs* 96.4%, $P = 0.54$) and stone clearance in the first ERCP session (87.9% *vs* 84.2%, $P = 0.21$), although EST+EPLBD significantly decreased the use of mechanical lithotripsy (OR: 0.51, $P = 0.01$). Regarding biliary stenting, some authors have reported that the temporary placement of plastic stents may be able to fragment large BDS, and that this could possibly constitute an alternative method for clearing difficult stones not amenable to extraction at the first attempt^[33,34]. In our study, 60.5% of patients submitted to EST alone required the placement of at least one plastic biliary stent, while this was the case in just 17.6% of patients who underwent EST+EPLBD.

Beyond improving efficacy outcomes, this combined technique has been shown to potentially reduce the complications typically associated with the performance of EST or EPBD alone. The risk of pancreatitis after EPBD seems to be related to the pressure overload on the orifice of the main pancreatic duct during balloon dilation, particularly when dilations are performed above the diameter of 10 mm or if the balloon is inflated very abruptly^[3-10,35,36]. Conversely, the combined EST+EPBD approach does not appear to increase significantly the

risk of post-ERCP pancreatitis. This may be due to the fact that EST guides the orientation of the dilating balloon towards the common bile duct, thus preventing the pressure overload on the main pancreatic duct^[20]. The risk of post-EPLBD pancreatitis may, however, be increased in the case of lower bile duct diameter or longer procedure time^[29]. In our study, we could not exclude that the comparable rate of post-EPLBD (9/68, 13.2% *vs* 2/43, 4.7%) might be related to the relatively low case number in this series. Patients from Group A had a trend towards increased complications when two or more BDS were present. Although differences were not statistically significant, it should be noted that 9/10 patients who experienced a complication after EST+EPLBD, particularly acute pancreatitis, presented with multiple BDS. Conversely, in patients from Group B, the rate of complications did not seem to be influenced either by the size or the number of the stones. In a recent meta-analysis^[32], EST+EPLBD was associated with fewer overall complications than EST (5.8 *vs* 13.1%, $P = 0.0007$). In particular, bleeding occurred less frequently with EST+EPLBD than with EST (OR: 0.15, $P = 0.002$), suggesting that compression by ballooning may be effective for haemostasis. The authors did not find significant differences in post-ERCP pancreatitis, perforation and cholangitis. Based on EST+EPLBD being associated with fewer cases of significant bleeding, it may be reasonable to recommend this technique for the removal of difficult BDS in patients with underlying coagulopathy or need for anticoagulation, as well as for those in whom the local anatomy may increase the risks of a large sphincterotomy, such as patients with peripapillary diverticulum^[37], Billroth II gastrectomy^[38,39] or Roux-en-y anastomosis^[40]. The risk of duodenal perforation during EST+EPLBD seems quite low, possibly due to the fact that EST guides the orientation of the dilation and controls the impact of its radial force, which is furthermore monitored in real time by the endoscopist, both endoscopically and fluoroscopically.

Finally, the most frequent long-term complication after bile duct stone extraction is the recurrence of symptomatic BDS^[3,41,42]. The recurrence rate seems to be higher in patients who undergo EST (6%-24%)^[43,44] than in those submitted to EPBD alone, which may be due to the preservation of the sphincter of Oddi in the latter group, preventing the chronic reflux of duodenal contents and bacteria into the biliary tree. Currently, our patients are enrolled in a controlled prospective study to evaluate the rate of recurrence of BDS after EST+EPLBD. One study evaluated the recurrence rate and the risk factors in 100 patients with BDS after EST+EPLBD, *vs* a control group of 109 patients submitted to EST alone^[13], with a mean follow-up of over 30 mo in both groups. The recurrence rate was similar in patients who underwent EST+EPLBD (11.0%) and EST (13.8%). The larger diameter of the bile duct was the only risk factor for stone recurrence in this study^[13].

In conclusion, EST+EPLBD should be considered among the first line therapeutic options for the treatment of difficult bile duct lithiasis. The results from our study

showed that it is an effective technique for the management of large BDS, being superior to isolated EST in all efficacy outcomes, with no significant increase of complications.

COMMENTS

Background

The combined endoscopic technique of limited sphincterotomy followed by papillary large balloon dilation, described by Ersoz *et al* in 2003, is an attractive approach for the removal of large bile duct stones. In a recent meta-analysis, it was found to achieve high rates of complete bile duct stone clearance while reducing the use of mechanical lithotripsy.

Research frontiers

In this study, the authors aimed to evaluate the efficacy and safety of endoscopic papillary large balloon dilation after sphincterotomy in the treatment of large (≥ 10 mm) bile duct stones, in a comparative analysis with a control group of patients with similarly large bile duct stones that was submitted to isolated sphincterotomy.

Innovations and breakthroughs

In the authors' case-controlled study, the combined technique achieved higher rate of complete stone clearance than isolated endoscopic sphincterotomy (EST), and this was more often achieved within the first therapeutic session, reducing the need for further endoscopic retrograde cholangio-pancreatography. Moreover, it reduced the need for lithotripsy and biliary stenting, with a similar safety profile.

Applications

The results of this study suggest that the use of endoscopic papillary balloon dilation after limited sphincterotomy should be considered among the first line therapeutic options for the treatment of difficult bile duct lithiasis.

Terminology

Endoscopic papillary balloon dilation involves the progressive dilation of the papillary orifice after limited sphincterotomy, using a through-the-scope oesophageal/pyloric balloon catheter, gradually inflated up to the size of the largest stone and/or the maximal diameter of the distal bile duct according to the cholangiogram. Mechanical lithotripsy is performed when there is a need to fragment the stones prior to removal, using a through-the-scope lithotripsy basket under radiologic guidance. Extracorporeal lithotripsy focuses high-pressure shock wave energy to fragment the stones while minimizing energy exposure to adjacent tissues.

Peer review

In this study, the authors concluded that EST followed by papillary large balloon dilation can achieve a higher rate of complete stone clearance and a less need for lithotripsy and biliary stenting, with equivalent safety to isolated sphincterotomy.

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Small bowel polypectomy by double balloon enteroscopy: Correlation with prior capsule endoscopy

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Abstract

AIM: To investigate the feasibility of small bowel polypectomy using double balloon enteroscopy and to evaluate the correlation with capsule endoscopy (CE).

METHODS: This is a retrospective review of a single tertiary hospital. Twenty-five patients treated by enteroscopy for small bowel polyps diagnosed by CE or other imaging techniques were included. The correlation between CE and enteroscopy (correlation coefficient of Kendall for the number of polyps, intra-class coefficient for the size and coefficient of correlation kappa for the location) was evaluated.

RESULTS: There were 31 polypectomies and 12 endoscopic mucosal resections with limited morbidity and no mortality. Histological analysis revealed 27 hamartomas, 6 adenomas and 3 lipomas. Strong agreement between CE and optical enteroscopy was observed for both location (Kappa value: 0.90) and polyp size (Kappa value: 0.76), but only moderate agreement was found for the number of polyps (Kendall value: 0.47).

CONCLUSION: Double balloon enteroscopy is safe for performing polypectomy. Previous CE is useful in selecting the endoscopic approach and to predicting the difficulty of the procedure.

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Key words: Small bowel polyps; Double balloon enteroscopy; Capsule endoscopy; Polypectomy; Correlation

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INTRODUCTION

The main indication for double balloon enteroscopy (DBE) and capsule endoscopy (CE) is the endoscopic exploration of patients with obscure gastrointestinal bleeding^[1-5]. Small bowel polyps and tumours are important causes of small bowel pathology, which occur most frequently in familial or non-familial polyposis syndromes^[1,6-10]; the most frequent are familial adenomatous

polyposis (FAP) and Peutz-Jeghers syndrome (PJS)^[11,12]. The advent of CE and DBE has improved our ability to perform deep exploration of the small bowel. DBE has the additional advantage of permitting the retrieval of tissue and removal of premalignant polyps. The primary aim of the present study was to assess the feasibility of polypectomy by DBE in patients with small bowel polyps diagnosed by CE or other imaging techniques including computer tomography (CT) scan and magnetic resonance imaging (MRI). The secondary aim was to evaluate the correlation between CE and DBE in terms of determining the size, location and number of polyps.

MATERIALS AND METHODS

This retrospective cohort study included patients treated by DBE for small bowel polyps diagnosed with CE (84%) or other imaging techniques (16% of cases) in our tertiary referral centre between January 2005 and January 2008. Patients were included or excluded based on the following keywords in the CE or radiology reports: (1) Inclusion criteria for CE were “pedunculated or sessile polyps” and for MRI or abdominal CT scan “lesions with polyp aspects”; (2) Exclusion criteria for CE were “the tumour or mass appears as a thickened fold with pathologically abnormal vessels, aspects of stenosis, aspects of diffuse infiltration of the small bowel wall and aspects of submucosal lesions with intact overlying mucosa”, and MRI or abdominal CT scan “the tumour or mass appears with tissue density picture and aspects of stenosis”.

All patients had previously undergone at least one upper gastrointestinal endoscopy and colonoscopy. The data were obtained from the patient medical records and were entered into a semi-standardised electronic database. If one DBE route did not yield a diagnosis, the opposite route was used for the second investigation. Complete DBE was confirmed by tattooing the small bowel.

The lesions diagnosed by the physician in charge of interpreting CE were classified according to their size, location and imputability according to Saurin *et al*^[13], using the following criteria: P3 (presence of blood), P2 (high imputability), P1 (intermediate imputability) and P0 (low imputability). Capsule video endoscopy was performed with the PillCam™ SB (Given Imaging Ltd, Yoqneam, Israel). All patients were prepared with 2 L of polyethyleneglycol (PEG) solution the night before examination. The capsule transmitted continuous video images at a rate of 2 frames per second for about 8 h during its passage through the gastrointestinal tract. The route of insertion of the DBE was found by calculating Gay's index; the oral route was chosen if the time to lesion/time to cecum was less than 0.75^[14]. The oral and anal routes were not taken during the same procedure because of the long procedure duration. In our series, no patients received total enteroscopy. For 6 patients, DBE from the anal route permitted the resection of polyps. For one patient, CE showed polyps in the jejunum and ileum, and DBE by the oral and anal routes was performed 48 h

apart for the resection of these polyps. We failed to perform a complete enteroscopy. For the other 5 patients, CE showed polyps in the ileal position; in these cases, DBE by the anal route was the first choice and permitted the resection of polyps.

The following locations were examined: the proximal jejunum (the first quarter of the small intestine), distal jejunum (the second quarter of the small intestine), proximal ileum (the third quarter of the small intestine) and distal ileum (the fourth quarter of the small intestine). No a posteriori readings of CE or DBE were performed.

All of the DBE procedures were performed by an experienced endoscopists aided by an assistant holding the overtube. The DBEs (Fujinon Inc., EN-450P5 or EN-450T5) had a diameter of 8.5 and 9.3 mm with an operating channel of 2.2 and 2.8 mm, respectively. All of the patients were sedated by propofol with endotracheal intubation. Fluoroscopy was reserved for difficult cases. The depth of insertion into the small bowel was calculated according to the method described by May *et al*^[10]; the advancement of the instrument was measured by counting the number of full 40 cm advancement sequences carried out after the reference point established by an initial full-length insertion of the endoscope. The procedure for enteroscopy *via* the anal route was different; in this case, the initial introduction was performed *via* the colon to the ileocecal valve, with or without the balloons. The advancement was measured by counting the number of 40 cm sequences from the ileocecal valve. For the oral route, the endoscopic procedure was performed in the left lateral position, and no bowel preparation was required. For the anal route, four litres of PEG solution was given to the patient the day before the procedure.

Analogous to the Paris classification for gastrointestinal superficial tumours, we treated small bowel lesions according to the endoscopic appearance^[15]. A simple snare polypectomy was performed to remove pedunculated polyps, which was the most frequent situation. Endoscopic mucosal resection (EMR) was performed for any superficial polypoid sessile tumours or non-polypoid tumours (slightly elevated, flat, and slightly depressed). After the lesion was lifted by a submucosal saline injection, we used a polypectomy snare. EMR was not attempted in ulcerated or excavated lesions because of the risk of invasion depth.

The polyp number and size in each small bowel segment (proximal and distal jejunum and proximal and distal ileum) were documented. Polyp size was estimated using open biopsy forceps. Depending on the polyp size, a submucosal injection of epinephrine-saline solution (1:10000) was delivered before resection. PJS polyps measuring over 10 mm were resected, and the smaller polyps were left in place. It is consensus not to remove small polyps (less than 10 mm) in PJS because the malignant transformation of small bowel polyps in these patients is a rare event^[16,17]. Patients with Lynch syndrome, PJS and FAP syndrome received genetic counselling and, if necessary, genetic testing.

Table 1 Clinical and demographic characteristics of patients with small bowel polyps diagnosed with double balloon enteroscopy *n* (%)

Patient characteristics	
Total	25
Males	18 (72)
Mean age (yr, range)	44 (8-83)
Only 1 DBE	20 (80)
DBE characteristics	
Total	32
Insertion	
Oral route	26 (81)
Anal route	6 (19)
Indications	
Occult bleeding	11 (34)
Overt bleeding	4 (12)
Peutz-Jeghers syndrome	10 (31)
Hereditary non-polyposis colon cancer	3 (9)
Familial adenomatous polyposis	3 (9)
Familial liver adenomatosis	1 (3)
Others (abdominal pain)	3 (9)

DBE: Double balloon enteroscopy.

Statistical analysis

For statistical analysis, categorical variables are presented as number (%), and continuous variables are presented as the mean \pm one SD or median (25% percentile - 75% percentile). The correlation between the number of diagnosed polyps by CE and DBE was estimated using the Kendall coefficient of concordance (*W*); the closer the *W* is to 1, the higher the correlation. To compare the size of the polyps, we considered the first polyp measured at CE or DBE, and the correlation was calculated by an intra-class correlation coefficient (Fleiss formula: two-way mixed model, with a random effect for the subject and a fixed effect for the method). Finally, the agreement between CE and DBE for polyp location was estimated using a weighted kappa. All calculations were performed with the SAS statistical software (version 9.1). Statistical tests were two-sided with an alpha level of 0.05.

RESULTS

From January 2005 to January 2008, 403 enteroscopies were performed at our centre; thirty-two (8%) were performed for small bowel polyps in 25 patients (Table 1). The indications were occult or overt gastrointestinal bleeding (34% and 12%, respectively); PJS, Lynch syndrome or FAP follow-up (31%, 9% and 9%, respectively); and one case of familial liver adenomatosis. Two patients with polyps suspected on CE had a negative DBE; the first of these patients underwent a second CE that did not show any polyps, and the second patient, who had multiple suspected polyps in the ileum based on CE, was diagnosed with lymphoid hyperplasia without polyps on DBE (anal route).

The results of the CE and DBE are summarised in Table 2. CE showed lesions with P1 (11%), P2 (81%) and P3 (8%) imputability (Figure 1). The median number of

Table 2 Results of capsule endoscopy and double balloon enteroscopy: polyp number, size and location *n* (%)

	Capsule endoscopy <i>n</i> = 27	Double balloon enteroscopy <i>n</i> = 32
Median number of polyps	1.5 (1-10)	1 (1-13)
Mean size (mm)	30 (5-50)	20 (8-50)
Location		
Proximal jejunum	17 (63)	20 (63)
Distal jejunum	4 (15)	6 (19)
Proximal ileum	6 (22)	3 (10)
Distal ileum	6 (22)	4 (12)



Figure 1 Polyp showed by capsule endoscopy in patient with Peutz-Jeghers syndrome.

polyps diagnosed by CE was 1.5 (range: 1-10), and the median size was 30 mm (range: 5-50 mm). The results of the CE determined the route of DBE insertion; the oral route was designated for 26 procedures (81%) in patients with a Gay's index < 0.75 and anal route was designated for the other patients. No total enteroscopy was possible. The mean total duration of the procedure for the oral and anal routes was 65 min (35-250 min) and 80 min (50-280 min), respectively. The mean polyp size with DBE was 20 mm (8-50 mm) (Figure 2). More than 50% of the polyps were located in the proximal small bowel. Using DBE, we found one small bowel polyp in 22 procedures and more than one in 10 procedures. In total, 31 polypectomies and 12 mucosectomies were performed. Eight polyps were not resected (simple biopsies) because their size was over 5 cm, and two of these polyps appeared as large submucosal lesions.

Immediate bleeding occurred in 6 patients, and there was no delayed bleeding. No patient had anticoagulant or antiplatelet therapy before or during the procedure. In 4 cases, there was a large peduncle and a polyp with a size of 30 to 40 mm, which was treated by polypectomy with a snare; two of them were bilobed and ulcerated on the top. Bleeding was stopped using haemostatic clips and a diluted adrenalin injection. In the other 2 cases, the polyps were sessile, measuring 20 to 30 mm. Haemostatic clips stopped the bleeding and closed the EMR wound. For one patient, acute pancreatitis occurred after a long

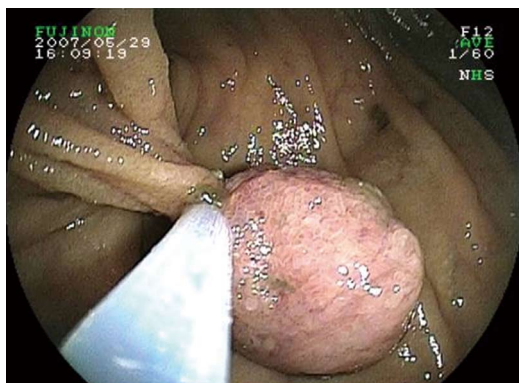


Figure 2 Polypectomy during double balloon enteroscopy for a patient with Peutz-Jeghers syndrome.

and difficult procedure resulting in the large resection of a polyp located in the distal part of the jejunum (grade D of Balthazar's classification); this condition resolved within 2 d after medical treatment. There was no mortality related to DBE.

Histological analysis was available for 36 of the 43 polyps (83%) because of an inability to retrieve all of the polyps after resection, especially in the case of multiple polyps. There were 27 hamartomatous polyps (three with low-grade dysplasia), all of which occurred in patients with PJS; six were adenomatous polyps (five with low-grade and one with high-grade dysplasia), and three were lipomas (all were small, ulcerated and responsible for the gastrointestinal bleeding). All of the adenomas polyps were observed in patients with Lynch syndrome or FAP. All the margins were tumor free.

Polyp resection was impossible in 9 patients who underwent surgical treatment with small bowel resection; among these patients, 2 had an ulcerated lesion mimicking a sessile polyp causing bleeding and had surgery as the bleeding failed to stop despite an argon plasma coagulation and adrenalin solution injection. Histological examination of the polyps from these 2 patients showed gastro-intestinal stromal tumour (GIST). For 6 patients, the polyp was larger than 5 cm with difficult enteroscopic positioning, making resection impossible; post-procedure histological examination showed hamartomas in PJS. The remaining patient had more than 10 large polyps, leading to a decision to perform intraoperative enteroscopy.

The agreement between CE and DBE was good for the location and size of polyps with kappa values of 0.90 (95%CI: 0.73-1) and 0.76 (95%CI: 0.43-0.91), respectively, but moderate for the number of polyps (Kendall coefficient value, 0.47, $P = 0.0076$).

Five treated patients were lost to follow-up. Among the 20 remaining patients, the median follow-up was 14.2 mo (range: 2-36 mo). Another polypectomy was necessary in 4 patients during the follow-up period. Three patients had PJS, and the initial CE showed multiple lesions that could not be removed during one DBE. One patient with PJS had an ileal polypectomy during the first DBE by the anal route. One year later, CE showed

a large polyp in the proximal jejunum that was probably not detected on the previous CE. The polyp was resected by DBE using the oral route. For patients with adenoma polyps, one was lost to follow-up; there was no recurrence for the other patients, with a mean follow-up of 26 mo (range: 3-35 mo).

DISCUSSION

We report 25 patients treated for small bowel polyps by DBE. All of the procedures were well tolerated. The agreement between CE and DBE was good for both the location and size of polyps, but was poor for the number of polyps.

Therapeutic DBE is associated with an incidence of complications of approximately 1%-5%, the most frequent of which are perforation, bleeding and pancreatitis^[18,19]. In our series, only 1 case of acute pancreatitis out of 403 enteroscopies occurred, which was rapidly resolved with medication. Episodes of bleeding were successfully treated during DBE with an injection of epinephrine-saline solution and clips. In a recent study describing complications after DBE^[19], the perforation rate was 1.5% per polyp (2 among 137 polyps removed) and 2.9% per patient (2 among 68 patients). In their series of 79 polyps in 15 patients with PJS, Gao *et al*^[20] reported no perforation after polyp removal, and we observed the same results. The majority of the removed polyps in our series were pedunculated, and all sessile polyps had a good elevation after serum sub-mucosa injection. Good exposure of the polyp is very important in the case of large polyp size because of a higher risk of perforation. The change in position of the patient (left lateral or supine position) can reduce this risk during resection. We believe that polyp resection should not be attempt when there is no lifting sign or when the appearance is a sub-mucosal lesion.

In our series, most of the polyps were localised to the proximal region of the jejunum, and some of the polyps were nearly 5 centimetres in size. The polyp location shown on CE was used to indicate whether the DBE route should be oral or anal using Gay's Index. Moreover, when CE showed a large polyp, it was possible to predict the resection difficulty and the duration of the procedure. The moderate correlation between CE and DBE count is probably due to DBE distension of the small bowel by air insufflation in the case of numerous polyps, which provided a more accurate way of counting a larger number of small polyps compared to CE. In studies addressing the same issue, Marmo *et al*^[21] showed that CE and DBE show good agreement for vascular and inflammatory lesions, but not for polyps or neoplasia. In this study, in concordance for the polyp size, the number or the location of the polyp was not analysed separately.

In our study, 10 patients had PJS. This high number of PJS can be explained by the presence of a genetics unit in our centre that treats patients with gastrointestinal polyposis. Several studies have shown that polypectomy

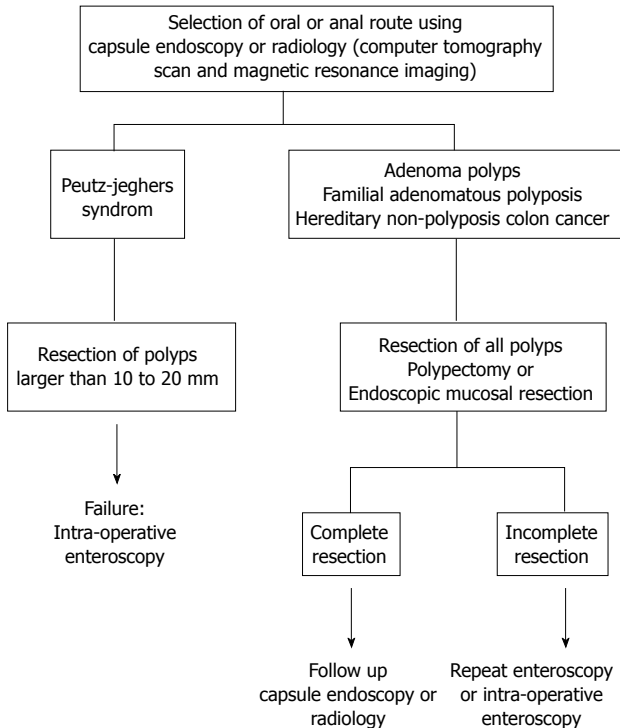


Figure 3 Suggested algorithm for resection of small bowel polyps by double balloon enteroscopy.

during DBE is effective and may decrease the need for urgent laparotomy for occlusion due to a large polyp. Chen *et al*^[22] showed that a total of 17 enteroscopies resulted in polypectomy in six patients with PJS without complications. All patients underwent complete small bowel exploration in 1 or 2 steps. Another technique that allows for small bowel polypectomy is intraoperative enteroscopy, but DBE is less invasive and more convenient for the patient^[23].

The screening and management of small bowel polyps and tumours is important for patients with familial and non-familial polyposis syndromes. Mönkemüller *et al*^[24] studied the usefulness of DBE-assisted chromoendoscopy for the detection and characterisation of small bowel polyps in patients with FAP; jejunal polyps were detected in 67% of the patients, and chromoendoscopy helped detect additional polyps in two patients.

The second most frequent and most important site, after the colon, of adenomas in FAP is the duodenum. The three patients in our study were stage I or II according to the Spigelman score (between 5 and 20 polyps, measuring between 1 and 10 mm, tubular and without high-grade dysplasia).

Our study has the potential limitation of being a single-centre retrospective study in a university setting with an associated recruitment bias. However, to our knowledge, this is one of the largest endoscopic series focusing on the diagnosis and management of small bowel polyps excluding tumours. Another criticism could be that our patient sample has been selected based on a positive CE, which can lead to an optimistic estimation of agreement

because these patients are not taken into account for kappa calculation. However, any missed patients probably harbour small lesions, and their absence from our sample probably has no influence on our estimation of the complication rate. Another limitation is the lack of complete small bowel exploration. Sakamoto *et al*^[25] showed that several sessions of enteroscopy in PJS patients with resection of polyps more than 20 mm in size was useful for reducing polyp size and number, preventing intussusceptions, and avoiding laparotomy. In our study is the use of the first small-bowel CE device PillCam™ SB (Given imaging, Yoqneam, israel). Actually, improvements have been made as the PillCam™ SB2, and new capsules were developed: EndoCapsule™ (Olympus, Tokyo, Japan), MiroCam™ (introMedic Co., seoul, South Korea) and OMOM capsule endoscope (Jianshan Science and Technology Group Co., Ltd., Chongqing, China)^[26-28]. Advantages are deeper field of view (up to 156°), higher frame rate (3 per second for MiroCam™), longer battery life (over 11 h) and the possibility of real-time image acquisition. With the OMOM capsule, the frame rate can be changed during the study. All these improvements allow a better visualization of the intestinal mucosa and may help for polyps' detection. In Figure 3, we have summarized our endoscopic strategy for small bowel polyp resection in PJS patients and in adenoma polyps in patients with Lynch syndrome and FAP. For patients with FAP, the resection of small bowel polyps should be always attempted because of the potential risk of progression to adenocarcinoma. For those suffering from PJS syndrome, we suggest to remove only larger polyps more than 10 mm, since the major risk is bleeding and intussusception. Follow-up by CE or DBE should be recommended after the removal of adenomatous or hamartomatous polyps, but future studies have to determine which interval should be chosen for the follow-up.

In summary, DBE is a safe and effective technique for diagnosing and resecting most polyps in the small bowel with a low complication rate. However, it is a time-consuming procedure that is not always capable of visualising the entire small bowel and should be preceded by CE which is a less invasive technique. CE allows to show the number, location and size of the polyps and thus, indicate the route (*i.e.*, oral or anal) and predict the difficulty of the polypectomy during optical enteroscopy.

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COMMENTS

Background

Capsule endoscopy (CE), after being ingested by the patient, allows entire small bowel exploration. Double balloon enteroscopy (DBE) is an overtube-assisted endoscopic technique which allows deep exploration of the small bowel and resection of polyps diagnosed by CE. Polyps must be resected because of the risk of malignant transformation and/or the risk of small bowel obstruction.

Research frontiers

Endoscopic techniques, as DBE, allow mini-invasive treatment for small bowel polyps as an alternative to surgery.

Innovations and breakthroughs

DBE is a safe and effective technique for diagnosing and resecting most polyps in the small bowel with a low complication rate. CE allows to show the number, location and size of the polyps and thus, indicate the route (*i.e.*, oral or anal) and predict the difficulty of the polypectomy during optical enteroscopy.

Applications

Any patient with suspected small bowel disease should be eligible to an endoscopic small bowel exploration by DBE and CE.

Terminology

Enteroscopy: endoscopic exploration of small bowel; Polypectomy: polyp's resection.

Peer review

This study demonstrates the utility of C followed by DBE to better care for patients with small bowel polyps.

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Colonoscopy in rats: An endoscopic, histological and tomographic study

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and microscopic examinations were examined with a conventional technique (hematoxylin and eosin). Colonic wall thickness, length and diameter measurements were taken from the anus, 3, 7, 14 and 20 cm from the anal margin.

RESULTS: The median colonoscope depth was 24 cm (range 20-28 cm). Endoscopic and tomographic study of colon morphology showed an easy access with tubular morphology in the entire left colon (proximal left colon and rectum). Transverse colon was unapparent on colonoscopy. Right colon, proximal to the splenic flexure, was the largest part of the colon and assumed saccular morphology with tangential trabecula. Radiological measurements of the colonic length and diameter substantiate a subdivision of the right colon into two parts, the cecum and distal right colon. In addition, histological measurement of the colonic wall thickness confirmed a progressive decrease from rectum to cecum. The muscular layer was thinner in the proximal left colon.

CONCLUSION: The combination of colonoscopy, tomography and histology leads to a better characterization of the entire colon. These data are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments.

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Key words: Rat; Colonoscopy; Tomography; Colon anatomy; Histological measurements

Core tip: There is a need for a solid colonoscopy animal model, complemented with digital radiology. Our subdivision of the rat colon constitutes a simplification of subdivisions presented by others who have emphasized the theoretical anatomical data. Our proposed subdivision of the colon is practical and justified by the

Abstract

AIM: To describe colon anatomy with colonoscopy and computed tomography (CT) to develop a rat model for future studies of therapeutic colonoscopy.

METHODS: Eighteen male Sprague-Dawley rats, on average 400-420 g, underwent total colonoscopy, CT and histological examination. Colonoscopy was performed after bowel preparation with a baby upper gastrointestinal endoscopy with an outer diameter of 6.7 mm. CT obtained a 3D image of total colon after a rectal enema with radiological contrast. Macroscopic

importance of endoscopic access and the thickness of various portions of the colon wall. This study identified that the muscular layer was thinner in the proximal left colon. These findings are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments.

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INTRODUCTION

The rat is widely used as a laboratory animal for medical biological and molecular research. The anatomy and topography of the rat colon have been described on the basis of macroscopic and conventional radiological observations on the whole animal^[1]. Radiology is useful for studying normal arterial and mucosal anatomy of the explanted rat colon. In contrast, in clinical practice, endoscopy is one of the keystone diagnostic techniques allowing follow-up and management of gastrointestinal inflammation^[2-9]. Interestingly, there are no detailed endoscopic descriptions of the gross anatomy of the colon by total colonoscopy (TC)^[10-19]. Significant progress in endoscopic techniques has been made in the last years. There is a need for a solid colonoscopy animal model, complemented with digital radiology. The aim of the present study was to describe the colon anatomy with high-definition colonoscopy and computed tomography (CT) to develop a rat model for future studies of therapeutic colonoscopy.

MATERIALS AND METHODS

Rats

Eighteen male Sprague-Dawley, on average 400-420 g, were used in this study. Rats were acclimatized for a minimum of 7 d preoperatively. Rats were kept at constant room temperature (20-22 °C) with a relative humidity (27%-31%) with aeration under an alternating 12 h cycle of fluorescent light and darkness. The rats were housed individually in polycarbonate box cages with free access to water and food (Teklad Global 2014, Harlan Laboratories Models SL, Barcelona, Spain). Rats are the smallest and lowest among the species suitable for TC. The rats suffered minimal pain and distress due to the use of anesthesia. The protocol was approved by the Institutional Animal Care and Use Committee of Hospital Universitari Germans Trias i Pujol.

Bowel preparation

The animals had free access to water but food was withdrawn 8 h prior to the initiation of bowel preparation. A

rectal enema with saline solution was performed immediately prior to TC^[20].

Colonoscopic examination

Colonoscopy was performed with a baby upper gastrointestinal Olympus GIF-XP160 video endoscope with an outer diameter of 6.7 mm and a 2.3 mm working channel (Olympus, Tokyo). After a 24 h fasting period with free access to drinking water, the rats were anesthetized by isoflurane inhalation (1.5% with 98% O₂) and placed in a supine position. Remaining feces were flushed away by injecting water through the anus. A drop of lubricating jelly (Aquagel®, Ecolab, Leeds, England) was applied on the anal sphincter to facilitate insertion of the scope. The endoscope was then gently passed through the anus and under endoscopic vision further introduced. Water was injected through the scope's working channel to visualize the lumen of the colon. Occasionally the colon was inflated with air for better visualisation of the lumen. The tip of the endoscope was introduced to the cecum, about 24 cm proximal from the anus. Pictures were captured in each procedure. Rats were placed under surveillance during recovery and were returned to their cages when regaining consciousness.

CT

In vivo X-ray Microtomograph (SkyScan 2002, Aartselaar, Belgium) was used in order to obtain a 3D image of total colon. Briefly, animals were anesthetized with isoflurane, 20 mL of radiological contrast (Plenigraf®, Juste, Madrid, Spain) was administered through a rectal enema and then the animals were placed in the scanning area. Acquisition images for 3D reconstruction of the whole colon lasted over 40 min with a resolution of 32 µm.

Macroscopic examination

Rats were sacrificed 48 h after colonoscopy by anesthetic overdose (60 mg pentobarbital, *ip*). After sacrifice, the colon was collected and rinsed with ice-cold Krebs solution. The colon was opened longitudinally and pinned out on a Petri dish to examine the colonic mucosa. The mucosal surface of the distal colon was inspected with a binocular microscope (Harvard Apparatus, Panlab, Barcelona, Spain).

Microscopic examination

Full-thickness samples of approximately 1 cm were taken from anus, 3, 7, 14 and 20 cm from the anal margin. Segments were fixed in 4% formaldehyde for 24 h, embedded in paraffin and cross sections of 5 µm were stained with hematoxylin and eosin. Histological sections were examined using a conventional microscope (Olympus, Shinjuku-ku, Tokyo, Japan).

RESULTS

Colonoscopic examination

Bowel preparation resulted in complete evacuation of

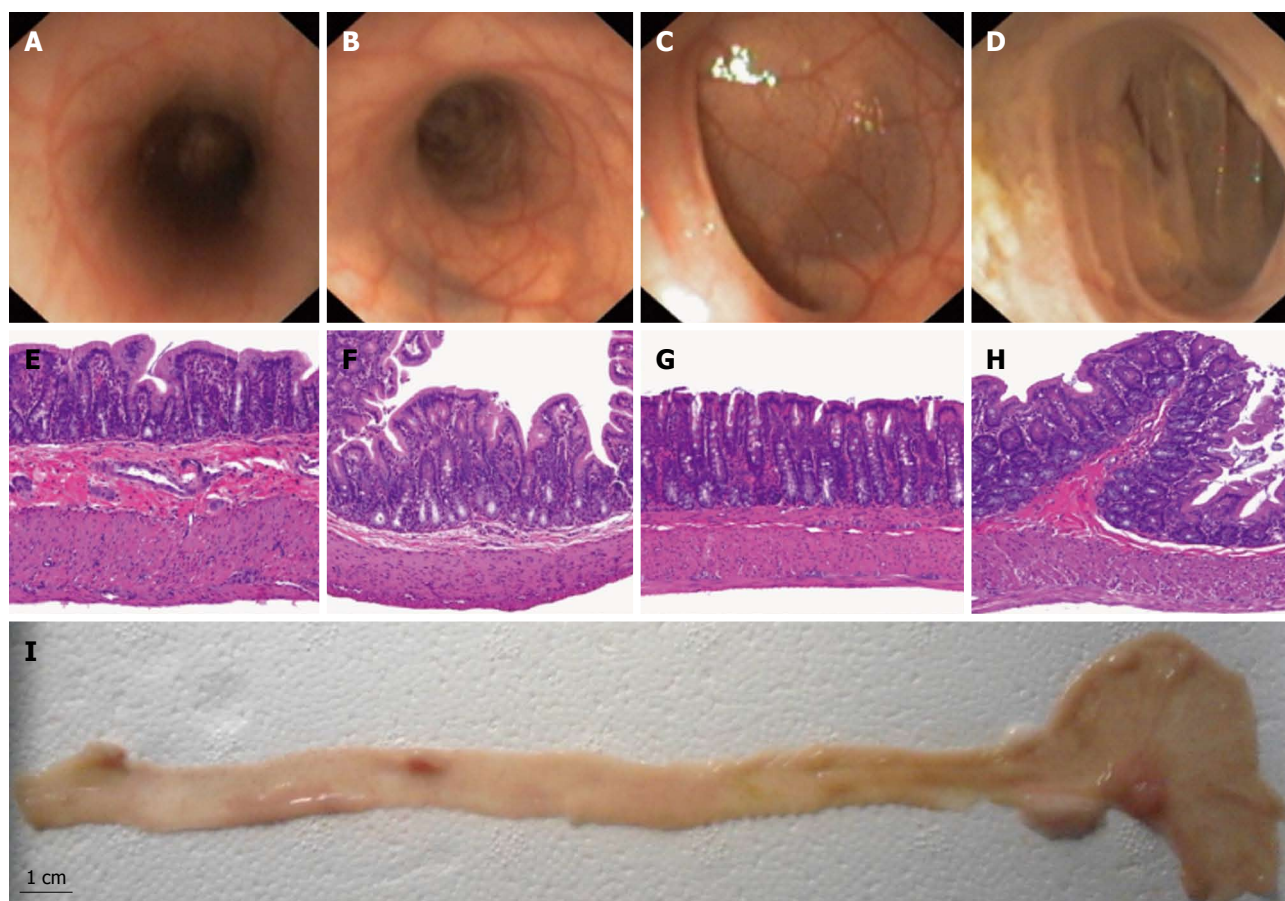


Figure 1 Representative pictures of *in vivo* colonoscopy (A-D), photomicrograph of histological study with hematoxylin and eosin stains of colon sections (E-H) in rats at 3 (A,E), 7 (B,F), 14 (C,G) and 20 cm (D, H) from the anal margin. Macroscopic picture of the entire colon (I).

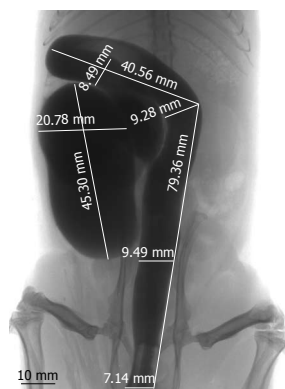


Figure 2 Tomographic picture of rat colon with length and diameter measurements.

stools in the left colon. In the right colon we found one solid stool and liquid feces that were flushed away. The median colonoscope depth was 24 cm (range 20-28 cm). Confirmation of cecal intubation during colonoscopy was achieved by transillumination through the abdominal wall. The appendiceal orifice was not identified in any case. The scope reached the splenic flexure easily and the tube went straight up from the anus so that the entire left colon (proximal left colon and rectum) assumed a tubular morphology. The transverse colon was unapparent on

colonoscopy. The right colon, proximal to the splenic flexure including the cecum, was the largest part of the colon and assumed saccular morphology with tangential trabecula. Splenic and liver impronta were evident in both flexures. Mucosal and vascular pattern were similar in the left and distal right colon. In the cecum, the mucosal surface of the insufflated colon presents folds (Figure 1).

CT

Radiological measurements of the colonic length and diameter substantiate a subdivision of the right colon into two parts, the cecum and distal right colon (Figure 2). The cecum of the rat is 54.6 ± 22.1 mm long, is the most prominent part of the colon and assumes a sack form with a major diameter measurement of 20.78 ± 1.88 mm. The cecum does not have a vermiform appendix. Straight down from the cecum, the colon has a tubular morphology, curved in the distal right colon and linear in the left colon. The distal right colon is 89.3 ± 17.6 mm long with a diameter of 8.49 ± 0.29 mm. The left colon in the rat is 95.4 ± 13.5 mm long, with a diameter of 9.28 ± 0.37 mm in the proximal part and 8.05 ± 0.39 mm in the distal part (Table 1).

Histological examination

Histological measurement of the colonic wall thickness

Table 1 Histological and radiological features of the rat colons

Measurements	Left colon (distal to splenic flexure)		Right colon	
	Rectum	Proximal left colon	Distal right colon	Cecum
Distance to anal margin (mm)	0-45.6 ± 8.4	45.6 ± 8.4 - 95.4 ± 13.5	95.4 ± 13.5 - 184.7 ± 20.1	184.7 ± 20.1-244.3 ± 25.8
Length (mm)	45.6 ± 8.4	49.8 ± 10.5	89.3 ± 17.6	54.6 ± 22.1
Macroscopic diameter (mm)	7.79 ± 0.46	8.18 ± 0.28	8.01 ± 0.32	20.11 ± 2.31
Radiological diameter (mm)	8.05 ± 0.39	9.28 ± 0.37	8.49 ± 0.29	20.78 ± 1.88
Full-thickness samples to anal margin (cm)	3	7	14	20
Wall thickness (µm)	658.3 ± 50.7	600.0 ± 58.6	562.5 ± 21.6	550.0 ± 49.2
Muscular thickness (µm)	229 ± 42.9	118.8 ± 11.3	170.0 ± 33.6	140.0 ± 24.3
Mucosal thickness (µm)	283.0 ± 25.6	289.0 ± 23.4	256.3 ± 16.0	260.0 ± 22.8

and description of the mucosal pattern substantiates a subdivision of the colon into 4 parts (cecum, distal right colon, proximal left colon and rectum). The wall thickness progressively decreases from the rectum to cecum, whereas the muscular layer was thinner in the proximal left colon (Table 1 and Figure 1).

DISCUSSION

The present study successfully described the rat colon anatomy to develop a rat model for future studies of therapeutic colonoscopy. Endoscopic and tomographic study of colon morphology showed an easy access with tubular morphology in the entire left colon. The right colon does not assume a linear morphology, the cecum being the most prominent part. In addition, histological measurement of the colonic wall thickness confirmed a progressive decrease from rectum to cecum. The muscular layer was thinner in the proximal left colon. These findings are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments because of the effects of thermal injury and coagulation necrosis of the muscularis propria and serosa. Colonoscopic perforation is a potentially life-threatening complication with an incidence rate ranging from 0.07% to 0.1% in diagnostic and therapeutic colonoscopies, respectively^[21,22].

Our anatomical description differs from that of others^[23] because in colonoscopy the colonic inflexions are much less evident. Currently available animal models in rats for endoscopy research contain inherent flaws, fail to meet the criteria for extrapolation to humans, and therefore are unlikely to be valid. The description of the normal anatomy is an indispensable premise in experimental therapeutic endoscopy. Proposals have been made to distinguish subdivisions of the rat colon resembling those used for human anatomy with conventional radiology^[1,24]. A solution was presented 15 years ago when Hull *et al*^[10] showed that it was feasible to perform bowel preparation and TC on rats. The authors successfully performed TC with a pediatric bronchoscope. Colonoscopy limited to the splenic flexure in rats has been previously reported^[10]. Confirmation that the cecum was reached was done by visualizing liquid stool which was present only in the cecum in all rats^[25,26].

Our subdivision of the rat colon constitutes a simplification of subdivisions presented by others^[11] who have emphasized the theoretical anatomical data. Our proposed subdivision of the colon is practical and justified by the importance of endoscopic access and the thickness of various portions of the colon wall.

In conclusion, a reproducible rat model has been achieved. These data are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments.

COMMENTS

Background

Significant progress in endoscopic techniques has been made in the last years. There is a need for a solid colonoscopy animal model, complemented with digital radiology.

Research frontiers

The present study successfully described the rat colon anatomy to develop a rat model for future studies of therapeutic colonoscopy.

Innovations and breakthroughs

The subdivision of the rat colon constitutes a simplification of subdivisions presented by others who have emphasized the theoretical anatomical data. The proposed subdivision of the colon is practical and justified by the importance of endoscopic access and the thickness of various portions of the colon wall. This study identified that the muscular layer was thinner in the proximal left colon.

Applications

These findings are important for deciding when to perform endoscopic resections or when to induce perforations to apply endoscopic treatments.

Terminology

Colonoscopy is an invasive technique that permits a direct visualization of the colon mucosa. Computed tomography is a radiology technique that allows obtaining 3D images.

Peer review

The authors described the rat colon anatomy to develop a rat model for future studies of therapeutic colonoscopy. Endoscopic and tomographic study of colon morphology showed an easy access with tubular morphology in the complete left colon. Otherwise, the results identified that the muscular layer was thinner in the proximal left colon.

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Usefulness of applying lidocaine in esophagogastroduodenoscopy performed under sedation with propofol

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Abstract

AIM: To determine whether topical lidocaine benefits esophagogastroduodenoscopy (EGD) by decreasing propofol dose necessary for sedation or procedure-related complications.

METHODS: The study was designed as a prospective, single centre, double blind, randomised clinical trial and was conducted in 2012 between January and May

(NCT01489891). Consecutive patients undergoing EGD were randomly assigned to receive supplemental topical lidocaine (L; 50 mg in an excipient solution which was applied as a spray to the oropharynx) or placebo (P; taste excipients solution without active substance, similarly delivered) prior to the standard propofol sedation procedure. The propofol was administered as a bolus intravenous (*iv*) dose, with patients in the L and P groups receiving initial doses based on the patient's American Society of Anaesthesiologists (ASA) classification (ASA I - II : 0.50-0.60 mg/kg; ASA III-IV: 0.25-0.35 mg/kg), followed by 10-20 mg *iv* dose every 30-60 s at the anaesthetist's discretion. Vital signs, anthropometric measurements, amount of propofol administered, sedation level reached, examination time, and the subjective assessments of the endoscopist's and anaesthetist's satisfaction (based upon a four point Likert scale) were recorded. All statistical tests were performed by the Stata statistical software suite (Release 11, 2009; StataCorp, LP, College Station, TX, United States).

RESULTS: No significant differences were found between the groups treated with lidocaine or placebo in terms of total propofol dose (310.7 ± 139.2 mg/kg per minute *vs* 280.1 ± 87.7 mg/kg per minute, $P = 0.15$) or intraprocedural propofol dose (135.3 ± 151.7 mg/kg per minute *vs* 122.7 ± 96.5 mg/kg per minute, $P = 0.58$). Only when the L and P groups were analysed with the particular subgroups of female, < 65-year-old, and lower anaesthetic risk level (ASA I - II) was a statistically significant difference found (L: 336.5 ± 141.2 mg/kg per minute *vs* P: 284.6 ± 91.2 mg/kg per minute, $P = 0.03$) for greater total propofol requirements). The total incidence of complications was also similar between the two groups, with the L group showing a complication rate of 32.2% (95%CI: 21.6-45.0) and the P group showing a complication rate of 26.7% (95%CI: 17.0-39.0). In addition, the use of lidocaine had no ef-

fect on the anaesthetist's or endoscopist's satisfaction with the procedure. Thus, the endoscopist's satisfaction Likert assessments were equally distributed among the L and P groups: unsatisfactory, [L: 6.8% (95%CI: 2.2-15.5) *vs* P: 0% (95%CI: 0-4.8); neutral, L: 10.1% (95%CI: 4.2-19.9) *vs* P: 15% (95%CI: 7.6-25.7)]; satisfactory, [L: 25.4% (95%CI: 10-29.6) *vs* P: 18.3% (95%CI: 15.5-37.6)]; and very satisfactory, L: 57.6% (95%CI: 54-77.7) *vs* P: 66.6% (95%CI: 44.8-69.7)]. Likewise, the anaesthetist's satisfaction Likert assessments regarding the ease of maintaining a patient at an optimum sedation level without agitation or modification of the projected sedation protocol were not affected by the application of lidocaine, as evidenced by the lack of significant differences between the scores for the placebo group: unsatisfactory, L: 5.8% (95%CI: 1.3-13.2) *vs* P: 0% (95%CI: 0-4.8); neutral, L: 16.9% (95%CI: 8.9-28.4) *vs* P: 16.7% (95%CI: 8.8-27.7); satisfactory, L: 15.2% (95%CI: 7.7-26.1) *vs* P: 20.3% (95%CI: 11.3-31.6); and very satisfactory, L: 62.7% (95%CI: 49.9-74.3) *vs* P: 63.3% (95%CI: 50.6-74.7).

CONCLUSION: Topical pharyngeal anaesthesia is safe in EGD but does not reduce the necessary dose of propofol or improve the anaesthetist's or endoscopist's satisfaction with the procedure.

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Key words: Lidocaine; Propofol; Esophagogastroduodenoscopy; Sedation; Adverse effects

Core tip: We are pleased to report the second study in the literature about the possible efficacy of using an adjuvant topical anaesthesia, in this case lidocaine applied as a spray to the oropharynx, during esophagogastroduodenoscopy performed under sedation with propofol. This study is unique, however, in that it is the first randomized controlled trial demonstrating that this routine application has no beneficial effect on reduction of propofol dose or procedure-related complications, or on improved satisfaction of the endoscopist or anaesthetist. These findings may help to improve and streamline the current procedures used for endoscopy sedation, saving resources such as time during surgery and monetary costs for the topical agent.

de la Morena F, Santander C, Esteban C, de Cuenca B, García JA, Sánchez J, Moreno R. Usefulness of applying lidocaine in esophagogastroduodenoscopy performed under sedation with propofol. *World J Gastrointest Endosc* 2013; 5(5): 231-239 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/231.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.231>

INTRODUCTION

Sedation in gastrointestinal endoscopy was traditionally performed with benzodiazepines in isolation or in com-

bination with opioids. However, since the introduction of propofol nearly two decades ago, this very powerful ultra-short action hypnotic agent has emerged as the primary method for sedation in digestive endoscopy^[1-4]. Nevertheless, its use is not without risk^[5], such as serious cardiorespiratory consequences^[6], and the ability to resolve cases of over-sedation is hindered by the lack of antagonists.

Previous studies of non-sedated esophagogastroduodenoscopy (EGD) have shown that the use of topical pharyngeal anaesthesia improves the patients' perceived satisfaction with the procedure^[7,8]. Another study of patients undergoing EGD with sedation *via* the traditional drugs indicated that administration of topical anaesthesia facilitated the endoscopic examination and increased patients' tolerance^[9]. However, this beneficial effect has not been sufficiently researched in patients sedated *via* propofol^[10]. Therefore, the purpose of this study was to establish whether application of topical pharyngeal anaesthesia benefits patients undergoing EGD by reducing total propofol dosage required for sedation or affecting the rate of procedure-related adverse effects. In addition, this study assessed whether the use of topical lidocaine impacts the quality of the endoscopic examination as perceived by the endoscopist/anaesthetist.

MATERIALS AND METHODS

Patients

Consecutive patients over 18-year-old referred to the Endoscopy Unit of the Infanta Cristina Hospital for diagnostic or therapeutic EGD with sedation were recruited for the study. Patients were excluded from enrolment according to the following criteria: undergoing urgent endoscopy; presence of encephalopathy; refusal of cooperation for the treatment or study procedures; refusal to provide informed consent; not having fasted; having a history of or predisposition to methemoglobinemia (NADH reductase, pyruvate kinase, or glucose-6-phosphate dehydrogenase deficiency); women who were pregnant or lactating; or presence of known allergies to propofol and/or lidocaine (or the amide group of local anaesthetics). All enrolled study participants provided informed consent prior to the treatment procedure. The study was approved by the Clinical Trials and Research Committee, the Spanish lidocaine drug manufacturer (Inibsa, Spain), and the Spanish Medical Products Agency (AEMPS 2012-01-02).

Study design

Designed as a double blind, randomised, prospective trial, this study was conducted with patients from a single centre (Infanta Cristina Hospital Endoscopy Unit in Parla, Madrid, Spain) treated between January 2012 and May 2012. The 120 enrolled patients were randomised by computer-generated numerical codes that were marked on spray devices containing lidocaine (L) or placebo (P) and enclosed in opaque envelopes that were unsealed for use during the surgical procedure. Thus, the patient, endoscopist, and anaesthetist were all "blinded" to the

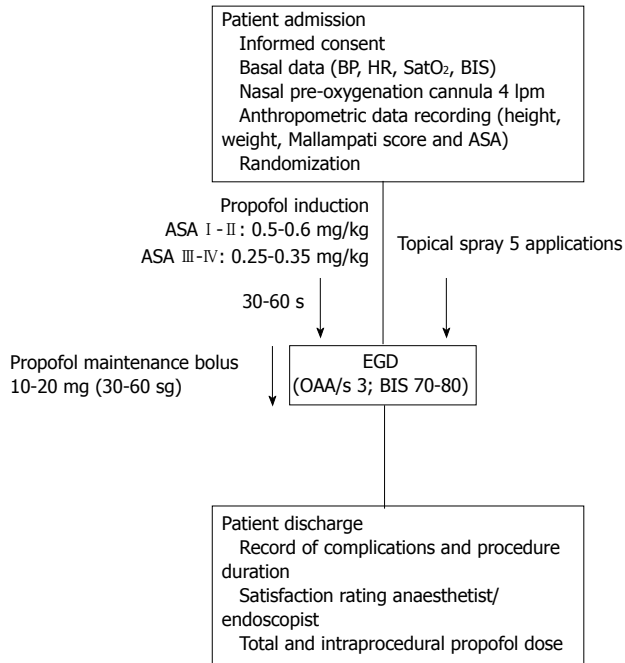


Figure 1 The sedation protocol used in this trial. BP: Blood pressure; HR: Heart rate; BIS: Bispectral index; EGD: Esophagogastroduodenoscopy; ASA: American Society of Anaesthesiologists.

group assignment. The spray application and subsequent sedation procedure are illustrated in Figure 1 and described in the proceeding section.

To guarantee the integrity of the treating physicians being blinded to the group assignment during the physical application of the spray, eight pressurized phials with controlled dosage release mechanisms were used, four of them contained 10% lidocaine (10 mg = 1 puff; Xilonibsa, Inibsa, Spain) mixed with excipients (menthol, saccharine, banana aroma, macrogol 600, and ethanol) and the other four contained the excipient solution without lidocaine (for use as placebo, so that the patient could not distinguish the two by taste). In the event of an adverse reaction and the need to unmask, only the number of the phial concerned would be identified, so that the study could continue.

A single endoscopist and anaesthetist, both experts in their fields, performed the respective procedures on all study participants. All endoscopies were performed with a EG-2990K video-esophagogastroduodenoscope equipped with a 9 mm diameter insertion tube (Pentax Corporation, Tokyo, Japan).

Anaesthesia and sedation protocols

The topical pharyngeal anaesthesia or placebo was administered 180 s prior to endoscope insertion. The various spray dispensers administered a controlled volume of 10 mg per spray. A total 50 mg of lidocaine or placebo was administered to each patient by five sequential spray applications. Gentle tongue traction was used to expose the targeted spray area: the posterior wall of the oropharynx, tonsillar pillars, soft palate and base of tongue. Be-

tween each spray, patients were asked to swallow in order to maximize the anaesthetic effect on the hypopharynx. The spray procedure was performed in a room adjoining the endoscopy unit and by trained nurses who were not involved in the subsequent endoscopy and sedation procedures, thereby further ensuring masking.

Sedation was administered by bolus intravenous (*iv*) injection of 1% propofol at various dosages adjusted by patient weight and corresponding to the patient's physical status classification according to the American Society of Anaesthesiologists (ASA) guidelines^[11]. ASA I - II patients received an initial dose of 0.5-0.6 mg/kg, followed by sequential 10-20 mg maintenance doses every 30-60 s given at the anaesthetist's discretion. ASA III-IV patients received an initial dose of 0.25-0.35 mg/kg, followed by the same maintenance protocol. This regimen aimed to achieve and maintain an optimum level of moderate sedation for the EGD procedure, which was defined as a score of 3 on the observer alertness assessment scale (OAA/S3) and estimated values of 70-80 for the bispectral range (BIS) measured by four frontal electrodes and the BIS View monitoring system (Aspect Medical System Inc., Norwood, MA, United States). Once the desired sedation level was reached, the endoscopic examination began. Regulation of maintenance propofol doses and administration frequency fluctuated according to three factors: patient's tolerance as perceived by the anaesthetist (indicated by movement, coughing, nausea, agitation), sedation level (to maintain OAA/S3), and pre-determined physical characteristics and individual factors of each patient (including age, weight, and toxic habits).

All patients were fitted with a nasal cannula prior to the procedure to deliver oxygen at 4 lpm, which was initiated at least 180 s prior to the endoscopy procedure and continuing until completion. Pulsoxymetry, electrocardiography and blood pressure measurements were taken and recorded every 120 s.

Occurrence of the following adverse effects was recorded: hypoxemia ($\text{SatO}_2 < 90\%$, or a $> 4\%$ drop relative to the baseline value if it was $\leq 93\%$), bradycardia (< 60 bpm, or a $> 10\%$ drop in relation to the baseline value), hypotension (systolic blood pressure < 90 mmHg or diastolic blood pressure < 60 mmHg), anaphylactic reaction, bronchoaspiration (clinical diagnosis based on coughing, fever and/or lung infiltrations up to 48 h after the endoscopic examination), or methemoglobinemia. Suspicion of methemoglobinemia secondary to lidocaine or cyanosis with normal oxygen saturation was addressed by sampling the arterial blood for assessment by CO-oxymetry to determine the necessary treatment.

This protocol is registered at ClinicalTrials.gov under identifier number NCT01489891.

Data recorded for statistical analyses

The following data were recorded for each patient: age, sex, weight (kg), height (m), ASA classification, medical recommendation, Mallampati score, prior history of EGD under sedation, history of or on-going alcohol/

Table 1 Comparison of basal characteristics of patients randomly assigned to the lidocaine and placebo treatment groups

	Lidocaine	Placebo	Diff ¹	P ²
<i>n</i>	59	60		
Age, yr	49.7 ± 15.81	51.7 ± 14.9	-2.0 (-7.6, 3.5)	0.47
Male sex	51.10% (37.0-65.0)	48.60% (37.6-51.8)	1.10% (0.5-2.3)	0.85
Weight, kg	70.8 ± 14.0	76.6 ± 17.0	-5.8 (-0.1, -11.4)	0.04
Height, cm	162.1 ± 9.0	162.2 ± 11.0	0.10 (-3.6, 3.7)	0.50
ASA I - II	50.4 (40.5-60.5)	46.1 (28.7-64.5)	1.10 (0.7-1.7)	0.60
Mallampati I - II	51 (41.2-60.7)	48.9 (24.4-66.5)	0.84 (0.5-1.4)	0.49
Drug abuse	50 (26.3-76.3)	49.5 (40.3-58.7)	1.00 (0.5-1.9)	1.00
Previous sedated EGD	47.6 (28.3-67.6)	50 (40.2-59.7)	0.95 (0.6-1.5)	0.80

¹Differences are expressed as RR with their respective CIs or absolute values; ²Values in bold are statistically significant. Quantitative and qualitative variables are expressed as average ± SD and as percentage with 95%CI, respectively. EGD: Esophagogastroduodenoscopy.

drug abuse, total propofol dose administered (mg), initial and maintenance propofol doses administered (mg), total and partial examination time (defined as the period from endoscope insertion to removal, in s), average BIS level reached, complete or incomplete examination, and complications. In addition, the endoscopist recorded a global satisfaction rating for the ease of performing each examination and the anaesthetist recorded a rating on the ease of reaching and maintaining the desired sedation level; these subjective ratings were based on a Likert-type 4-element scale of very satisfactory, satisfactory, neutral, and unsatisfactory.

Study objectives

The primary study objective was to determine whether use of lidocaine reduced the subsequent need for total propofol without increasing adverse effects or incomplete endoscopies, or causing significant variations in the subjective rating scales of the endoscopist and the anaesthetist. The secondary objectives were to determine the precise differences in adverse effect incidence between the lidocaine and placebo groups, and to establish the existing differences between the procedure-related satisfaction ratings awarded by the endoscopist and the anaesthetist.

Statistical analysis

Continuous variables are expressed as average ± SD and were compared between groups using the Student's *t*-test. Categorical variables are expressed as percentage and were compared between groups using the Pearson's χ^2 test. The threshold of statistical significance was set at 0.05. Stratification analysis was carried out to control for effects by potentially confounding variables. All statistical tests were performed by the Stata statistical software suite (Release 11, 2009; StataCorp, LP, College Station, TX, United States).

Sample size was calculated based on achieving a reduction of the total average propofol dose by at least

Table 2 Influence of lidocaine on propofol dose

	Lidocaine	Placebo	Diff ¹	P
Average BIS	68.1 ± 7.5	68.8 ± 7.6	0.76 (-2.0, 3.5)	0.58
Total examination values				
Total examination time, s	405.0 ± 134.8	387.0 ± 127.6	18.6 (-29.0, 66.2)	0.44
Total propofol dose, mg	134.9 ± 42.5	129.2 ± 40.4	5.6 (-9.4, 20.7)	0.45
Total propofol dose adjusted weight and time, mg/kg per minute	310.7 ± 139.2	280.1 ± 87.7	30.6 (-11.5, 72.7)	0.15
Intraprocedural examination values ²				
Partial examination time, s	281.8 ± 137.3	265.5 ± 122.3	16.3 (-30.8, 63.5)	0.49
Partial propofol dose, mg	40.9 ± 33.7	38.9 ± 31.4	2 (-9.7, 13.8)	0.73
Partial propofol dose adjusted weight and time, mg/kg per minute	135.3 ± 151.7	122.7 ± 96.5	12.6 (-33.5, 58.7)	0.58

¹Differences are expressed as RR with their respective absolute values;

²Measurements recorded from the time of endoscope insertion into the oral cavity up to the time of withdrawal, excluding the time of anaesthetic induction. Quantitative and qualitative variables are expressed as average ± standard deviation and as percentage with 95%CI, respectively. BIS: Bispectral index.

30 mg to reach and maintain the same level of objective sedation in the lidocaine group as in the placebo group. It was estimated that at least 59 patients were required for each study section (L and P) to detect statistically significant differences, admitting a risk α of 0.05 and a statistical power of 90%.

RESULTS

Patient characteristics

A total of 127 patients were prospectively recruited between January and May 2012. After applying the exclusion criteria, three patients were denied enrolment: two for age < 18 years and one for history of sensitivity to amide group anaesthetics. Four additional patients refused to participate in the study. Thus, 120 patients were initially enrolled. One enrolled patient from the lidocaine group was subsequently excluded from analysis due to a technical problem that occurred in the endoscopy room during the examination procedure.

The randomization process assigned 59 patients to the L group and 60 patients to the P group. Comparison of the two groups showed no statistically significant differences in anaesthetic risk, age, sex, Mallampati scale, drug abuse, and prior experience regarding endoscopies under sedation. However, the average weight of individuals in the placebo group was significantly higher: 5.8 kg [95%CI: (-0.1)-(-11.4)] higher than those in the lidocaine

Table 3 Influence of potentially confounding factors on the propofol dose (mg/kg per minute, adjusted for patient weight and examination time)

	Diff ¹		P ²
Age, yr			
	< 65	> 65	
Total propofol dose	315.3 ± 118.9	223.9 ± 73.7	91.4 (49.3, 133.5) < 0.001
Partial ³ propofol dose	138.2 ± 135.5	96.0 ± 81.4	42.2 (-5.6, 90.0) 0.08
Sex			
	Male	Female	
Total propofol dose	263.7 ± 87.9	314.6 ± 127.9	-59.9 (-93.8, -8.0) 0.02
Partial propofol dose	111.5 ± 101.9	139.6 ± 139	-28.1 (-75.4, 19.2) 0.20
ASA classification			
	I - II	III-IV	
Total propofol dose	310.8 ± 121.3	239.8 ± 77.7	71.0 (21.2, 120.8) < 0.001
Partial propofol dose	135.9 ± 136.3	104.1 ± 80.1	31.9 (-23.6, 87.4) 0.20
Mallampati classification			
	I - II	III-IV	
Total propofol dose	302.4 ± 119.5	262.4 ± 98.6	40.0 (-15.3, 95.3) 0.10
Partial propofol dose	127.1 ± 133.9	137.7 ± 85.9	-10.6 (-71.5, 49.9) 0.70
Drug abuse			
	Yes	No	
Total propofol dose	320.5 ± 92.1	293.0 ± 118.7	27.5 (-48.9, 103.9) 0.40
Partial propofol dose	120.3 ± 87.1	129.8 ± 129	-9.5 (-92.6, 73.6) 0.80
Previous sedated EGD			
	Yes	No	
Total propofol dose	260.2 ± 102.7	302.8 ± 118.6	-42.6 (-97.4, 12.2) 0.10
Partial propofol dose	128.9 ± 108.4	129.0 ± 130.6	-0.1 (-60.1, 59.9) 0.90

Quantitative and qualitative variables are expressed as average ± SD and as percentage with 95%CI, respectively. ¹Differences are expressed as RR with their respective absolute values; ²Values in bold are statistically significant; ³Measurements recorded from the time of endoscope insertion into the oral cavity up to the time of withdrawal, excluding the time of anaesthetic induction. ASA: American Society of Anaesthesiologists; EGD: Esophagogastroduodenoscopy.

group. The results are summarized in Table 1.

Propofol dose (primary objective)

As shown in Table 2, no statistically significant differences were found between the L and P groups in total or partial propofol doses, sedation level reached by BIS, or average total or partial examination time. However, there was a trend towards longer examination time for the L group. Stratification analysis of the increased examination time (using patient weight) indicated that the differences for total values (mg/kg per minute) and for time from endoscope insertion to removal were not significant.

Table 3 summarizes the results of stratification analyses to assess the influences of potentially confounding factors on the propofol dose. Statistically significant differ-

ences were found between the L and P groups for greater total propofol requirements among patients who were female, < 65-years old, and with lower anaesthetic risk level (ASA I - II). The latter two factors were found to be related, with the low ASA groups having a significantly greater proportion of young patients [relative risk (RR) = 3.2 (95%CI: 1.75-6.01)]. The significance of these differences was lost, however, when only the patients receiving partial doses were considered in each of these categories.

Table 4 summarizes the results of stratification analyses to assess the influence of lidocaine on the propofol dose variations according to the potential confounding factors. Lidocaine only produced a significant modifying effect on the amount of total or partial propofol administered in any the ASA I - II patients, for whom lidocaine administration prior to endoscopy appeared to have a pernicious effect, with greater total doses of propofol required as compared to the corresponding patients in the P group. However, there were no significant differences between the ASA I - II patients in the L and P groups in terms of age (45.3 ± 13.5 years *vs* 48.7 ± 14.8 years), female sex [66.6% *vs* 67.4%; RR = 0.98 (95%CI: 0.74-1.31)], and BIS level (67.4 ± 7.5 *vs* 69.6 ± 7.6), and the underlying influential factor remains unknown. Nevertheless, the significance of the pernicious effect in the ASA I - II group was lost when only the patients receiving partial propofol doses were considered for each category.

Adverse events and endoscopist/anaesthetist satisfaction (secondary objectives)

Minor complications occurred in 29.4% of the endoscopic examinations, none of which necessitated suspension of the procedure. None of the patients showed signs of methemoglobinemia. There were no significant differences between the L and P groups for total complication rates or incidence rates of the various types of adverse events (Table 5). Furthermore, stratification analysis of the complication incidences and the various risk factors (*i.e.*, advanced age, ASA level, female sex, Mallampati score, previous drug abuse, previous endoscopy, total propofol dose administered, and BIS depth) revealed no significant differences between the groups (Table 6).

Finally, the systematic use of lidocaine in EGDs under propofol sedation did not significantly affect the endoscopist's or anaesthetist's perception of satisfaction with the procedure (Figure 2, respectively).

DISCUSSION

This study shows the ineffectiveness of lidocaine as a standard sedation coadjuvant to propofol in EGDs; specifically, the systematic use of lidocaine did not reduce total or partial doses of propofol, lower incidence of adverse effects, nor increase the treating physician's satisfaction with the performance of endoscopic or anaesthetic procedures. Our data generally coincided with those of the only other study reported to date on clinical application and utility of lidocaine with propofol^[12]. In addition

Table 4 Influence of lidocaine treatment on propofol dose (mg/kg per minute, adjusted for patient weight and examination time) in relation to patients' individual characteristics

	Lidocaine	Placebo	Diff ¹	P ²
Age, yr				
< 65				
Total propofol dose	338.1 ± 138.7	292.0 ± 90.3	46.1 (-2.2, 94.4)	0.06
Partial ³ propofol dose	147.2 ± 165.6	128.9 ± 96.5	18.3 (-37.7, 74.3)	0.51
> 65				
Total propofol dose	203.6 ± 77.8	241.1 ± 68.0	-37.5 (-96.5, 21.5)	0.20
Partial propofol dose	88.7 ± 61.6	102.3 ± 97.1	-13.6 (-80.8, 53.6)	0.67
Sex				
Male				
Total propofol dose	280.0 ± 101.3	246.7 ± 69.6	33.3 (-19.2, 85.8)	0.20
Partial propofol dose	97.3 ± 95.5	125.0 ± 108.0	-27.7 (-33.7, 89.1)	0.36
Female				
Total propofol dose	330.4 ± 157.0	299.6 ± 92.1	30.8 (-28.5, 90.0)	0.30
Partial propofol dose	141.9 ± 175.2	137.5 ± 95.2	4.4 (-60.5, 69.3)	0.89
ASA classification				
I - II				
Total propofol dose	336.5 ± 141.2	284.6 ± 91.2	51.9 (2.8, 100.9)	0.03
Partial propofol dose	149.6 ± 164.5	122.1 ± 99.6	27.5 (-28.6, 83.6)	0.16
III - IV				
Total propofol dose	209.7 ± 70.0	265.7 ± 76.7	56.0 (-3.8, 115.8)	0.06
Partial propofol dose	79.4 ± 63.3	125.0 ± 88.9	-45.6 (-19.3, 110.5)	0.16
Mallampati classification				
I - II				
Total propofol dose	319.6 ± 140.0	284.3 ± 91.4	35.4 (-12.2, 83.0)	0.14
Partial propofol dose	136.1 ± 159.2	117.7 ± 102.1	18.4 (-35.4, 72.2)	0.49
III - IV				
Total propofol dose	260.8 ± 130.7	263.6 ± 72.3	-2.8 (-96.0, 90.5)	0.95
Partial propofol dose	130.8 ± 108.0	142.8 ± 69.9	-12.0 (-93.2, 69.2)	0.76
Drug abuse				
Yes				
Total propofol dose	313.5 ± 115.2	327.6 ± 75.4	-14.1 (-156.1, 127.9)	0.82

Partial propofol dose	96.1 ± 100.8	144.4 ± 73.8	-48.3 (-177.1, 80.5)	0.41
No				
Total propofol dose	310.5 ± 142.2	275.9 ± 88.2	34.6 (-10.2, 79.4)	0.12
Partial propofol dose	138.9 ± 155.1	120.8 ± 98.6	18.1 (-31.1, 67.3)	0.46
Previous sedated EGD				
Yes				
Total propofol dose	297.6 ± 116.3	226.1 ± 79.1	71.6 (-18.4, 161.7)	0.11
Partial propofol dose	124.4 ± 129.5	132.9 ± 91.5	-8.5 (-110.1, 93.1)	0.86
No				
Total propofol dose	313.4 ± 144.4	292.3 ± 85.7	21.1 (-26.9, 69.1)	0.38
Partial propofol dose	137.5 ± 157.0	120.4 ± 98.4	17.1 (-35.8, 70.0)	0.52

Quantitative and qualitative variables are expressed as average ± SD and as percentage with 95%CI, respectively. ¹Differences are expressed as RR with their respective absolute values; ²Values in bold are statistically significant; ³Measurements recorded from the time of endoscope insertion into the oral cavity up to the time of withdrawal, excluding the time of anaesthetic induction. ASA: American Society of Anaesthesiologists; EGD: Esophagogastroduodenoscopy.

to the main conclusions stated above, the previous study also showed that the application of lidocaine may help to reduce the gag reflex. Some important differences that exist between their study design and our own may explain their unique result. First, the previous study used a lower dose of lidocaine (40 mg *vs* 50 mg in our current study). Second, the previous study did not consider dosage as an objective, and did not monitor sedation levels using objective methods. These differences may affect the comparative interpretation of the previous and current studies' results.

In the current study, univariate stratified analysis indicated that advanced age, male sex, and elevated anaesthetic risk were independent factors related to reduced total propofol, but not partial, dose required during an EDG examination. In concordance with these results, both advanced age and male sex are factors that have been previously demonstrated as related to need for a lower dose of sedatives during endoscopy^[13]. It is important to note here that the patients in our study with a higher ASA classification were administered lower total propofol doses for the sedation induction. Neither the patient's Mallampati score, drug abuse history, nor previous endoscopy under sedation affected the propofol dose. In relation to the Mallampati score, two previous studies have shown modifications in the tolerance perceived by patients from the subgroup with less retropharyngeal space (Mallampati III-IV). It has been suggested that occlusive morphology of the oropharynx may be related to greater endoscope friction on the posterior wall and tonsillar pillars, possibly

Table 5 Distribution of complications between groups

	Lidocaine	Placebo	Diff ¹	P
Complications	32.2 (21.6-45.0)	26.7 (17.0-39.0)	1.2 (0.7-2.1)	0.50
Desaturation	57.1 (25.0-84.2)	54.5 (38.0-70.1)	1.0 (0.5-2.1)	0.90
Hypotension	63.6 (42.9-80.3)	66.6 (43.6-84.0)	0.95 (0.6-1.5)	0.80
Bradycardia	13.6 (3.9-34.2)	25.0 (6.3-55.9)	0.5 (0.1-2.7)	0.46
Aspiration	0 (0-17.4)	5.5 (0-27.6)	-	0.26
Bronchospasm	9.0 (1.3-29.0)	0 (0-20.7)	-	0.19

¹Differences are expressed as RR with their respective CIs. Variables are expressed as percentage with 95%CI. The complication subcategories report incidence in relation to total complications.

Table 6 Distribution of complications according to individual risk factors of patients in endoscopy sedation

			Diff ¹	P
Age, yr	< 65	> 65		
	22.8 (11.8-39.2)	17.6 (10.8-27.2)	1.3 (0.6-2.7)	0.25
Sex	Male	Female		
	31.4 (18.4-48.1)	41.2 (31.3-51.8)	0.7 (0.4-1.3)	0.15
ASA classification	I - II	III - IV		
	22.8 (11.8-39.2)	21.2 (13.7-31.1)	1.1 (0.5-2.2)	0.41
Mallampati classification	I - II	III - IV		
	17.1 (7.7-33.0)	17.6 (10.9-27.2)	0.9 (0.4-2.3)	0.47
Drug abuse	Yes	No		
	2.8 (0-15.8)	10.6 (5.4-19.1)	0.2 (0.01-2.0)	0.08
Propofol dose ²	> 277	< 277		
	30.5 (20.2-43.2)	26.7 (17.0-39.1)	1.1 (0.6-2.0)	0.32
Average BIS	< 70	> 70		
	33.3 (24.0-44.2)	21.0 (10.8-36.6)	1.6 (0.8-3.1)	0.08
Previous sedated EGD	Yes	No		
	17.1 (7.7-33.0)	20.0 (12.4-30.5)	0.8 (0.3-2.0)	0.36

¹Differences are expressed as RR with their respective CIs; ²The propofol dose is reported as the cut-off point calculated as the mean of the total propofol dose administered to the patients in the trial: 277 mg/kg per minute. Variables are expressed as percentage with 95%CI. BIS: Bispectral index; ASA: American Society of Anaesthesiologists; EGD: Esophagogastroduodenoscopy.

explaining the lower tolerance of non-sedated EGD observed in this subgroup of patients^[14]. Indeed, lidocaine has been shown to have a beneficial effect in Mallampati III-IV patients undergoing non-sedated EGD^[7]. Likewise, factors such as not having undergone a previous endoscopy with sedation or drug abuse have been previously identified as factors predisposing to poorer patient tolerance of the EGD procedure^[15,16]; the fact that these patients in our study cohort did not require greater propofol doses may suggest a marginal influence of these factors.

The significant difference found in greater total propofol dose requirements for patients with ASA I - II who received lidocaine were did not exist when intrapro-

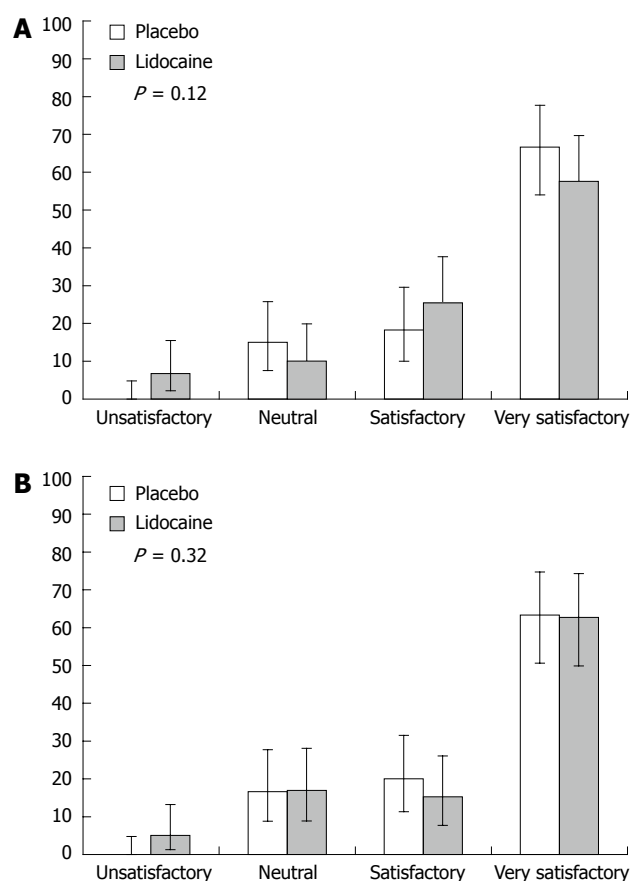


Figure 2 Endoscopist satisfaction index and anaesthetist satisfaction index. A: Endoscopist satisfaction index; B: Anaesthetist satisfaction index. Each category is expressed as a percentage value, with confidence interval adjusted for a significance of 95%.

cedural doses were considered for the analysis. Therefore, the essential difference between these groups lies in the different induction doses that were used to reach an OAA/S3 sedation level prior to the start of the endoscopic examination. Subordinate analysis of the potential factors that may have explained this different response in ASA I - II patients (such as the Mallampati score, drug abuse, age, sex, or average BIS level) did not identify any as significantly associated. Only the variation between individuals in relation to the necessary propofol doses and uncontrollable randomization of the study groups for the above-mentioned patient factors might explain the differences found.

Although not statistically significant, the differences observed regarding the increase in the necessary dose (both partial and total) in the lidocaine group as compared to the placebo group may be explained by several factors. First, we propose that the greater average weight of patients in the placebo group, and uncontrollable effect of the randomization process, may have contributed to the results. The patient's individual weights affected the propofol dose administered in the initial bolus as per the protocol used (such that an obese patient received an initially higher dose which may have caused a quicker and more effected sedation level than in the non-obese

or thin patients). These individual responses to propofol doses and dosage administration might paradoxically explain the greater induction phase dose requirement in the lidocaine group (characterized as thinner) as compared to the placebo group (characterized as heavier). Thus, while the placebo group received a bolus with a higher initial dose, the lidocaine group received a lower overall dose.

One of the most important advantages of our study design is the quality control of sedation levels during endoscopic procedures. The optimum sedation level for upper digestive endoscopy has been defined by consensus as moderate in ASA III-IV patients and moderate-deep in ASA I-II patients^[17]. This sedation level is roughly equivalent to level 3 on the OAA/S alert-sedation scale^[18]. We believe that the use of a single anaesthetist, who specialises in endoscopic sedation, for all of the examinations performed in this study cohort benefitted the quality of this study by helping to achieve a possibly homogenous sedation level across the patient population. In addition, however, we made objective measurements of the sedation levels reached and performed analysis with the average BIS index of the groups and subgroups. It is known that moderate sedation in correlation with the Ramsay scale at levels 3-4 encompasses BIS values 70-80^[19], which was found in 65 of our patients.

Our study showed a greater overall incidence of side effects arising from sedation with propofol as compared to previous reports, but with no significant differences between the lidocaine and placebo groups^[20,21]. The most frequent adverse effects observed were hypotension and desaturation, both of which occurred in minor ranges. No serious adverse reactions occurred in any of the 119 participants. In our study, only 5.8% of cases experienced a hypoventilation incident (as defined in endoscopic procedures under sedation with propofol at 50%-84%, with repercussions in mild transitory hypoxemia between 4%-7%^[2,20,21]), none of which required ventilation with a mask bag (data not shown). Hypotension occurred in 21.8% of patients, but there was no difference between the incidence in the lidocaine and placebo groups. The incidence of this complication in our study cohort was greater than previously reported in the literature, which ranges between 3%-7%^[21]. The possibility of incidentally recording blood pressure figures very close to the initial induction bolus may explain our results, as the method of bolus administration has known risk for causing hypotension, as compared to the continual infusion methods^[22,23].

Regarding procedural satisfaction perceived by the treating physician, a Likert scale of four elements was designed for use by the anaesthetist and the endoscopist immediately after the procedure completion to assess the ease of attaining and maintaining an appropriate sedation level for the former and the ease of achieving examination objectives for the latter. Such results may overlap with those recently obtained by Heuss *et al.*^[12], who also demonstrated the inefficacy of lidocaine to improve the satisfaction of endoscopists.

Our study has three relevant limitations that must be

considered when interpreting our findings. The first is the absence of a patient satisfaction assessment. In our opinion, the greater depth of sedation reached with propofol might affect these results and their comparability with results from the older protocols with lower doses. The second limitation is the sedation level achieved, which, while sufficient and subjectively monitored by an expert anaesthetist, had recorded BIS levels at the lower limit of the interpolation validated as OAA/S3. This raises the question as to whether possible over-sedation in some patients might interfere with the conclusions of our study, and whether different results might have been obtained with more superficial sedation. Lastly, the use of patients from a single centre, treated by a single endoscopist, a single anaesthetist and a single nursing team, may have caused some bias.

In conclusion, the use of topical pharyngeal anaesthesia does not reduce the propofol dose required to maintain optimum sedation levels in EGD. While its use does not increase the incidence or type of adverse effects, it also does not improve the treating physician's satisfaction with the procedure itself. This lack of benefit suggests that topical lidocaine application may be removed from the EDG procedure carried out with propofol sedation, and further studies should consider this option.

COMMENTS

Background

Application of topical pharyngeal anaesthesia has been shown to improve patient tolerance of and satisfaction with both non-sedated and traditional sedated endoscopy procedures. However, this effect has not yet been demonstrated specifically with propofol sedation protocols.

Research frontiers

Lidocaine is a common topical aesthetic applied routinely and frequently as coadjuvant with sedation agents in endoscopy procedures, such as esophagogastroduodenoscopies (EGDs), performed without sedation. However, no systematic investigations have yet reported on its utility in propofol-based sedation protocols in terms of reduction of doses or of side effects. This study demonstrates that the systematic use of lidocaine in esophagogastroduodenoscopy with propofol sedation is ineffective for reducing the doses required for or side effects related to propofol sedation.

Innovations and breakthroughs

Potential pitfalls of using a procedure or coadjuvant agent - such topical lidocaine application with propofol-sedated endoscopy - without evidence of actual clinical utility or benefit include unnecessary increases in monetary costs and risk and discomfort to the patient. This is the first study to report that application of topical lidocaine does not decrease the dose of propofol necessary to reach and maintain an optimal level of sedation during an esophagogastroduodenoscopic procedure. Furthermore, the results suggest that its use may increase the propofol dosage required in certain patients.

Applications

Topical pharyngeal anaesthesia neither reduces the necessary doses of propofol nor improves the endoscopist's or anaesthetist's satisfaction with the procedure's performance. However, its use does not increase the incidence or type of adverse effects related to the propofol-sedated esophagogastroduodenoscopy. Therefore, the authors suggest that the routine use of lidocaine in all EGDs performed with propofol sedation be reconsidered.

Terminology

The bispectral index was introduced by Aspect Medical Systems, Inc. in 1994 as a novel measure of the level of a consciousness while under general anaesthesia by using algorithmic analysis of a patient's electroencephalogram. This measurement is used in conjunction with other physiologic monitoring

procedures, such as electromyography, to estimate the dose and administration of anaesthesia in order to minimize the possibility of intraoperative awareness. Meanwhile, the observer's assessment of alertness/sedation scale was developed to measure the level of alertness in subjects who are sedated.

Peer review

In this randomized controlled trial, de la Morena *et al* compare the potential benefit of topical lidocaine as a coadjuvant to propofol sedation during esophagogastroduodenoscopy. In particular, they investigate whether the lidocaine application may reduce the dose and/or side effects of propofol. The study is designed as a single centre, double blinded, prospective trial, in which 119 patients received propofol-sedated EGDs with or without lidocaine. Comparative analysis of quantitative and qualitative variables revealed that the lidocaine application may be safe but unnecessary, providing neither increased risk of complications nor clinical benefit to the patient or the treating physicians.

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Risk of colorectal polyps in patients with sporadic gastric polyps: A case-control study

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Abstract

AIM: To assess the risk of colonic polyps, adenomas and advanced neoplastic lesions (ANL) in patients with sporadic gastric polyps, especially those with fundic gland polyps (FGP).

METHODS: Clinical records of patients who had performed an upper and a lower digestive endoscopy between September 2007 and August 2008 were retrospectively analyzed. A case-control study was carried out, calling patients with gastric polyps as "cases" and patients without gastric polyps as "controls". The risk of colonic polyps, adenomas and ANL (villous component $\geq 25\%$, size ≥ 10 mm, or high grade dysplasia) was assessed [odds ratio (OR) and its corresponding 95%CI].

RESULTS: Two hundred and forty seven patients were analyzed: 78 with gastric polyps (cases) and 169 without gastric polyps (controls). Among the cases, the majority of gastric polyps were FGP (80%, CI: 69-88) and hyperplastic (20%, CI: 12-31); 25% had colonic polyps (25% hyperplastic and 68% adenomas, from which 45% were ANL). Among the controls, 20% had colonic polyps (31% hyperplastic and 63% adenomas, from which 41% were ANL). The patients with sporadic FGP had an OR of 1.56 (CI: 0.80-3.04) for colonic polyps, an OR of 1.78 (CI: 0.82-3.84) for colonic adenomas, and an OR of 0.80 (CI: 0.21-2.98) for ANL. Similar results were found in patients with gastric polyps in general.

CONCLUSION: The results of this study did not show more risk of colorectal adenomas or ANL neither in patients with sporadic gastric polyps nor in those with FGP.

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Key words: Colorectal polyps; Advanced neoplastic lesions; Gastric polyps; Fundic gland polyps gastric polyps; Case-control study

Core tip: The risk of colonic adenomas in patients who have sporadic gastric polyps, especially those of fundic gland polyps (FGP), is still to be definitely determined. The purpose of our study was to assess the risk of colonic polyps, adenomas and advanced neoplastic lesions in patients who have sporadic gastric polyps, especially of FGP, due to the fact that these are the most common gastric polyps in our population.

Cimmino DG, Mella JM, Luna P, González R, Pereyra L, Fischer C, Mohaidle A, Vizcaino B, Medrano MA, Hadad A, Pedreira S, Boerr L. Risk of colorectal polyps in patients with sporadic gastric polyps: A case-control study. *World J Gastrointest En-*

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INTRODUCTION

The occurrence of gastric and duodenal polyps is higher in several colonic polyposis syndromes^[1,2]. However, the risk of colonic polyps and adenomas in patients who have sporadic gastric polyps, especially the fundic gland polyps (FGP), remains controversial.

Several authors have studied the relationship between the presence of different types of gastric polyps and the risk of colonic polyps and adenomas^[3]. Yang *et al*^[4] reported that the patients who have gastric adenomas could be more prone to present colorectal adenomas, and suggested that in the case of gastric adenomas the patient should be prescribed a screening colonoscopy.

However, the risk of colonic adenomas in patients who have sporadic gastric polyps, especially those of FGP, is still to be definitely determined.

It has been reported that patients suffering from familial adenomatous polyposis (FAP) show an increased incidence of gastric fundic gland polyps; there are series^[5] showing that up to 88% of these patients have FGP. The presence of this type of gastric polyps is supposed to be a marker of colonic neoplasia among the general population. In a retrospective study, Teichmann *et al*^[6] showed that patients who had gastric fundic gland polyps were more prone to suffer from colorectal neoplasias. Nevertheless, Dickey *et al*^[7] could not confirm Teichmann's findings in a prospective study.

The purpose of our study was to assess the risk of colonic polyps, adenomas and advanced neoplastic lesions (ANL) in patients who have sporadic gastric polyps, especially of FGP, due to the fact that these are the most common gastric polyps in our population.

MATERIALS AND METHODS

A case-control study was carried out. Patients with gastric polyps were regarded as "cases" and those without them as "controls". The clinical records of patients who had undergone an upper and a lower digestive endoscopy between September 2007 and August 2008 were retrospectively analysed. Those patients with previous digestive endoscopies, an inadequate colonic cleansing, an incomplete colonoscopy, gastric or colonic surgeries, and intestinal inflammatory disease were excluded.

Those patients with gastric polyps were identified by an electronic search in the Endoscopy database. The final diagnosis of the different types of gastric polyps was histopathologically assessed. The presence of fundic gland polyps was suspected by the finding of sessile polyps at the body or fundus of the stomach, with their typical appearance (Figure 1). The diagnosis was confirmed by the histological analysis of polyps resections (polypectomies

with forceps or snares). The fundic gland polyps diagnosis was based on the finding of enlarged glands in a cystic shape, covered with fundic epithelium (parietal cells and chief cells) mixed with normal glands, generally without inflammation or evidence of dysplasia. Besides, the grade of inflammation of the gastric mucosa was mostly determined by antral and gastric body biopsies. Gastritis were arbitrarily classified in two types. Firstly, "active or severe gastritis" were analysed together and they were diagnosed when the gastric mucosa showed acute inflammatory infiltrate. Secondly, "mild or inactive gastritis" were also analysed together and they were diagnosed by the presence of minor inflammatory lymphoplasmacytic infiltrates. Normal gastric biopsies (which is unusual in our medical field) were also analysed together with those that showed "mild-minor or inactive" inflammation. Infection with *Helicobacter pylori* (*H. pylori*) was histopathologically determined due to the presence of curved bacilli typical of *H. pylori* by using Giemsa's stain. The diagnosis of the different types of colonic polyps was histopathologically determined.

The risk of colonic polyps, adenomas and ANL (defined as villous component $\geq 25\%$, size ≥ 10 mm or high grade dysplasia) was assessed in patients with gastric polyps in general, and in particular, in those with FGP.

Statistical analysis

For constant variables, the media with its corresponding SD was calculated. The nominal variables were expressed in percentages with their corresponding 95%CI. The risk of colonic polyps, adenomas and ANL was calculated, measured in odds ratio (OR) with its corresponding 95%CI, using the Fischer's test. Results were considered significant when the OR's with their CI did not include the 1. In order to assess the influence on the main outcomes of the variables that were significantly different between the cases and controls (Table 1), a binary logistic regression model was carried out by introducing these variables, in order to prove if these variables were independent predictor of the outcomes. The relationship between the presence of FGP and the *H. pylori* infection was also analysed. The SPSS 17.1 software for Windows was used.

RESULTS

We analyzed 247 patients (Table 1). Seventy-eight had gastric polyps, from which 62 were of FGP. Table 1 shows the characteristics of patients with and the without gastric polyps.

Among the cases the media age was 62 ± 11 years old, and 71% (CI: 59%-81%) of the patients were women. Most of gastric polyps were FGP (80%, CI: 69%-88%) and hyperplastic (20%, CI: 12%-31%); no gastric adenomas were found. Seventy six percent (76%, CI: 65%-85%) of the patients had inactive or minor gastritis in the gastric mucosa biopsies, and 24% (CI: 15%-35%) had active or severe gastritis. *H. pylori* infection detected

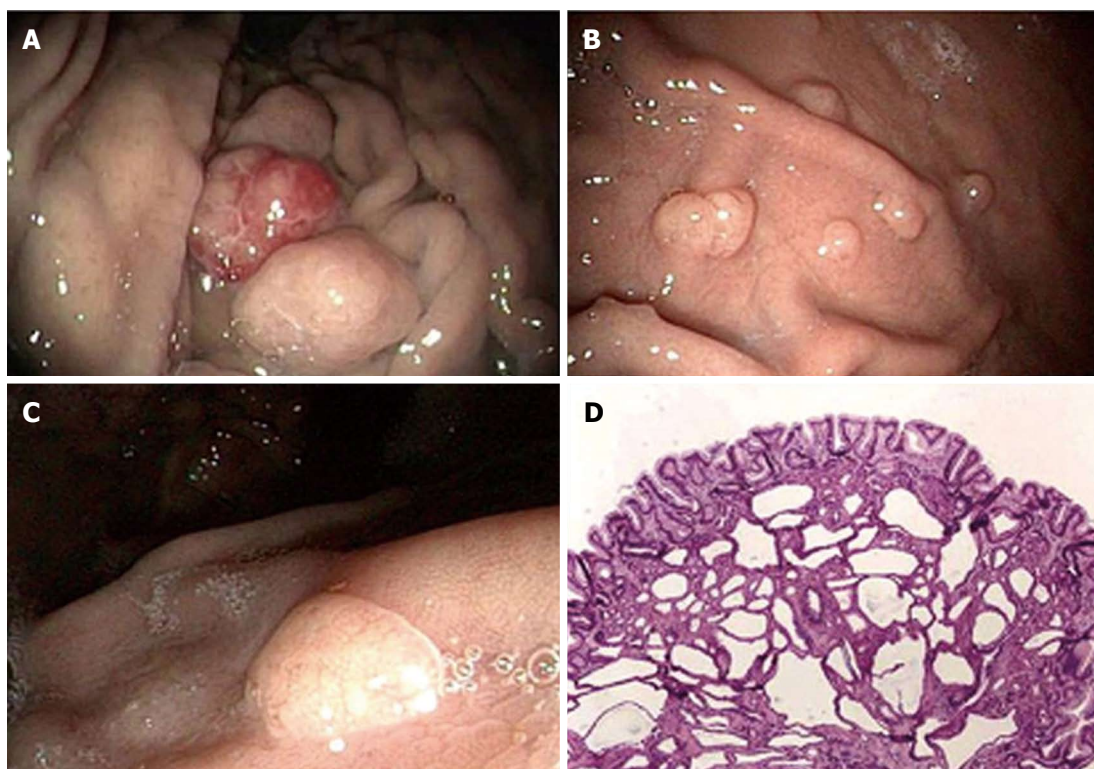


Figure 1 Fundic gland polyps: Sessile polyps at the body or fundus of the stomach, with their typical appearance. The fundic gland polyps diagnosis is based on the finding of enlarged glands in a cystic shape, covered with fundic epithelium mixed with normal glands, generally without inflammation or evidence of dysplasia.

Table 1 Characteristics of the patients (cases and controls)

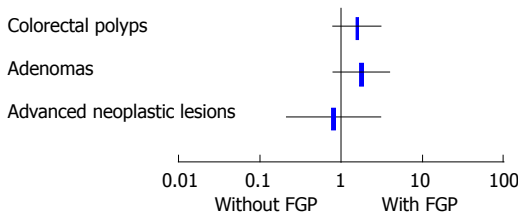
Characteristics of patients	With gastric polyps (<i>n</i> = 78)	Without gastric polyps (<i>n</i> = 169)	<i>P</i> value
Age years old (average \pm SD)	62 \pm 11	61 \pm 14	0.51
Sex (%women, CI)	71% (59-81)	61% (53-68)	0.11
Gastric polyps (%patients, CI)			
Fundic gland polyps	80% (69-88)	Did not have gastric polyps	
Hyperplastic	20% (12-31)		
Indications of the UGIEs (%patients, CI)			
Epigastralgia	38% (29-50)	46% (39-54)	0.14
Gastroesophageal reflux	22% (13-32)	9% (5-15)	< 0.01
Anemia	10% (4-19)	8% (4-13)	0.32
Abdominal pain	8% (3-16)	10% (6-16)	0.31
Digestive bleeding	4% (1-10)	6% (3-11)	0.30
Screening	6% (2-14)	9% (5-14)	0.35
Other	12% (4-19)	12% (4-13)	0.32
Gastric mucosa histology (%patients, CI)			
Minor gastritis	76% (65-85)	68% (60-76)	0.15
Severe gastritis	24% (15-35)	32% (24-39)	0.15
<i>Helicobacter pylori</i> infection (%positives, CI)	20% (11-31)	29% (22-38)	0.07
Indications of the colonoscopies (%patients, CI)			
Screening	37% (26-49)	43% (35-50)	0.25
Abdominal pain	17% (9-27)	23% (17-30)	0.16
Constipation	18% (10-28)	7% (3-11)	< 0.01
Anemia	13% (6-22)	9% (5-14)	0.23
Digestive bleeding	4% (1-11)	7% (3-12)	0.24
Other	11% (5-21)	11% (6-15)	0.12
Colonic polyps (%patients, CI)	25% (16-37)	20% (14-26)	0.17
Type of colonic polyps (%colonic polyps, CI)			
Hyperplastic	25% (7-52)	31% (16-49)	0.95
Adenomas	68% (41-89)	63% (45-78)	0.63
ANL	45% (16-76) of the adenomas	41% (21-63) of the adenomas	0.82

UGIEs: Upper gastrointestinal endoscopies; ANL: Advanced neoplastic lesions.

Table 2 Risk of developing colorectal polyps, adenomas and advanced neoplastic lesions

	Colonic polyps (OR, 95%CI)	Colonic adenomas (OR, 95%CI)	ANL (OR, 95%CI)
Presence of gastric polyps	1.41 (0.75-2.68)	1.63 (0.77-3.42)	1.67 (0.56-5.01)
Presence of gastric fundic gland polyps	1.56 (0.80-3.04)	1.78 (0.82-3.84)	0.8 (0.21-2.98)

ANL: Advanced neoplastic lesions; OR: Odds ratio.


Figure 2 Risk of presenting colonic lesions in patients with fundic gland polyps (odds ratio, 95%CI). FGP: Fundic gland polyps.

by gastric biopsies was found in 20% (CI: 11%-31%) of patients. The most common indications for the upper gastrointestinal endoscopies (UGIEs) were: epigastralgia (38%) and typical gastroesophageal reflux disease (GERD) symptoms (22%). Twenty five percent (25%, CI: 16%-37%) of the cases had colonic polyps from which 25% were hyperplastic and 68% were adenomas (45% of the adenomas were ANL). The most common indications for colonoscopies were: colorectal cancer screening (37%) and constipation (18%).

Among the controls, the media age was 61 ± 14 years old, and 61% (CI: 53%-68%) of the patients were women. Sixty eight percent (68%, CI: 60%-76%) of the controls had inactive or minor gastritis in the gastric biopsies and 32% (CI: 24%-39%) had active or severe gastritis. The gastric biopsies showed that 29% (CI: 22%-38%) of the patients had *H. pylori* infection. The most common indications for the UGIEs were: epigastralgia (46%) and typical GERD symptoms (9%). Twenty percent (20%, CI: 14%-26%) of patients had colonic polyps, from which 31% were hyperplastic and 63% were adenomas (41% of these adenomas were ANL). The most common indications for the colonoscopies were: colorectal cancer screening (43%) and abdominal pain (23%).

Within the patients who had colonic polyps, none of them had colonic polyposis at the moment of the colonic examination. The average number of colonic polyps in each patient who had colonic polyps was 1.46 ± 1 polyp, and the range was from 1 to 6 polyps (in only one patient we found 6 polyps in the colon, from which 3 were hyperplastic and 3 adenomas).

The prevalence of gastric infection due to *H. pylori* was lower among the patients who had gastric polyps in comparison with the ones without them (29% *vs* 20%, $P = 0.07$). This difference was significantly bigger when the group of patients with and without FGP were analyzed

Table 3 Logistic regression

	P value		
	Colonic polyps	Colonic adenomas	ANL
Female sex	0.488	0.121	0.369
GERD	0.457	0.969	0.525
Constipation	0.083	0.865	0.613
<i>Helicobacter pylori</i> infection	0.557	0.292	0.772

Influences of the analysed variables in the main outcomes. GERD: Gastroesophageal reflux disease; ANL: Advanced neoplastic lesions.

(31% *vs* 14%, $P = 0.01$); the relative chances of having the *H. pylori* infection were 63% less (OR: 0.37, CI: 0.16-0.86) in the patients who had FGP.

Table 2 shows the main outcomes. Patients with gastric polyps had an OR of 1.41 (CI: 0.75-2.68) for having colonic polyps, an OR of 1.63 (CI: 0.77-3.42) for having adenomas, and an OR of 1.67 (CI: 0.56-5.01) for ANL. Patients with FGP (Figure 2) had an OR of 1.56 (CI: 0.80-3.04) for having colonic polyps, an OR of 1.78 (CI: 0.82-3.84) for having colonic adenomas, and an OR of 0.80 (CI: 0.21-2.98) for ANL. When using a binary logistic regression model for detecting influences on the risk of colonic polyps, adenomas and ANL between cases and controls (Table 3), we observed that the indications of the endoscopies (especially typical GERD symptoms and constipation) and the *H. pylori* infection were not determinants of our main outcomes.

DISCUSSION

The aim of this study was to establish the risk of colonic polyps and adenomas in patients with gastric polyps, especially those of FGP. We did not find any relationship between the presence of FGP and colorectal polyps (OR: 1.56, CI: 0.80-3.04). In addition, we could not prove that the presence of this kind of gastric polyps predisposed patients to ANL (which might be considered as a surrogate outcome of colorectal cancer; OR: 0.80, CI: 0.21-2.98). It is very important to point out that in our study there were no patients with colonic polyposis syndromes, and therefore, among the patients who had gastric polyps, their origin could be labelled as "sporadic". Our results are important because they are different from other author's.

In 2002, in a prospective study, Jung *et al*^[8] concluded that patients who had FGP (Elster's cysts) could have a higher incidence of colorectal tumours and should undergo a diagnostic colonoscopy. These authors found a highly remarkable preponderance of colon adenocarcinoma (12.5%) among the 65 patients analysed who had FGP. In our study none of the 62 patients who had FGP presented colorectal cancer.

In 2005, Declich *et al*^[9] suggested that patients who had sporadic FGP should undergo a colonoscopy since they could be more prone to have colonic adenomas. However, in their study, such conclusion is not clearly justified or stated.

In 2008, in a retrospective study, Teichmann *et al*^[6] showed that patients who had gastric fundic gland polyps were more prone to suffer from colorectal neoplasias (15.5% in patients with FGP *vs* 9.2% in controls, $P < 0.05$), although they could not prove a higher occurrence of colonic polyps. In their study, the FGPs were diagnosed in patients undergoing endoscopies because of gastrointestinal bleeding, which in term could have originated a selection bias. According to this, the positive relationship between gastric fundic gland polyps and colorectal cancer could be influenced by bias in the process of selection of the patients included in the study. In our study, the gastrointestinal bleeding accounted for less than 10% of the endoscopy indications. We also carried out a logistic regression to determine the influence of the endoscopy indications on the main outcomes.

In 2009, Genta *et al*^[10] published the biggest cohort, so far, of patients who had FGP. They assessed the risk of presenting colorectal neoplasias in patients with FGP. The authors analysed 6081 patients who had FGP and showed that the risk of presenting colorectal adenomas was higher among the women who had FGP (OR: 1.43, 95%CI: 1.26-1.63) and would not be increased among the men. They also showed that patients without FGP could be 29 times more prone to be infected with the *H. pylori* bacteria as compared to the patients who had FGP (OR: 29, 95%CI: 20-41). In our study, gastric infection with the bacteria *H. pylori* was almost 3 times more frequent in patients without FGP than in patients with them (OR: 2.65, CI: 1.15-6.27). The presence of FGP was related to a relative reduction of 63% in the risk of *H. pylori* infection. We couldn't infer that female sex could be a conclusive element in the presence of colonic lesions in patients with FGP as we found that sex had not influence in our main outcomes (Table 3).

Advantages: (1) strict exclusion criteria based on the factors which could increase the power of the bias and modify the analysed groups; (2) thorough description of the characteristics of the patients analysed in both groups; (3) none of the patients included was given a colonic polyposis diagnosis; and (4) correct statistical analysis. Limits: it is a retrospective study.

In the daily practice it is very common to attend patients with "sporadic" FGP which are nowadays the most usual type of gastric polyps in our medical field. The results of this study did not show an increase in the risk of colorectal adenomas or ANL neither in patients with sporadic polyps of FGP, nor in patients with gastric polyps in general. It is very important to point out that we didn't find gastric adenomas in the patients included, because it is well known that the presence of gastric adenomas have already been shown to be a risk for colorectal adenomas^[4]. In our population, the prevalence of gastric adenomas is extremely low. It might be because Argentina has a population with low basal risk for gastric cancer, and also because of the low prevalence of *H. pylori* infection (close to 15%-30%) in our patients."

These results are important because they mark a dis-

tinguishing difference between patients with "sporadic" gastric fundic gland polyps and patients who present colonic polyposis hereditary syndromes and who have gastric fundic gland polyps.

In accordance with the findings of other authors, the patients with FGP would be more prone to have "normal" stomachs ("normal, mild or minor" gastritis) and would have less chances of having the *H. pylori* infection. Unfortunately, as our study was retrospective, we could not analyze any connection between proton pump inhibitors (PPI) intake and the presence of FGP, because we could not get secure data about how many patients were on long PPI treatment at the moment of their endoscopies.

COMMENTS

Background

Nowadays, it is common to find incidental gastric polyps in upper gastrointestinal endoscopies. It is well known that the incidence of gastric and duodenal polyps is higher in several colonic polyposis syndromes. However, the risk of finding colonic polyps and adenomas in patients with sporadic gastric polyps, especially the fundic gland polyps (FGP), is not well established. The aim of this study was to assess the risk of presenting colonic polyps, adenomas and advanced neoplastic lesions (ANL) in patients with sporadic gastric polyps, especially those with sporadic FGP.

Innovations and breakthroughs

These results are important because they are different from other author's. The authors did not find any relationship between the presence of FGP and colorectal polyps [odds ratio (OR) 1.56, CI: 0.80-3.04]. In addition, the authors could not prove that the presence of this kind of gastric polyps predisposed patients to ANL (which might be considered as a surrogate outcome of colorectal cancer; OR: 0.80, CI: 0.21-2.98). It is very important to point out that in this study there were no patients with colonic polyposis syndromes, and therefore, among the patients who had gastric polyps, their origin could be labelled as "sporadic".

Applications

In the daily practice it is very common to attend patients with "sporadic" FGP which are nowadays the most usual type of gastric polyps in this medical field. The results of this study suggest that patients with FGP gastric polyps do not have an increase in the risk of colorectal adenomas or ANL.

Peer review

The study by Dr. Cimmino *et al* is interesting and important from clinical point of view. During advanced upper gastrointestinal (GI) endoscopy and colonoscopy person see more and more polyps either in the upper GI tract or in the large bowel. The authors analyzed 78 gastric polyp cases and 169 controls without gastric polyps. Colonoscopy was performed in all cases and the authors studied whether the presence of gastric polyps increases the risk of colorectal polyps. They detected that neither sporadic gastric polyps nor FGP are risks for colorectal adenomas and polyps.

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Endocoil placement after endoscopic ultrasound-guided biliary drainage may prevent a bile leak

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ary drainage was achieved in all patients. Placement of an endocoil was possible in 5/6 patients. All patients responded to biliary drainage and no complications occurred.

CONCLUSION: We show that placing endocoils at the time of endoscopic ultrasound guided biliary stenting is feasible and may reduce the risk of bleeding or bile leakage.

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Key words: Endoscopic ultrasound; Biliary drainage; Transhepatic; Endocoil

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Abstract

AIM: To further reduce the risk of bleeding or bile leakage.

METHODS: We performed endoscopic ultrasound guided biliary drainage in 6 patients in whom endoscopic retrograde cholangiopancreatography (ERCP) had failed. Biliary access of a dilated segment 2 or 3 duct was achieved from the stomach using a 19G needle. After radiologically confirming access a guide wire was placed, a transhepatic tract created using a 6 Fr cystotome followed by balloon dilation of the stricture and antegrade metallic stent placement across the malignant obstruction. This was followed by placement of an endocoil in the transhepatic tract.

RESULTS: Dilated segmental ducts were observed in all patients with the linear endoscopic ultrasound scope from the proximal stomach. Transgastric biliary access was obtained using a 19G needle in all patients. Bili-

INTRODUCTION

Advanced biliary tract malignancy complicated by obstructive jaundice has traditionally been managed by palliative stent placement during endoscopic retrograde cholangiopancreatography (ERCP). In 3%-12% of patients with advanced disease tumour involvement of the small bowel or peri-ampullary region may preclude the use of ERCP, necessitating percutaneous transhepatic biliary drainage (PTBD) or surgery^[1]. However, surgery has been associated with high complication rates and morbidity^[2,3]. In recent years various groups have described endoscopic ultrasound guided access of the left system, allowing placement of metal or plastic stents either across the distal stricture or in the stomach (hepatico-gastrostomy), with high technical success^[4,5]. Since the initial case series which described the feasibility of endoscopic ultrasound

guided biliary drainage, various groups mainly from tertiary care academic expert centres have reported similar success rates in small case series^[6-8]. However, various obstacles still exist to extending the general applicability of this technique outside expert centres. Firstly, no randomized control trials exist comparing the safety and efficacy of endoscopic ultrasound (EUS) biliary access to percutaneous transhepatic cholangiography (PTC). Secondly, current endoscopic techniques utilize standard endoscopic accessories not specifically developed for use within the biliary system when advanced through the gastric wall. Thirdly, specific EUS strategies are needed to prevent or reduce complications associated with percutaneous approaches. We used an endocoin in the transhepatic tract following biliary access and stent placement to further reduce the risk of bleeding or bile leakage.

MATERIALS AND METHODS

All procedures were performed in an expert referral centre for biliary interventional endoscopy where patients undergoing ERCP for drainage of malignant biliary tract disease are routinely asked to consent to possible EUS-guided biliary drainage in the event of ERCP failure to obtain access. Consensus was always reached between the hepatobiliary surgeon (JO), the interventional radiologist (CS) and the hepatobiliary endoscopist (SvdM) regarding the optimal management of the patient. All EUS-guided biliary access procedures were prospectively entered into a database. All except one patient received general anaesthesia, and were intubated and mechanically ventilated in the supine position for the duration of the procedures (Table 1).

Case 1

A 67-year-old female presented with obstructive jaundice. Spiral computed tomography (CT) of the abdomen showed unresectable locally-advanced pancreatic carcinoma. At ERCP the ampulla could not be identified due to extensive tumour infiltration of the duodenal wall.

Case 2

A 50-year-old female patient was referred with metastatic pancreatic carcinoma with duodenal infiltration and liver metastasis. She also suffered from type II diabetes and systolic arterial hypertension. At ERCP the ampulla could not be identified in the tumour mass.

Case 3

A 46-year-old-female patient was diagnosed with unresectable locally advanced gallbladder carcinoma invading the common bile duct. The patient was managed by percutaneous drainage of both the left and right systems after ERCP failed. However, the stricture could not be transversed and external drainage catheters were placed during interventional radiology. The patient developed cholangitis. EUS-guided biliary access was requested to internalize biliary drainage. After EUS biliary access was achieved, a guidewire could be placed across a long stric-

ture into the duodenum.

Case 4

An 80-year-old male presented with obstructive jaundice. Spiral CT of the abdomen showed dilated intra- and extrahepatic bile ducts with the common bile duct (CBD) dilated up to the level of the ampulla where a mass lesion was seen. He was also known to have alcoholic liver disease. Spiral CT also showed evidence of liver cirrhosis and ascites in the upper abdomen. The patient had severe obstructive airway disease with type I respiratory failure and was oxygen dependent. A large peri-ampullary mass was confirmed by ERCP but the ampulla could not be identified. Due to the presence of ascites between the liver and the lateral abdominal wall, a PTC could not be considered. Endoscopic ultrasound showed no fluid between the stomach and the liver capsule and EUS guided biliary drainage was performed under light conscious sedation.

Case 5

A 44-year-old female patient diagnosed with stage IV metastatic ovarian cancer with liver metastasis and lymph node masses in the porta hepatis, presented with obstructive jaundice and ascites. Because of her age, third line chemotherapy was considered, but toxicity concerns because of severe cholestasis necessitated biliary drainage before chemotherapy could commence. Magnetic resonance cholangiopancreatography showed a mid-CBD stricture, a common bile duct severely displaced by the tumour and dilated intrahepatic ducts. Biliary cannulation was achieved during ERCP but the guidewire could not be advanced past the stricture into the proximal biliary tract. Ascites precluded the use of PTC. After successful EUS access was achieved, a guidewire could be passed into the duodenum.

Case 6

A 77-year-old female patient was diagnosed with locally advanced pancreatic carcinoma with duodenal infiltration and hypertensive cardiomyopathy. ERCP failed to identify the ampulla due to duodenal infiltration. She was not considered for surgery due to underlying co-morbidity and was referred for EUS-guided biliary drainage.

Endoscopic technique

Linear array endoscopic ultrasound (Pentax Hitachi 7500; Pentax Hitachi, Montvale, NJ) was used to identify the dilated left system. The Doppler mode was used to differentiate intrahepatic bile ducts from portal and hepatic vein branches. A 19G needle (Cook Medical, Limerick, Ireland) was used to puncture a peripherally located dilated segment 2 or 3 duct under EUS guidance. Under fluoroscopic control a cholangiogram was obtained and a standard 0.035 guidewire was advanced into the biliary system. Next, a 6Fr cystotome (Endoflex, Voerde, Germany) was used to create a transgastric tract through the liver parenchyma into the biliary system. A 0.038 catheter was advanced over the wire into the biliary system and

Table 1 Clinical characteristics of the patients

Age (yr)	Cancer diagnosis	Procedures performed	SEMS (cm × cm)	Technical success	Clinical success	Complications
67	Locally advanced	ERCP	8 × 10	Yes	Yes	None
50	Pancreatic	EUS-BD + coil	uncovered	Yes	Yes	None
	Metastatic	ERCP	8 × 10			
	pancreatic	EUS-BD + coil	uncovered			
46	Infiltrating gallbladder	Duodenal wall stent	8 × 10	Yes	Yes	None
		ERCP				
		EUS-BD + coil				
80	Ampullary	ERCP	8 × 10	Yes	Yes	None
		EUS-BD + coil	uncovered			
		Duodenal wall stent	8 × 10			
44	Metastatic Ovarian	ERCP	8 × 10	Yes	Yes	None
		EUS-BD + coil	uncovered			
77	Pancreatic	ERCP	6 × 10	Failed EUS-BD, Successful EUS-choledochenterostomy	Yes	None
		EUS-BD	covered			
		EUS-choledochenterostomy				

SEMS: Self-expandable metal stent; ERCP: Endoscopic retrograde cholangiopancreatography; EUS: Endoscopic ultrasound; BD: Biliary drainage.

advanced to the bifurcation. The guidewire was then manipulated across the stricture and into the duodenal lumen (Figure 1). A Hurricane biliary dilation balloon 4 cm × 4 mm (Boston Scientific, Natick, MA Boston Scientific) was advanced through the tract and used to dilate the common bile duct stricture without balloon dilation at the level of the gastric wall liver interface. A 10 mm × 80 mm uncovered metal stent (Boston) was advanced and deployed under fluoroscopy across the papilla and past the duodenal obstruction, when present. To reduce the risk of a bile leak the catheter was withdrawn using contrast injection to verify anatomy, and carefully positioned in the track between the liver capsule and dilated system with the guidewire still in place in the biliary system. The guide wire was then removed and an endocoil (0.035" Fibered Platinum Coils, 6 mm, Boston Scientific, Natick, MA Boston Scientific) loaded into the lumen of a 0.038 prototype catheter before advancing it using a 0.035 guidewire (Boston Scientific, Natick, MA Boston Scientific) under EUS and fluoroscopy guidance (Figure 1).

RESULTS

Transgastric EUS-guided biliary access was successful in 5 of 6 patients. In one patient (patient 6) transgastric biliary access was initially possible and a cholangiogram obtained but guidewire cannulation could not be achieved. The patient was rescued by EUS-guided retrograde placement of a transduodenal covered stent (choledochenterostomy) above the malignant stricture. In all cases no immediate procedure-related complications were observed. Two cases necessitated further duodenal stent placement during the same session. The mean procedure time (including anaesthesia) was 91 min (49-133). Levofloxacin (500 mg) was administered at the time of the procedure and continued for 5 d. Mild abdominal pain, not accompanied by peritoneal guarding and responding to Tramadol was experienced by two patients and resolved within 4 h. At 30 d all patients had responded with normalization of cholestasis and no late complications,

including infections, were observed.

DISCUSSION

In patients with advanced biliary tract malignancy extensive peri-ampullary and duodenal infiltration may occur that may prevent the use of ERCP for palliative stent placement. Under these circumstances percutaneous transhepatic biliary drainage is often utilized. PTBD necessitates transversing of the parietal and visceral peritoneum, potentially causing bile leakage and bleeding into the peritoneal cavity. This procedure is also associated with significant pain, lengthy hospital stays and an overall reduction in quality of life^[9]. Severe complications following PTBD including peritonitis, sepsis, bleeding requiring re-intervention, and even procedure-related mortality have been well described^[9,10]. Indeed, The Society of Interventional Radiology (SIR) quality improvement guidelines established the procedural risk of severe major complications at 2.5%^[11].

Embolization of biliary tracts using different materials including gel foam, fibrin glue, n-butyl cyanoacrylate and endocoils are routinely used in clinical practice at the time when biliary catheters are removed, in order to reduce the risk of bile leakage or bleeding. A recent randomized trial showed that transhepatic biliary tract embolization with n-butyl cyanoacrylate decreased both pain perception as assessed by a visual analog score and the need for analgesia, when compared to the non-embolization group^[12]. Endocoil placement is a well-established interventional radiology technique where coils placed in blood vessels (endovascular coils) obliterate flow and induce coagulation, thrombosis and the formation of neo-intimal proliferation^[13]. Coils have also been used outside the vascular setting, such as in coil embolization of needle tracks following PTC^[14]. In theory, such coils will obstruct the flow of bile, prevent leaking and induce a local tissue response, in the same way gel foam.

Recent advances in endoscopic ultrasound have allowed access to a dilated biliary system through either ret-

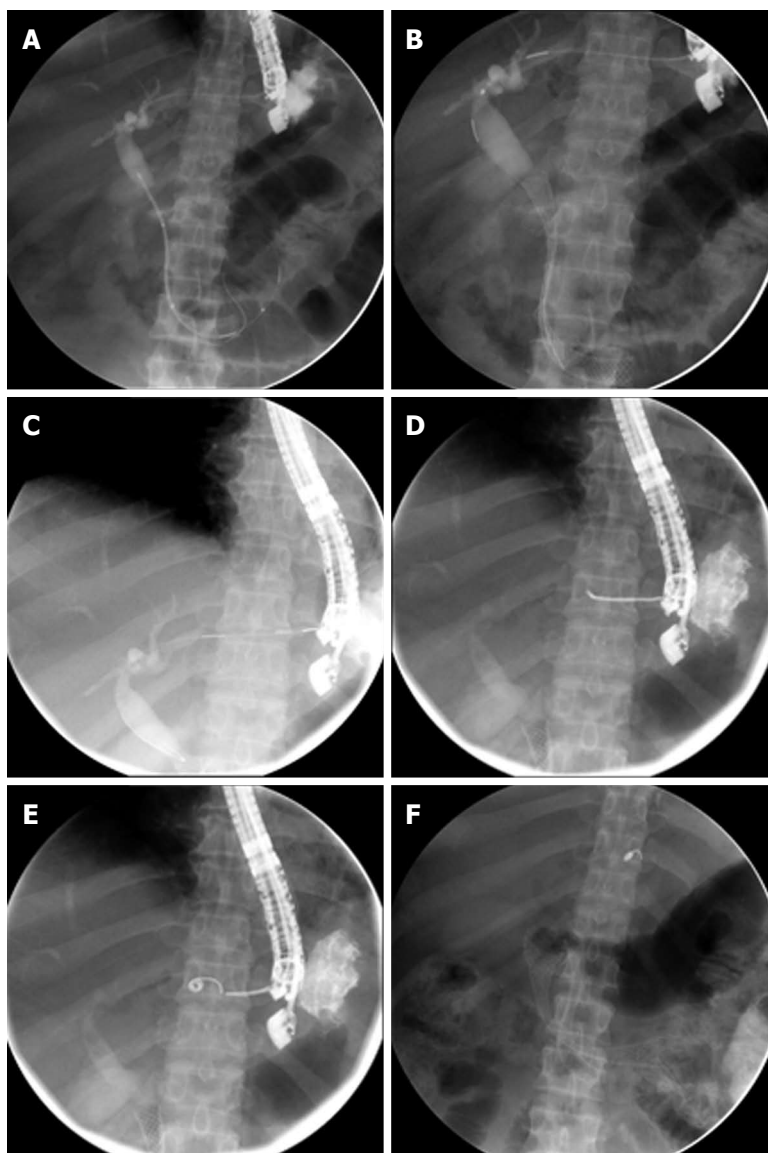


Figure 1 Endoscopic ultrasound-guided biliary drainage followed by endocoil placement. A,B: After successful endoscopic ultrasound cannulation of segment 3 duct a guide wire is passed into the duodenum, the stricture dilated and a 10 mm × 80 mm uncovered biliary stent deployed; C: Next the catheter is withdrawn with the guide wire still in place; D, E: Finally the guide wire is removed with the catheter in position in the track between the dilated segment and the liver capsule an endocoil is advanced and deployed using a standard 0.035 guide wire; F: The final result is shown after stenting of the stricture in the duodenum, showing the biliary stent, duodenal stent and endocoil.

rograde or antegrade approaches. Retrograde cannulation, normally performed from the duodenal bulb, allows access to the biliary tract above a malignant stricture with the intent either to pass a guide wire through the papilla and then perform a rendezvous procedure, or to place a covered metal stent in the stomach^[15]. Cannulation of a dilated segment 2 or 3 sectoral duct is also possible from the proximal stomach where the endoscopist performs all procedures in an antegrade fashion^[8]. Currently these procedures are selectively performed in specialist centres by expert endoscopists. Overall, EUS biliary drainage is technically successful in 75%-92% of cases, although there have been reports of bile leakage and peritonitis^[8]. Endoscopic ultrasound utilizes standard endoscopic accessories and there is a need to create a transhepatic tract, using a 6Fr cystotome, to allow passage of stents from the stomach across biliary strictures. These accessories

were not developed for use in EUS settings and are more difficult to use when advanced through the gastric wall. Valid concerns therefore still exist regarding the overall risk of bile leaks, peritonitis, and safety in EUS-guided biliary drainage. Ways should be developed by which these procedures may be improved and the risk of complications decreased. EUS guided biliary drainage theoretically exposes a tract between the dilated left system and the peritoneum.

Here we report the placement of an endocoil through a 0.038 catheter after completion of EUS-guided transgastric stent placement. The catheter was slowly withdrawn and positioned between the dilated sectoral duct and the liver capsule and a standard 0.035 guidewire was used to advance the coil into the tract created by the 6Fr cystotome. We could demonstrate that the placement of an endocoil is safe in all patients and does not add to the

overall complexity of the procedure. Endocoil placement is however not possible through a standard ERCP catheter with internal lumen diameters of 0.035, probably because of the angulation as it passes through the gastric wall and liver parenchyma. Catheters with larger internal lumen, at least 0.038 in diameter, are therefore needed. Currently such catheters do not exist, underscoring the need to develop catheters specific for EUS-guided biliary access. It remains to be seen whether coil placement will improve the overall safety of EUS transgastric procedures in the future. Randomized pilot studies will be needed to determine the usefulness this technique may offer over PTC in the prevention of bile leaks when accessing the biliary tract by EUS.

COMMENTS

Background

Advanced biliary tract malignancy, complicated by obstructive jaundice is managed by endoscopic retrograde cholangiopancreatography (ERCP) and stent placement. In some patients ERCP is not possible due to duodenal or perampullary infiltration, necessitating percutaneous transhepatic cholangiography.

Research frontiers

In recent years developments in endoscopic ultrasound have made it possible to gain access to a dilated left biliary system from the stomach. However only case series from expert medical centres have been reported. It therefore remains important to develop safer endoscopic techniques that can be used more widely and to compare endoscopic ultrasound guided biliary drainage with percutaneous transhepatic biliary drainage in randomized controlled trials.

Innovations and breakthroughs

Here the authors describe placement of an endocoil in the transhepatic tract following endoscopic ultrasound (EUS) guided biliary drainage. The authors propose that placement of an endocoil may prevent leakage of bile to the peritoneum and may thus improve the safety of EUS guided transgastric biliary drainage.

Applications

It remains imperative that further development in the field of interventional endoscopic ultrasound should be undertaken and that accessories specific for endoscopic ultrasound applications should be developed. This will improve efficacy and safety.

Terminology

Endoscopic ultrasound guided biliary drainage refers to the use of EUS in visualizing a dilated left biliary system. This is followed by gaining access to a dilated sectoral duct segment 2, 3 using a 19G endoscopic ultrasound needle. When this is established a guide wire can be passed into the biliary system and advanced past a malignant stricture so that a stent can be placed. This technology has theoretical benefits over percutaneous biliary drainage.

Peer review

Biliary leakage is very rare after balloon dilatation of biliary stenosis followed by self-expandable metallic stent. This manuscript could be accepted after revision.

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Endoscopic ultrasonography in patients with elevated carbohydrate antigen 19-9 of obscure origin

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RESULTS: Of the 17 patients, gallbladder sludge was detected in 16 patients (94.1%) and common bile duct sludge was observed in 3 patients (17.6%). After the administration of ursodeoxycholic acid to 12 of the patients with gallbladder sludge, CA 19-9 levels normalized in 6 of the patients after a median of 4.5 mo.

CONCLUSION: EUS is a useful diagnostic method for patients with elevated CA 19-9 levels of obscure origin, even if the reason for abnormal levels of this serum marker cannot be determined through prior examinations, including abdominal CT.

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Key words: Carbohydrate antigen 19-9; Endoscopic ultrasonography; Gallbladder; Ursodeoxycholic acid

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Abstract

AIM: To evaluate the efficacy of endoscopic ultrasonography (EUS) in patients with elevated carbohydrate antigen (CA) 19-9 levels of obscure origin.

METHODS: Patients who had visited Pusan National University Hospital because of elevated serum CA 19-9 levels, between January 2007 and December 2009, were retrospectively enrolled. EUS had been performed on all subjects, in addition to routine blood tests, endoscopy, abdominal computed tomography (CT) and other clinical exams, which had not revealed any abnormal findings suggestive of the origin of the elevated CA 19-9 levels.

INTRODUCTION

Serum carbohydrate antigen (CA) 19-9 is considered to be the best screening marker for pancreatic cancer because of its relatively high sensitivity (70%-90%) and specificity (70%-98%)^[1,2]. However, CA 19-9 is also elevated in many other digestive cancers, as well as in a number of benign diseases^[3,4]. Although the usefulness of CA 19-9 as a screening marker for the detection of malignancies has not yet been validated, it is not uncommon to measure serum CA 19-9 levels in asymptomatic individuals during routine health examinations.

Pancreaticobiliary disease is one of the most common

causes of benign abnormal serum CA 19-9 levels. Herein, we report 17 cases of patients with elevated serum CA 19-9 levels without any obvious pancreaticobiliary system abnormalities, as revealed on abdominal computed tomography (CT); endoscopic ultrasonography (EUS) was performed as an additional part of their diagnostic examination and was useful in these cases.

MATERIALS AND METHODS

All patients with elevated serum CA 19-9 levels of indeterminate cause who underwent EUS in our institution between January 2007 and December 2009 were retrospectively assessed. Elevated serum CA 19-9 levels had been detected during routine cancer screenings and none of the patients had a history of cancers, surgeries or acute infections. To identify the causes of the elevated serum CA 19-9 levels, the patients, prior to the EUS examination, had provided a medical history regarding their smoking and alcohol consumption habits and had undergone a physical examination, routine blood tests (including liver and thyroid function tests), esophagogastroduodenoscopy, colonoscopy, abdominal ultrasonography, abdominal/pelvic CT and for female patients, mammography and breast ultrasonography.

EUS examinations were performed using a radial echoendoscope (GF-UM2000; Olympus, Tokyo, Japan) at either 5 or 7.5 MHz, by one experienced endoscopist. This study was reviewed and approved by the Institutional Review Board at Pusan National University Hospital. Written informed consent was obtained from all patients.

RESULTS

Of the 17 patients, 13 (76.5%) were female and the median age of the patients was 51 years (range 28-85 years). Two of the patients consumed more than 20 g of alcohol daily. The median serum CA 19-9 level during the screening visit was 64.1 U/mL (range 40.0-381.0 IU/mL). Serum total bilirubin levels were normal in all but 1 patient. This patient had an initial value of 1.6 mg/mL (reference range was < 1.3 mg/mL), which subsequently decreased to within the normal range (1.2 mg/mL) (Table 1).

EUS revealed gallbladder (GB) sludge in 16 of the patients (94.1%) and common bile duct (CBD) sludge in 3 patients (17.6%). Mild CBD dilatation (8 mm) was noted in 1 patient, tiny GB polyps (2-3 mm in size) in 3 patients, and a pancreatic cyst (9 mm in size) was detected in 1 patient.

The median follow-up duration was 12 mo (range 3-51 mo). Of the 16 patients with GB sludge, 12 received ursodeoxycholic acid (UDCA; 600 mg/d) for 3-18 mo (median 6 mo). The median number of CA 19-9 measurements was 3, although subsequent measurements of CA 19-9 were not performed for 2 patients. Six of 11 patients who received UDCA achieved normal CA 19-9 levels after a median of 4.5 mo (range 3-8 mo) (in 1 patient, the subsequent CA 19-9 value was not assessed); 1 of the 4 patients who did not initially receive UDCA did

so 5 mo after the initial testing. Serum CA 19-9 levels remained within the normal range during the follow-up period in all patients who attained levels within the normal range as a result of UDCA therapy.

DISCUSSION

Biliary sludge, either GB or CBD sludge, is defined as a suspension of crystals (usually cholesterol monohydrate), mucin, glycoproteins, cellular debris, and/or proteinaceous material within the bile^[5-7]. Many studies have suggested that biliary sludge may be a precursor to stone formation^[8,9] and a source of potential complications^[10-13]. The exact mechanism underlying the elevation of serum CA 19-9 levels, associated with GB sludge, remains unclear. However, the mechanism underlying the elevation in CA 19-9 levels in patients with bile duct obstruction is assumed to be as follows. Increased biliary pressure induces bile duct cells to produce CA 19-9^[14], which accumulate in the lumen due to biliary obstruction. An increased permeability between the bile duct and the vasculature is believed to result in CA 19-9 reflux into the circulation^[15]. Increased biliary pressure is suspected to be the main outcome of clinically insignificant biliary obstruction, such as is caused by biliary sludge. Furthermore, we hypothesize that sludge may flow down to the CBD during GB contractions, causing transient obstructions of the CBD outlet and increasing bile duct pressure. In this study, CBD sludge was identified by EUS in 3 of 16 patients with GB sludge, which may support our hypothesis.

Sludge may be visualized by abdominal US or EUS. The accuracy of US in detecting cholelithiasis is high, with a reported sensitivity of 92%-96%^[16-19]. Nevertheless, when stones are less than 3 mm in diameter or located in the GB infundibulum, the sensitivity of US is only 65%^[20]. By contrast, the sensitivity of EUS is approximately 96%^[21,22]. Therefore, it is clear that EUS is the most sensitive imaging method for detecting GB sludge.

In patients in whom GB sludge has been detected in the absence of biliary symptoms, the natural history of sludge warrants appropriate management of the sludge. In patients with GB sludge and elevated serum CA 19-9 levels, GB sludge is likely to be responsible for the elevation in CA 19-9 levels. The elevated CA 19-9 levels may result in anxiety for patients regarding a potential malignancy; therefore, empirical treatment with UDCA may also represent a practical management option in such patients. The major role of UDCA is limited to the prevention of sludge formation in patients with predisposing conditions, such as weight reduction or total parenteral nutrition^[23-25]. Theoretically, however, GB sludge may be more responsive to UDCA treatment than gallstones due to its higher surface-to-volume ratio. Indeed, a prospective, multicenter study showed that UDCA was associated with a 100% dissolution rate for persistent biliary sludge^[26]. In the current study, 6 of 11 patients (54.5%) with GB sludge showed normalization of CA 19-9 levels after UDCA treatment, compared with 1 of 4 patients

Table 1 Summary of demographic and laboratory data and endoscopic ultrasonography findings in 17 patients with elevated serum carbohydrate antigen 19-9 values

Case	Gender	Age, yr	EUS findings			CA 19-9 level, IU/mL		Time to CA 19-9 normalization, mo	UDCA administration	Duration of UDCA administration, mo	Other findings	Follow-up duration, mo
			CBD size, mm	PD size, mm	GB sludge	CBD sludge	Last visit					
1	F	28	3	1	Yes	Yes	78.3	20.7	Yes	3		6
2	F	51	2	1	Yes	Yes	187.9	25.6	Yes	6		17
3	F	51	3	1	Yes	Yes	63.6	30.2	Yes	6	GB polyp	8
4	F	36	5	0.5	Yes	No	46.1	21.3	Yes	3		36
5	M	68	3	1	Yes	No	73.3	20.6	Yes	3		7
6	M	38	2	0.5	Yes	No	165.3	16	Yes	6		16
7	F	63	8	1	Yes	No	48.2	61.1	Yes	3		51
8	F	59	4	1	Yes	No	46.2	40.4	Yes	18		20
9	F	71	5	2	Yes	No	43.9	57.3	Yes	10		10
10	M	43	2	1	Yes	No	162.7	123.9	Yes	15		17
11	F	64	5	1	Yes	No	141.8	122.2	Yes	12	GB polyp	14
12	F	36	4	1	Yes	No	87.6	-	Yes	3		3
13	M	46	3	2	Yes	No	381	19.4	No	5		5
14	F	30	4	2	Yes	No	64.1	50.4	No			3
15	F	55	3	1	Yes	No	51.4	54.1	No			29
16	F	40	4	1	Yes	No	40	43.9	No			12
17	F	85	6	1	No	No	40.3	-	No		GB polyp, Pancreatic cyst	3

CBD: Common bile duct; PD: Pancreatic duct; GB: Gallbladder; UDCA: Ursodeoxycholic acid.

(25%) who did not receive UDCA. This finding appears to support the proposed relationship between GB sludge and elevated CA 19-9 levels.

Additionally, in this study, the median duration of UDCA administration was 4.5 mo in the 6 patients whose CA 19-9 levels normalized, compared with 12 mo for the patients who did not achieve CA 19-9 level normalization. Therefore, although UDCA treatment appears to be effective for normalizing CA 19-9 levels, it should be discontinued if CA 19-9 levels are not decreased after 6 mo of therapy.

To our knowledge, the utility of EUS in determining the potential cause of CA 19-9 level elevation in patients has not been previously described. This study demonstrated that EUS is a useful diagnostic method in patients with elevated CA 19-9 levels of obscure origin, despite inconclusive results from prior examinations, including endoscopy and abdominal/pelvic CT. In addition, the current findings indicate that UDCA therapy may be effective for normalizing CA 19-9 levels in patients with GB sludge. Additional large, prospective studies may clarify the association between CA 19-9 levels, the presence of GB sludge, and UDCA treatment.

COMMENTS

Background

Serum carbohydrate antigen (CA) 19-9 levels are commonly examined as part of cancer screening among asymptomatic individuals. However, it can also be elevated by conditions other than pancreatic cancer, as well as in the absence of any specific diseases. When physicians encounter a patient with an elevated CA 19-9 level, they search for possible hidden malignancies. In many cases, although several tests are performed, the putative cause remains unknown.

Research frontiers

Endoscopic ultrasonography (EUS) can detect small lesions in the pancreaticobiliary system that conventional ultrasound (US) or computed tomography (CT) cannot. Therefore, in this study, the authors examined the efficacy of EUS in patients with elevated CA 19-9 levels of obscure origin.

Innovations and breakthroughs

Using EUS, the authors identified gallbladder and bile duct sludge as possible causes of elevated CA 19-9 levels. The presence of this gallbladder sludge had not been detected by transabdominal US and abdominal CT.

Applications

EUS can be used to identify causes of elevated CA 19-9 levels in patients when other examinations show non-specific results.

Peer review

Although this paper is a single center study with a small number of subjects, the novel application of EUS for patients with elevated levels of this tumor marker is an attractive and potentially promising modality for investigating the pancreaticobiliary system.

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Miniprobe EUS in management of pancreatic pseudocyst

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tube) was performed after MEUS (20-MHz-miniprobe) identification of place for diathermy puncture and wire insertion. In 8 cases (61.5%), there was PP disappearance; one, surgical duodenotomy and marsupialization of retro-duodenal PP. In 4 cases (31%), there was successful MEUS-EGCD; stent removal after 3 mo. No complications and no PP relapse in 4 years of mean follow-up. MEUS EGCD represents an option for PP, allowing a safe and effective procedure.

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Key words: Endoscopic ultrasonography; Miniprobe; Pancreatic pseudocyst; Children; Endoscopic gastrocyst drainage

De Angelis P, Romeo E, Rea F, Torroni F, Caldaro T, Federici di Abriola G, Foschia F, Caloisi C, Lucidi V, Dall'Oglio L. Miniprobe EUS in management of pancreatic pseudocyst. *World J Gastrointest Endosc* 2013; 5(5): 255-260 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/255.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.255>

Abstract

Pancreatic pseudocysts (PP) arise from trauma and pancreatitis; endoscopic gastro-cyst drainage (EGCD) under endoscopic ultrasonography (EUS) in symptomatic PP is the treatment of choice. Miniprobe EUS (MEUS) allows EGCD in children. We report our experience on MEUS-EGCD in PP, reviewing 13 patients (12 children; male:female = 9:3; mean age: 10 years, 4 mo; one 27 years, malnourished male Belardinelli-syndrome; PP: 10 post-pancreatitis, 3 post-traumatic). All patients underwent ultrasonography, computed tomography and magnetic resonance imaging. Conservative treatment was the first option. MEUS EGCD was indicated for retrogastric cysts larger than 5 cm, diameter increase, symptoms or infection. EGCD (stent and/or nasogastric

INTRODUCTION

Pancreatic pseudocysts (PP) in children arise from pancreatic trauma and acute pancreatitis with a blunt duct caused by several pancreatic diseases (*i.e.*, Crohn's disease, cystic fibrosis, pancreas divisum, *etc.*).

Diagnosis is performed by complete radiological evaluation that includes ultrasonography (US), computed tomography (CT) and magnetic resonance imaging (MRI); serum amylase and imaging such as US are considered useful in monitoring the evolution, the occurrence of spontaneous resolution or the need for surgical intervention^[1]. Herman *et al*^[2] in a pediatric study in 2011 confirmed that maximal amylase (> 1100 U/L) is highly predictive of the risk of developing a pseudocyst.

Differential diagnosis is mandatory with neoplastic

diseases like mucinous cystic neoplasia and acinar cell cyst adenoma, and also of other malformations such as gastric duplication^[3-5].

Generally, conservative treatment is resolutive in most cases. According to D'Edigio *et al*^[6], in 30%-50% of cases after a period of 6 wk, PP can resolve spontaneously.

Several operative therapies are described for PP: open surgery was the traditional treatment for symptomatic pseudo cysts and abscess, but morbidity and mortality were too high; laparoscopic cyst gastrostomy has also been described in children as a safe and effective technique which gives good results and a good rate of resolution^[7].

Endoscopic transmural drainage, first introduced in the mid 1980s, has already been considered a minimally invasive, effective and safe approach in a series of adults affected by PP and abscesses, with success rates exceeding 90% among adults^[8,9] and also among children, despite complications such as bleeding and technical difficulties^[10-12].

During the last decade, in symptomatic long standing PP with a great increase in volume, endoscopic gastrocyst drainage (EGCD) under endoscopic ultrasonography (EUS) has become the chosen treatment; the endoscopic approach consists of the placement of a drainage catheter into the cysts under direct EUS guidance in order to identify the optimal site for puncture and stent placement, which guarantees greater safety and efficacy in both adults and children^[12-14]. Barthet *et al*^[15] proposed an algorithm for PP, including EUS-assisted drainage, transpapillary drainage and conventional endoscopic drainage, demonstrating that EUS is required for treatment in half of the cases. In children, few studies have been published on endoscopic marsupialization of PP with the addition of EUS; recent interesting data on ten children come from Jazrawi *et al*^[9] with dedicated echo endoscopes^[9].

The application of miniprobe endoscopic ultrasonography (MEUS) is not widespread. However, its use in pancreatobiliary disease allows the performance of complex procedures, especially in children and patients who have complications due to severe diseases^[16]. The application of MEUS was never prescribed in the management of PP.

CASE REPORT

In this study, we report our experience of EGCD under MEUS guidance in PP. Between 2005-2010, 4 patients with PP were treated with EGCD under MEUS guidance; they were enrolled between 13 consecutive patients with PP followed in our unit. Conservative treatment was always the first option for all the patients.

MEUS EGCD was indicated in retro gastric cysts, with close contact between the cyst and the gastric wall, with cysts larger than 5 cm or that had increased in diameter, or in persistence of symptoms or infection.

The steps of EUS guided drainage were the following: (1) endoscopy (GIF Q165-Q160 Olympus America

Corp. Melville, NY) and EUS (20 MHz radial miniprobes Olympus UM-BS 20-26R, balloon sheath Olympus MAJ-643-R inserted through the 2.8 mm biopsy channel of an Olympus GIF Q165-Q160) confirmation of the best contact between the pseudocyst and the gastric wall and identification of the correct place for diathermy needle puncture; (2) according to the patient's age and weight, exchange of the endoscope with a side view duodenoscopy was opted for (Olympus TJF 160 VR), diathermy needle puncture (Cook Zimmon needle knife papillotome PTW-1 Wilson Cook Medical Ireland 5 Fr) of the gastric wall in the previously identified correct place, up to entering the cyst; (3) guide wire (0.035 IN) placement under X-ray control; (4) extraction of the needle with the guide in place and opacification of the cystic cavity; (5) hydrostatic balloon dilation of the cystic opening, if necessary; (6) washing of the cyst and the removal of necrotic tissue; and (7) insertion of a biliary drainage pigtail stent (Boston Scientific S.A. France) 7 or a 10 Fr stent gastro-cystic and/or nasal-gastro-cystic 7 Fr drainage. Nasal-gastro-cystic drainage was in place for one week; the stent was planned for three months.

ERCP (TJF 160 VR; Olympus America Corp. Melville, NY) and double sphincterotomy with stent placement and nasopancreatic tube were performed in communicating PP with the main pancreatic duct.

These procedures were always performed under general anesthesia with orotracheal intubation and in the supine position. During all the procedures X-ray was used. Antibiotic prophylaxis with cefazolin administered intravenously was given to all patients prior to endoscopy.

Surgery was preferred when the endoscopic approach was not suitable because there was no evidence of safe contact between the gastric or duodenal posterior wall and the PP, after evaluation by either endoscopy or MEUS.

Informed consent from patients and parents was asked for to enable us to collect and analyze data retrospectively in a confidential manner.

The ethics board of Bambino Gesù Children's Hospital approved our study. Our series consisted of 12 children (male:female = 9:3) with a mean age of 124 mo (range 30 mo-16 years) and one adult (27 years old, male, Belardinelli syndrome, severe esophageal stricture and malnutrition, body mass index: 14 kg/m²) with PP (all chronic abdominal pain, 5 also had fever, one had enzyme elevation) due to pancreatitis (*n* = 10: biliary pancreatitis 1, idiopathic pancreatitis 6, mild cystic fibrosis 2, pancreas divisum 1) and trauma (*n* = 3).

All patients underwent pancreatobiliary examinations, ultrasound, CT and cholangio-pancreatic MRI. The outcome of patients is reported in Figure 1.

In 8 cases (61.5%), we observed a progressive PP disappearance; one patient (7.5%) with pancreas divisum and relapsed acute pancreatitis required surgical duodenotomy and marsupialization of retro-duodenal PP due to incomplete MEUS contact between the PP and the duodenal wall.

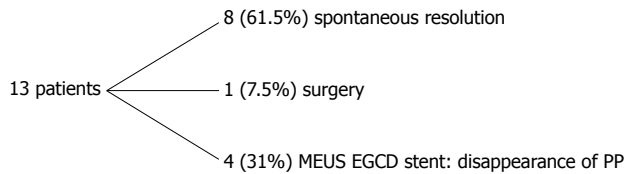


Figure 1 Outcome for patients. PP: Pancreatic pseudocysts; MEUS: Miniprobe endoscopic ultrasonography; EGCD: Endoscopic gastro-cyst drainage.

In Table 1, results of MEUS EGCD were resumed; in 4 patients, 31% (males, 7, 10, 11 and 27 years; one trauma, 3 pancreatitis), successful MEUS EGCD (Figure 2) was performed with stent placement (in all the patients, one 7 Fr stent, in one patient also a 10 Fr stent). In all these patients, we observed a bulge of the gastric wall corresponding to the pseudocyst below.

The patient with post traumatic PP was treated with naso-Wirsung drainage and a gastro-cystic pig tail stent (Figure 3), while those patients affected by cystic fibrosis and chronic pancreatitis even underwent sphincterotomy. Stent removal was performed after 3 mo in all patients. No immediate or late complications occurred and no relapse of PP in 4 years of mean follow up (range: 6 mo-6 years).

DISCUSSION

PP could be suspected in abdominal epigastric pain with an increase in pancreatic enzymes or biliary tree compression, after an acute pancreatitis or trauma (3-4 wk later). Non invasive radiological methods such as CT and MRI help to classify pancreatic trauma, contributing to planning the best and most adequate treatment. It is important to make a correct differential diagnosis for PP, even in pediatric cases.

Transient or persistent pancreatic duct disruption is the most common cause, but pancreatitis represents a spread factor on the basis of PP.

Pseudocysts frequently resolve spontaneously and so conservative treatment is the best option in children with PP. If the cyst is large with a persistency that goes beyond 6 wk, symptomatic and complicated by infection, it is correct to indicate the most appropriate treatment. Delgado Alvira *et al*^[17], an interesting study on the best management strategies in PP, reported two children with post-traumatic PP and a large series reviewed by literature between 1990 and 2007. They underlined that asymptomatic PP in children does not require any specific intervention other than expectant management, while children with persistent clinical symptoms or those who develop complications may need further interventions such as external percutaneous drainage, cystogastrostomy, cystojejunostomy or pancreatocystojejunostomy, endoscopic drainage or distal pancreatectomy^[17].

Surgical treatment has been proposed by several authors: Briem-Richter *et al*^[18] reported a rare case of pediatric Crohn's disease with the development of huge

pseudo cysts that required surgery; Yoder *et al*^[7] described laparoscopic treatment that realized cystogastrostomy in 13 children, with a high rate of complete resolution with minimal morbidity and rapid recovery.

During the last decade, it was gradually recognized that endoscopic treatment could be the preferred approach to manage PP^[15]. In 2004, Al-Shanafey *et al*^[19] had successfully treated two children with transpapillary drainage and one child with an endoscopic cystoduodenostomy.

The endoscopic therapeutic approach consists of transduct (transpapillar in recent Wirsung disruption) or transmural passage of a guide wire with stent placement to the drainage of the pseudo cyst content^[20], under EUS evaluation or through linear echo-endoscope (duodenal-cyst drainage or gastro-cyst drainage), almost 6 wk from evidence of a pseudo cyst^[21]. A 15% recurrence rate has been reported. If pseudo cysts persist lifelong, surgery is recommended.

Major ductal injuries caused by blunt abdominal trauma are rare and treated by surgery. ERCP with stent placement is useful to manage post-traumatic pseudo cysts, with rapid clinical improvement and complete resolution of clinical and biochemical pancreatitis.

Barthert *et al*^[13] in 2008 in a prospective study based on a systematic treatment algorithm concluded that endoscopic drainage is the first-line method of managing PP and EUS is required in half of the cases to obtain a definitive therapy.

EUS is already widespread in pediatric cases, but experience in pancreatobiliary disease is poor^[11]; pediatric experiences of EUS guided endoscopic treatment are very much limited due to several technical difficulties, few experienced centers and few case studies.

According to a study by Varadarajulu *et al*^[13] in 2005, EUS could give a diagnostic contribution to chronic pancreatitis, in pancreatic pseudo-cysts, in choledocholithiasis, in pancreas divisum and in duodenal duplications, because EUS can also be successfully performed in children aged 5 years and over using an adult echo endoscope. Cohen *et al*^[22] in 2008 verified the diagnostic impact of EUS, with a demonstration of a radical change of diagnostic and therapeutic strategies when this procedure was used.

In pediatric cases, EUS improved diagnostic and the therapeutic possibility of ERCP in chronic and recurrent pancreatitis, in treatment of pancreatic pseudocysts (gastrocystostomy EUS guided) and duodenal duplication (endoscopic therapy).

Even if endoscopic drainage of PP is successfully reported in children, EUS could add safety to the procedure. In 2010, Theodoros *et al*^[23] published the case of a child with post-traumatic PP who was successfully treated with a guided EUS transgastric approach. Jazrawi *et al*^[9] reported the largest series of pediatric patients with symptomatic PP due to pancreatitis and trauma; in all ten cases, successful EUS guided transgastric endoscopic drainage was achieved, with placement of double pig tail stents in eight patients and complete cyst aspiration and

Table 1 Results of patients treated by miniprobe endoscopic ultrasonography endoscopic gastro-cyst drainage

Sex	Age Body weight	Associated disease	Etiology	PP size (cm)	PP site	EUS common wall thickness (mm)	Endoscopic treatment	FU yr
M	7 yr 7 m 20 kg	Filippi's syndrome	Pancreatitis	8 × 7	Retrogastric	4.5	GIF Q165 pre-cut needle	0.5
M	27 yr 43 kg	Belardinelli's syndrome-SEIP	Iatrogenic Biliary pancreatitis	8 × 6 × 5	Retrogastric	3.5	7Fr stent GIFQ165 pre-cut needle, hydrostatic dilation 7 and 10 Fr stent	3
M	11 yr 31 kg	No	Trauma	7 × 5 × 9 10 × 5 × 11	Retrogastric and retroduodenal Pancreatic body and tail	3.5	Transduodenal drainage (TJF) GIFQ165, precut needle 7Fr and nasopancreatic tube	6
M	10 yr 5 m 25 kg	Cystic fibrosis	Pancreatitis	8 × 5 × 9 9 × 6 × 10	Retrogastric Pancreatic body and tail	3.8	TJF double sphincterotomy GIFQ165 precut needle 7Fr stent and naso-pancreatic tube	6

M: Male; F: Female; PP: Pancreatic pseudocysts; EUS: Endoscopic ultrasonography.

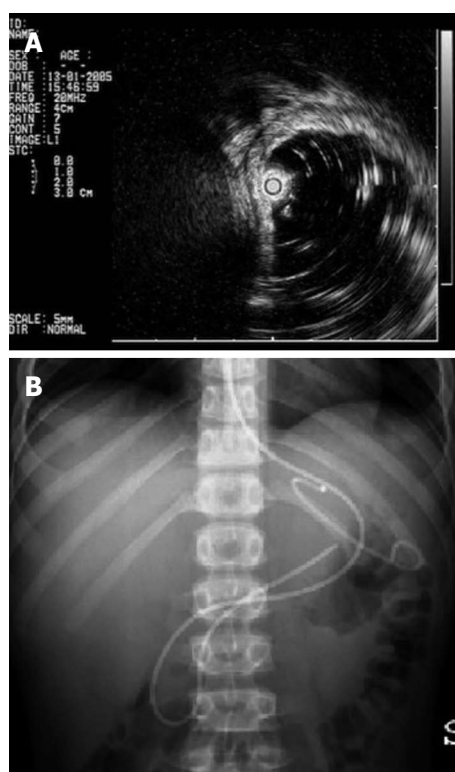


Figure 2 Miniprobe endoscopic ultrasonography endoscopic gastro-cyst drainage. A: Miniprobe endoscopic ultrasonography of pancreatic pseudocyst: the common wall between stomach and pseudocyst. B: Endoscopic view: gas-trocytic stent.

collapse by EUS fine-needle aspiration in two cases.

Miniprobe was never described in PP management; this technique is useful in small children and in particular situations such as esophageal stricture that does not allow a dedicated echo endoscope passage. This technique is safe and simple, even with a common endoscope.

The advantages of miniprobe EUS are numerous. We have the possibility of performing therapeutic procedures even when dedicated radial and linear echo endoscopes are not available; the MEUS equipment is less expensive



Figure 3 X ray: The naso-pancreatic drainage and the stent in the correct position.

than instruments and the ultrasound generator for linear EUS. MEUS also represents a useful instrument in pediatric surgery and pediatric endoscopy for many other different clinical situations, such as duodenal duplications^[16], esophageal congenital strictures^[24] and duodenal diaphragms^[25]. Generally, we perform EUS with standard front view endoscope to avoid miniprobe damage by the cannula elevator of side view duodenoscope; besides, we can use a small caliber endoscope (operative channel of 2.2 to allow miniprobe passage) with a “frontal vision” commonly used in the clinical practice, to complete the endoscopic therapy.

Miniprobe EUS has an indication in malnourished, small weight patients, syndromic or sick patients in a general bad condition (*i.e.*, cystic fibrosis) and in esophageal stenosis with consequent difficulty of the passage of the echo endoscope. The limitations of this procedure are the lack of a Doppler and difficulty to rule out with certainty the presence of vessels in the common wall with confirmation of blood flow; daily experience allows ascertaining suspected vascular structures inside the wall.

In our small series of four patients, we have applied this innovative technique in special patients, two syndromic cases (one with neurological retardation, Filippi's syndrome

and the other with an esophageal stricture and Belardinelli's syndrome), one cystic fibrosis child and a complex post-traumatic patient. Their clinical conditions and associated diseases contributed to determine a complex approach. Our experience with EUS miniprobe commonly used in our tertiary center for other diseases (*i.e.*, congenital esophageal stenosis, duodenal duplications, duodenal diaphragms, *etc.*) and with pediatric operative endoscopy allowed us to choose this original procedure in our cases and in one case in particular. The daily availability of digestive surgery gives us the possibility to choose the best treatment depending on specific situations, achieving an outcome for patients similar to the literature. While the unavailability of echo endoscope limits our decision making, on the other hand, we need a simple, rapid, safe technique, easy to reproduce, that could be taught during training.

Small series size does not allow a deep analysis that larger cases need to be able to confirm our preliminary data. The choice of the typology of endoscope to perform the puncture of the cyst depends on the availability of a side view adult duodenoscope, the age and weight of the patient, and the possible presence of esophageal stricture. We prefer to use the duodenoscope because it provides the best position in front of the gastric wall and the opportunity to insert large diameter stents.

The choice of the best treatment for PP depends on the medical-surgical team's experience and the management of the endoscopic technique, as well as the availability of interventionist radiology and dedicated pediatric accessories^[17]. Despite several techniques, PP therapy remains a challenge for both pediatric surgeons and pediatric endoscopists^[23]. A novel hybrid natural orifice transluminal endoscopic surgery has already been reported by Rossini *et al.*^[26]; probably, in the future, the model of a transgastric approach used to treat PP could be applied in several diseases, even in pediatric cases.

We can conclude that when conservative therapy is ineffective, EGCD represents a viable option to resolve PP permanently. MEUS provides a valuable contribution to help endoscopic cystogastrostomy in children and also in difficult situations, allowing a safe and effective endoscopic procedure.

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S-Editor Song XX **L-Editor** Roemmele A **E-Editor** Zhang DN



Serrated adenoma of the stomach: Case report and literature review

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Author contributions: Rubio CA performed the pathological examination, designed and wrote the paper; Björk J was the attending doctor for the patient, provided the clinical data and the endoscopic illustration; Both authors critically revised the draft and approved the final version to be published.

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Abstract

Gastric serrated adenomas are histologically characterized by protruding glands with lateral saw tooth-like indentations lined with stratified dysplastic cells containing abundant eosinophilic cytoplasm. Since the first case of gastric serrated adenoma found in 2001, 18 additional cases have been reported. Gastric serrated adenomas have a particular proclivity to progress to invasive carcinoma; 75% or 15% of the 20 cases now in record - including the present one - exhibited invasive carcinoma. The 20th case of gastric serrated adenoma reported here differs from the preceding ones in as much as it evolved in a patient with Lynch syndrome, implying that this adenoma phenotype may develop not only sporadically but also in patients with hereditary traits.

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Key words: Gastric; Serrated; Neoplasia; Lynch syndrome

Core tip: Gastric serrated adenomas have a particular proclivity to progress to invasive carcinoma; 75% or 15% of the 20 cases that are now in record - including the present one - exhibited invasive carcinoma.

Rubio CA, Björk J. Serrated adenoma of the stomach: Case report and literature review. *World J Gastrointest Endosc* 2013; 5(5): 261-264 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/261.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.261>

INTRODUCTION

Ninety years ago Konjetzny^[1] described mucosal polyps in gastric specimens. Six years later Stewart^[2] found among 11000 necropsies, 47 gastric polypoid lesions with mucosal aberrations that he called adenomas. Since then, much attention has been centred on gastric adenomas due to their propensity to evolve into invasive carcinoma^[3-11].

Throughout the years several classifications of gastric polyps have been proposed^[12-15]. Based on the endoscopic appearance, endoscopists have classified gastric polyps (adenomas being a histologic diagnosis) as flat^[16] (also called non-polypoid or non-protruding) and polypoid^[11] (also called protruding). Non-protruding polyps that appear thinner than the surrounding mucosa are called, depressed lesions^[17]. This endoscopic classification was subsequently confirmed at the histological level^[18]. Based on the gross appearance, Goldstein *et al*^[19] classified gastric polyps into flat topped, villiform, and pedunculated and Ming *et al*^[12] into flat and papillary. Based on their histological configuration, gastric polyps were classified by Elster^[14] into focal foveolar hyperplasia, hyperplasiogenic polyps, tubular and villous adenomas, and by Appelman^[20] into non-neoplastic (focal foveolar hyperplasia and hyperplastic polyps), non-neoplastic possibly

hamartomatous (Peutz-Jehgers-type polyps), and neoplastic adenomas (with or without invasive carcinoma). Nakamura^[7] grouped gastric polyps into types I and II (hyperplastic polyps), and types III and IV (adenomas), and Kozuka^[10] grouped them into common type (hyperplastic, adenomatous, and carcinomatous polyps), special-type hamartoma (Peutz-Jehgers polyps, juvenile polyps, polyps in Cronkhite-Canada syndrome, and fundic gland cyst polyps), polypoid lesions (inflammatory polyps and polypoid carcinoma), and polyps resulting from a submucosal mass.

In 2001 we reported a novel histologic phenotype of gastric adenoma characterized by protruding glands with lateral saw tooth-like notches due to scalloped epithelial indentations^[21]. The serrated elongations were lined with stratified dysplastic cells containing abundant eosinophilic cytoplasm; it was called gastric serrated adenoma since it mimicked other serrated adenomas evolving in the colon^[22] the appendix^[23], the duodenum^[24], the pancreatic duct^[25] and the Barretts's esophagus^[26]. Remarkably, this adenoma phenotype was not included in any of the aforementioned classifications of gastric polyps^[11,18,20-22]. One possible explanation could be that gastric serrated adenomas were classified together with gastric villous adenomas. Another possible explanation could be that this type of lesion is very rare in the stomach. In this context, it should be mentioned that no case of serrated adenoma was recorded in a survey of 67 consecutive gastric adenomas^[18], nor in larger series of gastric adenomas in the literature^[5,6,10-14].

Subsequently, we reported six additional cases of gastric serrated adenoma^[27,28]. More recently, cases with gastric serrated adenomas were reported from such disparate countries as Tunisia^[29], Japan^[30], Turkey^[31] and South Korea^[32].

The purpose of the present communication is to report another case of gastric serrated adenoma, this time occurring in a patient with Lynch syndrome, an autosomal dominant genetic condition with an increased risk to develop cancer in various organs, including the stomach.

CASE REPORT

The patient is a 57-year-old male with confirmed *MSH2* mutation Lynch syndrome. His mother was treated for endometrial cancer and an uncle for colorectal cancer. In 1995 the patient was operated for cancer in the right colon. In 2007, a second colon cancer was found at surveillance colonoscopy, this time in the transverse colon. A total colectomy with ileo-rectal anastomosis was performed. In 2009 he was operated for a metastasis in the small bowel. Histology revealed a metastasis from colon cancer.

A gastro-esophagoscopy was done in October 2012, because of protracted gastro-esophageal reflux. Histology showed short Barrett's esophagus with low-grade dysplasia. During the same séance, a 10 mm in diameter polypoid lesion was detected in the stomach (Figure 1).

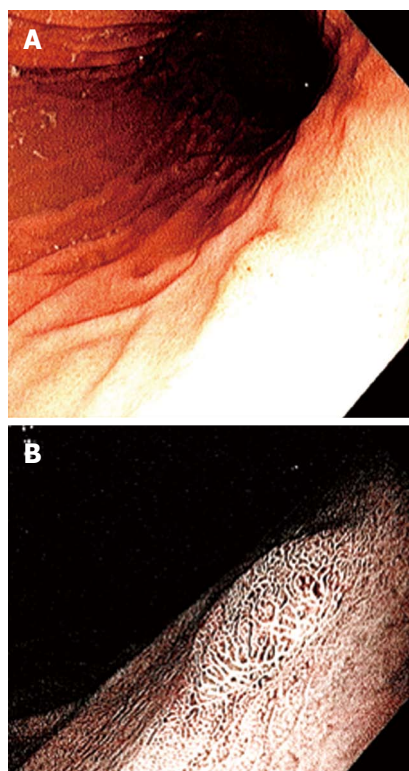


Figure 1 Endoscopic view. A: Gastric polyp; B: Gastric polyp after indigocarmine staining.

The polyp was endoscopically excised. No complications occurred during or after the procedure. The histological examination of the gastric polypoid lesion revealed a serrated adenoma showing protruding glands with lateral saw tooth-like notches due to scalloped epithelial indentations with high-grade dysplasia (Figure 2). In addition, an adenocarcinoma invading the submucosal tissues was demonstrated (Figure 3). The invasive carcinoma component retained the serrated configuration and the cytological features of the adenoma (Figure 4).

DISCUSSION

Despite decreasing incidence, gastric carcinoma continues to be one of the most common cancers world wide^[33]. It is generally assumed that the histogenesis of gastric carcinoma of intestinal type follows the atrophic gastritis-intestinal metaplasia-dysplasia-pathway^[34]. On the other hand, the histogenesis of gastric carcinomas of diffuse type remains elusive. Thus, the histogenesis in the majority of the gastric carcinomas has not yet being disclosed.

It is known that gastric tubular or villous adenomas may progress to gastric carcinoma of intestinal type^[9,10,12,35]. The same fate seems to apply to gastric serrated adenomas, since of the 20 gastric serrated adenomas now in record (including the one reported here), 75% had evolved into invasive carcinoma (Table 1).

Recently, Kwon *et al*^[32] reported 9 cases of gastric serrated adenomas. These authors found that MUC5AC expression was present in 66.7% (6/9) of the gastric

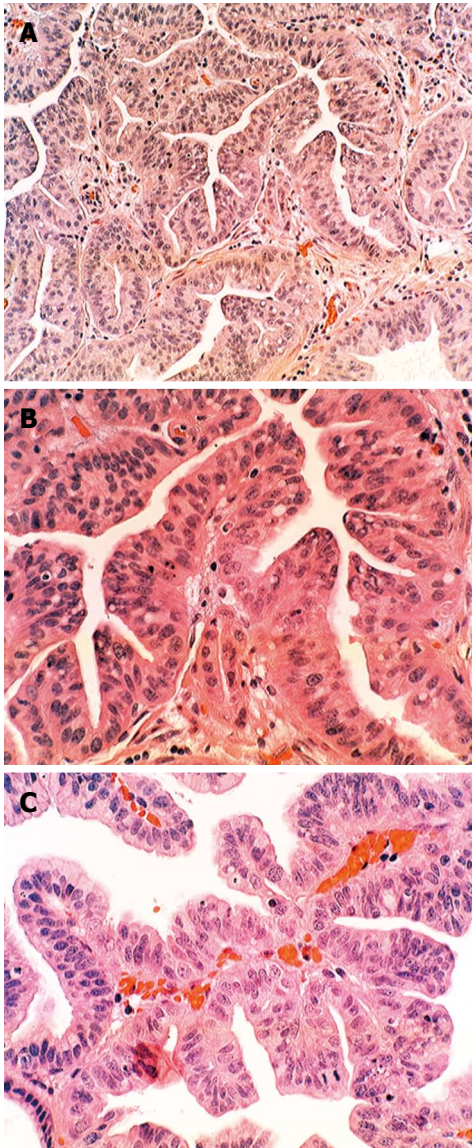


Figure 2 The histological examination of the gastric polypoid lesion revealed a serrated adenoma showing protruding glands with lateral saw tooth-like notches due to scalloped epithelial indentations with high-grade dysplasia. A: Adenoma showing serrated glands lined with high-grade dysplasia [hematoxylin and eosin (HE) $\times 10$]; B: High power view of the adenomatous component showing serrated glands with indentations lined with high-grade dysplasia (HE $\times 20$); C: View of a single elongated gland with saw-tooth-like configuration lined with high-grade dysplasia (HE $\times 20$).

serrated adenomas, in 71.4% (5/7) of the serrated adenocarcinomas, and *KRAS* mutations in 33.3% (3/9) of the cases. Kwon *et al*^[32] concluded that the high frequencies of malignant transformation and *KRAS* mutations suggested that gastric serrated adenomas might be precursors of gastric mucin-phenotype adenocarcinoma.

Here, we report the first case of serrated adenoma of the stomach in a patient with Lynch syndrome. Lynch syndrome is an autosomal dominant genetic condition which has a high risk of colon cancer as well as other cancers including endometrium, ovary, stomach, small intestine, hepatobiliary tract, upper urinary tract, brain, and

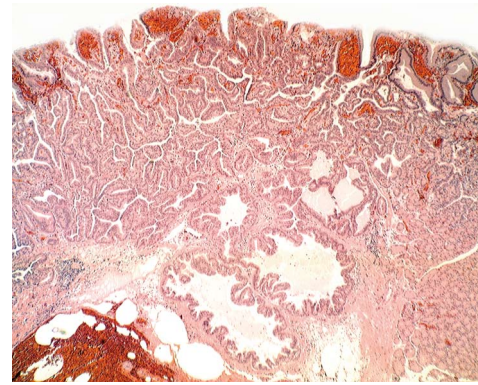


Figure 3 Low-power view of serrated adenoma with invasive carcinoma (hematoxylin and eosin $\times 10$).

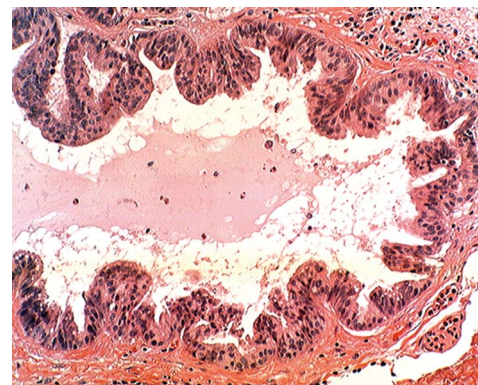


Figure 4 High power view of the invasive component with retained serrated configuration (hematoxylin and eosin $\times 10$).

Table 1 Gastric serrated adenomas case reports

Ref.	Year of publication	No. of cases	No. cases with invasive carcinoma
Rubio <i>et al</i> ^[21]	2001	1	1
Rubio <i>et al</i> ^[27]	2004	5	4
Rubio <i>et al</i> ^[28]	2007	1	1
M'sakni <i>et al</i> ^[29]	2007	1	0
Hasuo <i>et al</i> ^[30]	2009	1	1
Köklü <i>et al</i> ^[31]	2010	1	0
Kwon <i>et al</i> ^[32]	2013	9	7
Rubio <i>et al</i> ¹	2013	1	1

¹Present communication.

skin. The increased risk for these cancers is due to inherited mutations that impair DNA mismatch repair. The occurrence of this case of gastric serrated adenoma in a patient with Lynch syndrome implies that this adenoma phenotype may develop not only sporadically but also in patients with hereditary traits.

Paradoxically, eight out of 20 cases of serrated adenoma of the stomach now in record (including present case) have been reported from a single Institution^[21,27,28]. The increased awareness of the existence of these gastric aggressive adenomas may result in more cases being re-

ported from other Institutions in the future.

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Biodegradable stent for the treatment of a colonic stricture in Crohn's disease

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Core tip: Strictures in Crohn's disease (CD) are challenging. Until the development of medical therapy that can prevent or reverse intestinal fibrosis, endoscopic management is recommended to avoid surgery. Biodegradable polydioxanone stents originally developed to treat refractory esophageal benign strictures are a promising alternative to balloon dilation with the advantage over metallic stents that they do not need to be removed. However, data on their use in the bowel is limited to a few series, mostly in patients with postsurgical colorectal strictures. We report the case of a CD patient presenting with a symptomatic colonic fibrotic stricture that was successfully treated with a biodegradable stent.

Abstract

Biodegradable polydioxanone stents were developed for the treatment of refractory benign esophageal strictures but have been suggested as a new therapeutic option for intestinal strictures. The primary advantage of biodegradable stents over self-expandable metallic stents is that removal is not required. There are, however, few data available on their use in the small or large bowel. We herein describe the case of a 33-year-old patient with long-standing Crohn's disease (CD) who developed a fibrotic stricture of the sigmoid too long to be amenable to balloon dilation. The use of a biodegradable polydioxanone stent was chosen to avoid surgery. Combined endoscopic and fluoroscopic placement of the stent was technically simple, safe and clinically successful, and no recurrence of obstructive symptoms occurred during a 16-mo follow-up. Further studies are needed to evaluate the long-term efficacy and safety of biodegradable stents in the treatment of intestinal strictures, particularly in the context of CD.

Rodrigues C, Oliveira A, Santos L, Pires E, Deus J. Biodegradable stent for the treatment of a colonic stricture in Crohn's disease. *World J Gastrointest Endosc* 2013; 5(5): 265-269 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/265.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.265>

INTRODUCTION

Strictures are a common complication of Crohn's disease (CD), occurring in 1/3 of patients after 10 years of disease. They occur most frequently in the ileocecal region and rectum and at anastomotic sites where the disease is likely to recur^[1]. Medical therapy has not been shown to be effective in the treatment of fibrotic strictures, and its role in preventing stricture formation has been disappointing^[2]. As disease recurrence is common, endoscopic methods, such as balloon dilation or stenting for refractory strictures, have been advocated to decrease surgery.

Biodegradable stents were originally developed to treat refractory benign esophageal strictures but are a

promising therapeutic option for intestinal strictures because they do not require removal and may be able to overcome some of the drawbacks of self-expandable metallic stents (SEMS). We report our experience with the off-label use of a biodegradable esophageal polydioxanone stent in the management of a colonic stricture complicating CD.

CASE REPORT

A 33-year-old female with a history of CD was admitted to the hospital in February 2011 with abdominal cramps, constipation and air-fluid levels in the small and large bowel on X-ray. The CD diagnosis had been established at age 16 years. The disease involved the terminal ileum, colon and perianal region and presented with an inflammatory behavior (A1L3B1p according to the Montreal classification)^[3,4]. She was initially treated with oral corticosteroids and started on azathioprine, but in 2001 infliximab was added for persistent symptoms. The patient experienced some flares over the years until 2009, when she achieved sustained clinical and endoscopic remission while on azathioprine at 3 mg/kg per day and infliximab at 5 mg/kg every 4 wk.

The laboratory results were unremarkable with no signs of systemic inflammation. A computed tomography scan revealed concentric wall thickening over 6 cm lengths in the sigmoid colon with narrowing of the lumen and prestenotic dilation but no regional lymphadenopathy. The bowel obstruction resolved with nasogastric tube suction and intravenous fluids. Colonoscopy confirmed the existence of a distal sigmoid stricture that precluded the passage of the conventional colonoscope (CF-Q160AL, Olympus Optical Co., Tokyo, Japan). A slim colonoscope (PCF-Q180AL Olympus Optical Co., Tokyo, Japan) was used to reach the terminal ileum. There were no endoscopic signs of inflammation. The colon was shortened and showed extensive scarring and some inflammatory polyps; the ileal mucosa appeared to be normal. Dysplasia and malignancy were excluded by several biopsies of the entire length of the stricture.

A short cycle of oral corticosteroids was completed, but the stricture was refractory to medical therapy, and the patient complained of abdominal pain and experienced a new episode of bowel obstruction in September 2011. After having discussed the therapeutic options in a gastrointestinal multidisciplinary team meeting, we decided to place a SX-ELLA BD biodegradable esophageal stent (ELLA-CS, Hradec Kralove, Czech Republic; Figure 1) with a trunk diameter of 20 mm flaring to 25 mm at both ends and a length of 100 mm. The local ethics committee approved the procedure, and informed consent was obtained from the patient.

The procedure was performed under conscious sedation (intravenous midazolam) *via* an anal approach with the patient lying on her left side. Both margins of the stricture were marked by using intramucosal lipiodol injection. The stent was loaded into its dedicated 28 French



Figure 1 SX-ELLA biodegradable esophageal stent. The stent is flared at both ends to reduce the risk of migration and is fitted with radiopaque markers at the midpoint and at the ends to enable precise stent positioning under fluoroscopic control. Because of reduced long-term elasticity, the stent is supplied separate from the delivery system and needs to be manually loaded just before the implantation procedure (see manufacturer's "Instructions for Use").

delivery system and implanted under endoscopic and fluoroscopic guidance over a stiff 0.035-inch guidewire with a soft tip (Jagwire, Boston Scientific, Natick, United States) that was previously introduced through the stricture. Pre-dilation was not performed. An adequate expansion of the stent occurred immediately after its insertion (Figures 2 and 3). Significant stent shortening occurred upon deployment, and a water-soluble contrast (Xenetix 350, Guerbet Laboratories, Roissy, France) was injected at the end of the procedure to confirm proper stent position and luminal patency. There were no immediate or delayed procedure-related complications, namely perforation, pain, hemorrhage or stent migration. The stent insertion provided rapid clinical improvement and symptom relief, and the patient was discharged within 24 h.

A clinical and radiographic follow-up was performed one week after the stent insertion and again one month later, with no evidence of stent migration. At that time, an endoscopy follow-up was also performed to monitor the stent patency and degradation. There was no significant mucosal hyperplastic reaction and no resistance to the progression of the conventional scope through the stent (Figure 2). Complete stent degradation was confirmed on a plain abdominal X-ray 4 mo after the insertion (Figure 3). There was no recurrence of the obstructive symptoms during a 16-mo follow-up.

DISCUSSION

We report a case of a patient with a long-standing CD who developed a symptomatic fibrotic stricture of the colon despite optimized medical treatment with infliximab and azathioprine. Fibrotic strictures in CD patients have been traditionally treated with intestinal resection, which is often extensive and associated with high morbidity rates^[5]. Furthermore, disease recurrence is common. Within 4 years, approximately 40% of the patients will need another resection^[6,7]. Concerns over short-bowel

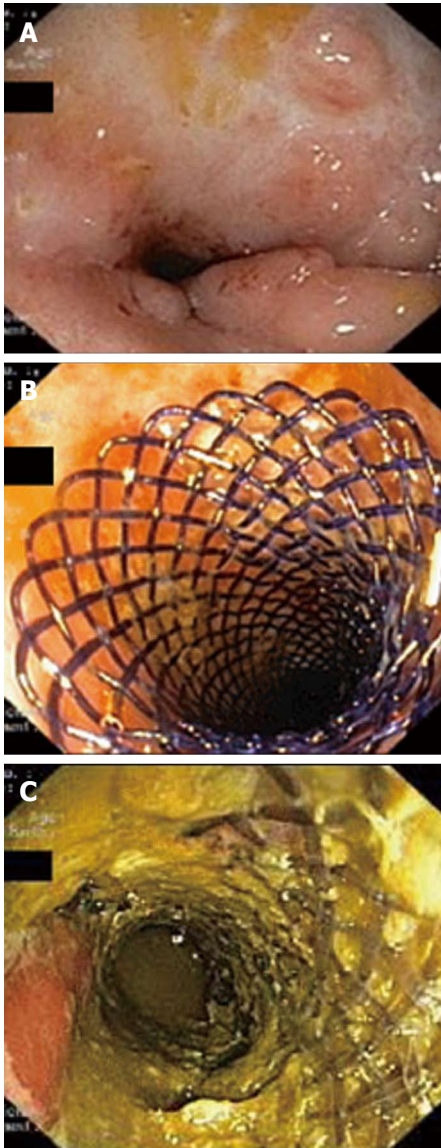


Figure 2 Endoscopic images. A: Stricture of the distal sigmoid colon before stent insertion. The surrounding mucosa show no signs of active inflammation and few inflammatory polyps; B: Biodegradable stent deployed in the stricture at the end of the procedure; C: Endoscopic view 1 mo after the stent placement. The stent fibers present a translucent appearance and partial fragmentation.

syndrome caused by multiple resections and large segment resections led to the development of bowel-sparing surgical techniques or strictureplasty, however, within 10 years, up to 50% of these patients will require repeated surgery because of obstruction recurrence^[8]. Facing the problems related to repeated surgery, endoscopic methods have been advocated for managing CD strictures. Balloon dilation (with or without steroid injection) is currently the endoscopic treatment of choice. Several uncontrolled observational studies have shown that balloon dilation is a safe and effective alternative to surgery in selected patients. It has and has a technical success rate that ranges from 71% to 90% and a major complications rate of 2% to 3%^[9-11]. However, it is generally accepted that strictures greater than 4 cm are not amenable to balloon

dilation, and the recurrence rate of obstructive symptoms is as high as 42% with the need for repeated dilations and their associated perforation risk.

Our patient was not a candidate for balloon dilation because of the extent of the stricture, and surgical resection would likely have been extensive because of the scarring colon. Stent placement was thus considered. Compared with balloon dilation, stents determine slower and more sustained stricture dilation, resulting in reduced trauma and subsequent fibrosis. Furthermore, the radial force is maintained for several weeks, allowing remodeling of the stricture and increased long-term luminal patency with a reduced need for repeated dilations. However, data regarding the efficacy and safety of extractable SEMS in the treatment of symptomatic intestinal strictures in CD are limited and conflicting^[12-16]. In general, the use of fully covered SEMS in this setting appears to be effective but has been associated with several drawbacks and complications, such as a high rate of spontaneous migrations and the need for removal, and remains controversial. The recently developed biodegradable stents are a promising option because of their longer patency and no need for removal, although radial force is lower compared with nitinol stents.

Biodegradable stents are manufactured from different synthetic polymers that have other well-established biomedical applications, particularly in the fields of sutures, tissue engineering and controlled drug delivery. The polymers are degraded by random hydrolysis of their molecules' ester bounds, and the degradation products are metabolized *via* normal metabolic pathways. This process compromises the structure and integrity of the stent filaments and leads to the loss of radial force, fracture of the stent skeleton and disintegration. The radial force of polydioxanone stents is maintained for approximately 6-8 wk following implantation and drops to 50% by week 9. Disintegration usually occurs within 11-12 wk, although the degradation rate is dependent on the size, structure, temperature, pH and type of body tissue in which the stent is implanted^[17].

Biodegradable polydioxanone stents were developed and licensed for the treatment of refractory benign esophageal strictures^[18-22]. The experience with their use in intestinal strictures is encouraging but still in its early stages. Published information regarding intestinal biodegradable stenting is limited to a few small case series that are both prospective and retrospective and focus on patients with refractory anastomotic colorectal strictures following resection for rectosigmoid carcinoma^[23-25]. Rejchrt *et al*^[26,27] reported the placement of biodegradable stents in patients with stricturing CD. This was the sole report of such a use in the small bowel and proximal large bowel. Proximal stent insertion was accomplished by use of a custom made introducer inserted into an overtube after endoscope removal. The standard delivery system for esophageal implantation has an active length of 75 cm and can only be used for intestinal strictures up to the distal descending colon.

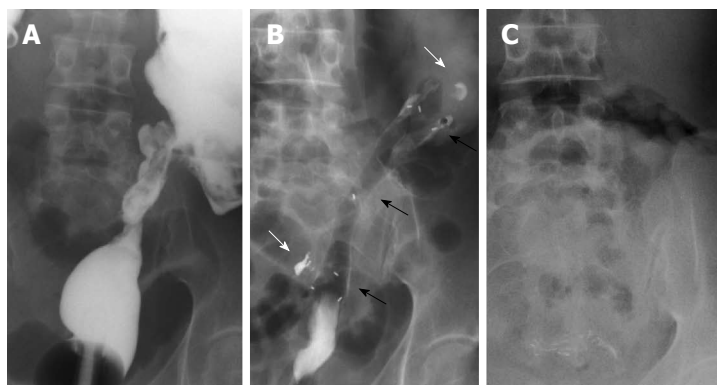


Figure 3 Radiographic images. A: Stricture of the distal sigmoid colon outlined by luminal filling with barium using a rectal catheter (supine position); B: Biodegradable stent *in situ* immediately after insertion (supine position). The stent is radiolucent, but the radiopaque markers at the midpoint and at the ends are visible (black arrows). The margins of the stricture are marked with lipiodol (white arrows); C: Disappearance of radiopaque markers at 4 mo confirming complete stent degradation (erect position).

Intestinal insertion of biodegradable polydioxanone stents is technically possible and relatively simple. However, it has been associated with a significant rate of early stent migration. This issue may be solved by improvements in stent design and appropriate strategies such as clip placement in the upper flare of the stents. It is necessary to clarify whether pre-dilation of the stricture should be performed (unless there is an inability to pass the delivery system through the stricture) because the radial force of biodegradable stents appears to be sufficient to ensure adequate stent expansion. Severe mucosal hyperplastic reaction resulting in obstruction after biodegradable stenting has been documented in esophageal strictures^[28,29] but not in intestinal strictures thus far. Most of these cases were treated successfully with single balloon dilation and resolved completely after stent degradation. Neither of these complications was observed in our patient.

In conclusion, early experience suggests that biodegradable polydioxanone stents may represent a new therapeutic option for CD patients with refractory bowel strictures or strictures in which balloon dilation is unsuitable. Further studies are necessary to fully assess their long-term efficacy and safety in this clinical setting.

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Boerhaave's syndrome during bowel preparation with polyethylene glycol in a patient with postpolypectomy bleeding

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Abstract

Boerhaave's syndrome is spontaneous rupture of the esophagus, a rare condition with high mortality that occurs most often after forceful vomiting. Polyethylene glycol (PEG) solution is the most common preparation used for colonoscopy. Since large volumes have to be ingested, PEG may induce severe vomiting or retching. However, Boerhaave's syndrome has rarely been reported as a potential problem related to PEG solution. We report a case of spontaneous esophageal rupture due to violent vomiting during bowel preparation with PEG solution in a patient with postpolypectomy bleeding.

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Key words: Esophageal perforation; Colonoscopy; Polyethylene glycols

Core tip: A bowel preparation with polyethylene glycol electrolyte solution should be used with care in patients

with postpolypectomy bleeding.

Yu JY, Kim SK, Jang EC, Yeom JO, Kim SY, Cho YS. Boerhaave's syndrome during bowel preparation with polyethylene glycol in a patient with postpolypectomy bleeding. *World J Gastrointest Endosc* 2013; 5(5): 270-272 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/270.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.270>

INTRODUCTION

Boerhaave's syndrome is a form of barogenic rupture caused by a sudden post-emetic rise in the intraluminal pressure in the distal esophagus^[1]. Esophageal perforation has high mortality, which increases to 40%-60% when treatment is delayed beyond 48 h, leading to mediastinal sepsis and multisystem organ failure^[2].

Electrolyte solution with sodium sulfate as the predominant salt and polyethylene glycol (PEG) was developed as an additional osmotic agent in 1980^[3]. Since PEG-electrolyte lavage solutions were shown to be safe, well-tolerated, and highly effective in patients with renal failure or congestive heart disease, this became the most common method of preparation for colonoscopy^[4]. The main disadvantage of PEG electrolyte solution is that large volumes have to be ingested. In addition, PEG electrolyte solution is poorly tolerated by some patients and may induce severe vomiting or retching^[5]. Some cases of Mallory-Weiss syndrome have been reported following the ingestion of PEG-electrolyte solutions^[6], but only a few cases of colonoscopy-related esophageal perforation^[7-11].

CASE REPORT

A 61-year-old man underwent a screening colonoscopy.

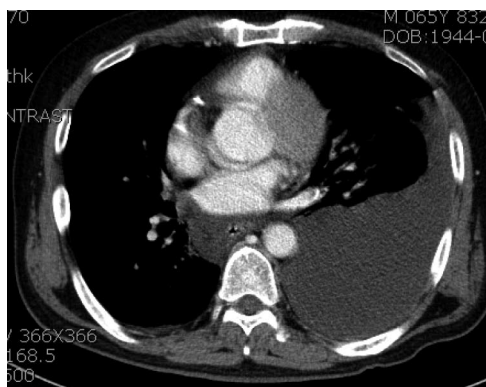


Figure 1 Chest computed tomography shows a left pleural effusion and peri-esophageal fluid collection.



Figure 2 Upper endoscopy shows a 15 mm × 12 mm perforation with stigmata of recent bleeding distal to the Z-line on the left side of the esophagus.

He had been healthy without specific complaints and no significant past medical or family history. The colonoscopy revealed nine small (< 10 mm) sessile polyps from the ascending colon to the descending colon and a 16-mm lateral spreading tumor (LST) in the sigmoid colon. The polyps were resected by hot biopsy for the smaller polyps (< 5 mm), conventional snare polypectomy, or endoscopic mucosal resection for the LST. Hemoclips were applied to the postpolypectomy wound to prevent bleeding, except for the smaller polyps. There were no apparent complications after the colonoscopic polypectomy. Twenty-four hours later, the patient presented to the emergency room with hematochezia. After drinking 2 L of PEG electrolyte solution over a 2-h period for an urgent colonoscopy, the patient had several sudden attacks of vomiting associated with severe chest pain and dyspnea. A chest examination revealed decreased air entry in the lower left lung; there was no subcutaneous emphysema. Abdominal examination revealed tenderness in the epigastric region and right upper quadrant, but no guarding or rigidity. A chest X-ray showed a layered fluid collection in the left chest. Emergency computed tomography (CT) showed a left pleural effusion and peri-esophageal fluid collection (Figure 1), but the esophagus was not clearly identified and no free air or fluid was seen in the abdomen. A left chest drain was inserted and 800 mL of blood tinged fluid were drained. An emergent upper endoscopy revealed a 15 mm × 12 mm perforation with stigmata of recent bleeding distal to the Z-line on the left side of the esophagus, but the perforation could not be clearly demarcated due to blood (Figure 2). Therefore, we diagnosed the patient with Boerhaave's syndrome that developed during bowel preparation using PEG electrolyte solution. The patient took immediate surgical intervention where the primary repair of a ruptured esophagus was reinforced with a pedicled flap of the eighth intercostal muscle. Further evaluation for hematochezia was not performed because it was stopped spontaneously. The patient made an uneventful recovery following surgical management and was discharged soon after without complications, having made a complete recovery.

DISCUSSION

Esophageal perforation is uncommon condition with a high mortality rate. The causes include endoscopic instrumentation, trauma, swallowed foreign bodies, and Boerhaave's syndrome, which is the most serious form of esophageal perforation^[2]. Boerhaave's syndrome is often misdiagnosed as acute pancreatitis, myocardial infarction, and peptic ulcer because of its rarity and nonspecific symptoms^[1]. A delay in diagnosis leads to more extensive contamination and inflammation of the mediastinum and results in a poor outcome. The rupture in Boerhaave's syndrome is usually in the left lateral wall of the esophagus, just superior to the diaphragm^[12]. This might be due to an anatomic weakness at that point. Distal esophageal perforations, most prevalent in Boerhaave's syndrome, commonly show a left-sided pleural effusion and pneumomediastinum on the chest X-ray^[13]. The presence and magnitude of these findings are usually related to the length of time since the perforation. The diagnosis can be made earlier and more accurately with additional radiological examinations, such as CT. Since our patient had severe chest pain immediately after violent vomiting in the emergency room, we had a heightened index of suspicion for esophageal perforation and made the diagnosis without delay. The management is still controversial because the treatment modalities range from conservative measures to extensive surgery^[12]. If the perforation is detected in less than 24 h, primary repair and wide irrigation of the mediastinum are usually possible^[14]. However, when the treatment is delayed beyond 48 h, the treatment is not clear. Recently, endoscopic treatment with stenting allows for non-operative management in selected patients, even if data on endoscopic management of perforations in benign disease are limited^[15]. The vacuum endo-sponge therapy, that is a kind of interventional therapy successfully for the treatment of anastomotic insufficiencies in upper gastrointestinal surgery, can be used for small perforation^[11]. After the prompt diagnosis in our case, operative management was chosen because endoscopy showed a relatively large perforation. Moreover, the patient had

intractable chest pain and hypotension despite the chest tube drainage.

Nausea is a common adverse effect of the use of PEG electrolyte solution and vomiting is sometimes seen because of the large volume needed to clean the colon. Other adverse effects include urticarial reaction, anaphylaxis, hypothermia, obstruction-perforation, and cardiac arrhythmia^[5]. Some cases of Mallory-Weiss syndrome after vomiting due to bowel preparation have been reported^[6]. However, only five cases of esophageal perforation related to the use of the PEG electrolyte solutions have been described in the English literature^[7-11]. Among these cases, the only reported death was of a patient who had been managed conservatively. This complication could have been avoided if the PEG-electrolyte solution had been given *via* a nasogastric tube before the colonoscopy. However, when administering the solution *via* a nasogastric tube, life-threatening complications such as aspiration and pulmonary edema after vomiting have been described^[16]. In addition, anti-emetic medication during the preparation process can prevent this complication in patients who have a tendency to nausea and vomiting^[11].

Urgent colonoscopy for acute lower gastrointestinal bleeding usually requires a PEG electrolyte solution purge, either orally or by nasogastric tube to rid the colon of clots, stool, and blood^[17]. However, a recent study showed that a bowel preparation for an urgent colonoscopy is not always needed in postpolypectomy patients^[18]. Therefore, a bowel preparation with PEG electrolyte solution should be used with care in patients with post-polypectomy bleeding.

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Is idiopathic recurrent pancreatitis attributed to small stones?

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Abstract

Idiopathic recurrent pancreatitis remains a clinical challenge. Intraductal ultrasonography in the management of idiopathic recurrent pancreatitis may be a new strategy for undetermined causes after initial diagnostic approaches, including endoscopic retrograde cholangio-pancreatography (ERCP). However, no definite cause after ERCP should be defined under optimal settings and with experienced technique.

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Key words: Endoscopic retrograde cholangio-pancreatography; Idiopathic recurrent pancreatitis; Biliary stone

Core tip: The diagnosis of patients with idiopathic recurrent pancreatitis was revised after intraductal US used the criterion of 0.2-0.3 cm for common biliary duct stones. This implied that endoscopic retrograde cholangio-pancreatography (ERCP) could not be effective

for identification of small biliary stones. For a more perfect ERCP study, an ERCP endoscopist should be aware that ERCP is a dynamic study, rather than image reading alone, and it should be possible to select an appropriate concentration of contrast medium for different conditions. Thus, even small stones could be detected without a second diagnostic tool.

Chow WK, Peng YC. Is idiopathic recurrent pancreatitis attributed to small stones? *World J Gastrointest Endosc* 2013; 5(5): 273-274 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i5/273.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i5.273>

TO THE EDITOR

We read with interest the paper by Kim *et al*^[1] entitled "The role of intraductal US in the management of idiopathic recurrent pancreatitis without a definite cause on endoscopic retrograde cholangio-pancreatography (ERCP)". It is difficult to identify possible causes and make a definite diagnosis in cases of idiopathic recurrent pancreatitis^[2]. The authors provided some ideas about the diagnostic process of idiopathic recurrent pancreatitis with intraductal US. However, they did not find biliary stones initially by an ERCP study in cases that were defined as idiopathic recurrent pancreatitis. Their revised diagnosis after intraductal US used the criterion of 0.2-0.3 cm for common biliary stones. This implied that ERCP could not be effective without identification of small biliary stones. We strongly disagree with this implication. In our opinion, ERCP depends on the endoscopist's experience and technique.

Therefore, several points need to be clarified. Firstly, and most importantly, every ERCP endoscopist should be aware that ERCP is a dynamic study, rather than an image reading alone. Once contrast medium is injected into the biliary tract, fluoroscopy should be performed.

Any filling defect, contrast medium flow direction and pressure resistance should be monitored by the endoscopist. It is difficult to clearly define the injection pressure, which may be applied according to individual perception. However, any suspicious lesion should be reviewed immediately on X-ray film because X-ray film is better than fluoroscopy for identifying lesions.

Secondly, an experienced ERCP endoscopist should be able to select an appropriate concentration of contrast medium for different conditions. The radiation quantities depend on concentration of contrast medium, fluoroscopy time and total radiation^[3]. Clinical experience suggests that small gallstones within large ducts may be better imaged with dilute contrast, whereas strictures and pancreatic duct anatomy are better imaged with full-strength contrast^[4]. A concentration of about 50%-100% (150-300 mg iodine/mL) is usually used to identify opacified stricture lesions and a 25%-30% concentration is used to identify small filling defects in the common bile duct. With a higher concentration of contrast medium, small lesions may be omitted.

Thirdly, ERCP is highly technical and depends on the

endoscopist's experience^[3]. An experienced endoscopist should have clear concepts, skillful technique and the ability to identify most lesions in an ERCP study. A second diagnostic tool should not be a routine procedure for ERCP.

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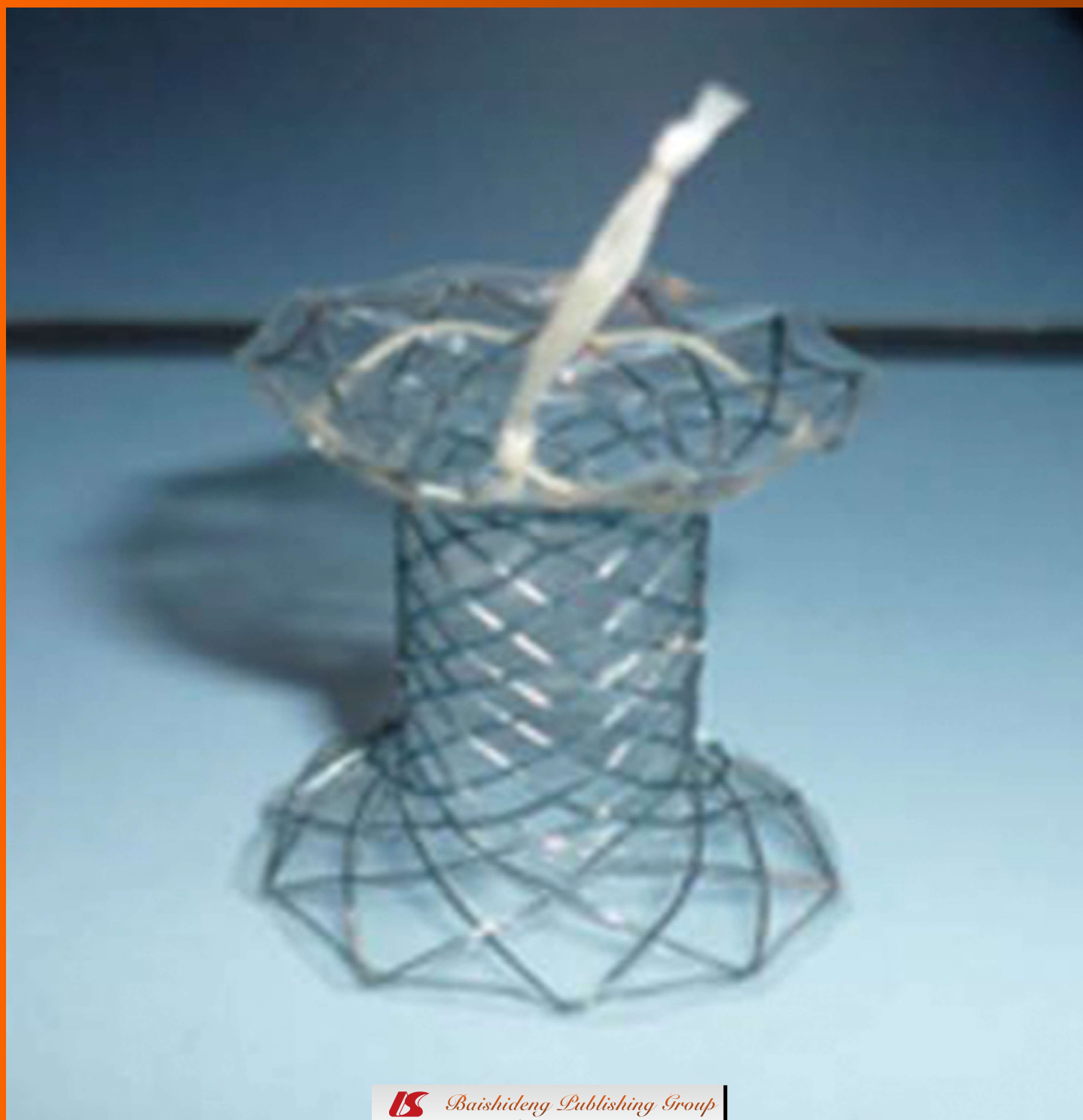
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APPENDIX I-V Instructions to authors

ABOUT COVER Téllez-Ávila FI, Villalobos-Garita Á, Ramírez-Luna MÁ. Use of a novel covered self-expandable metal stent with an anti-migration system for endoscopic ultrasound-guided drainage of a pseudocyst.
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Effectiveness of circumferential endoscopic mucosal resection with a novel tissue-anchoring device

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Abstract

AIM: To evaluate the efficacy of circumferential endoscopic mucosal resection (EMR) with a tissue-anchoring device in comparison to forceps precut EMR and conventional endoscopic submucosal dissection (ESD).

METHODS: The study was designed as a prospective, randomized, *ex vivo* study. Fresh *ex vivo* specimens were harvested from adult white Yorkshire pigs weighing 30-50 kg. Seventy-five standardized, artificial lesions measuring 3 cm × 3 cm were created by methylene blue tattoo at the greater curvature in fresh *ex vivo* stomachs using the EASIE-R simulator platform (Endosim LLC, Berlin, MA, United States). The three advanced endoscopists performed the three resection techniques such as circumferential EMR using the tissue-anchoring device (TA-EMR), forceps precut EMR (FP-EMR), and endoscopic submucosal dissection. The endoscopists and the type of cutting methods were determined randomly by grouped randomized selection.

The resection bed was grossly inspected to determine whether the lesion was resected "*en-bloc*" (defined as no remaining mucosal tattoo remaining on specimen). The resection bed was also probed for evidence of perforation. The procedural time of circumferential resection, submucosal dissection, and injection frequency were recorded by an independent observer.

RESULTS: All 75 created lesions were successfully resected by three advanced endoscopists using the three techniques. The mean ± SD size of resected specimens (long axis) were 39.5 ± 5.6 mm, 36.5 ± 7.3 mm, and 44.6 ± 5.6 mm for TA-EMR, FP-EMR, and ESD respectively. The overall mean dissection time of both the TA-EMR and FP-EMR was significant shorter than ESD (TA-EMR: 5.1 ± 3.3 min, FP-EMR: 3.5 ± 2.0 min vs ESD: 15.8 ± 9.5 min, $P < 0.001$, $P < 0.001$). The overall mean total procedure time of both the tissue-anchoring and forceps circumferential EMR was significantly shorter than ESD (TA-EMR: 17.5 ± 6.0 min, FP-EMR: 16.6 ± 6.6 min vs ESD: 28.6 ± 13.9 min, $P < 0.001$, $P < 0.001$). The *en-bloc* resection rate of ESD was 100% (25/25) and the *en-bloc* resection rate of the TA-EMR (84.0%, 21/25) was higher than for the FP-EMR (60.0%, 15/25), yet not statistically significant ($P = 0.18$). The perforation rate of each technique was 8.0% (2/25).

CONCLUSION: TA-EMR appears to be quicker than ESD, and there was a trend towards improved *en bloc* resection rate with the TA-EMR when compared to the FP-EMR.

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Key words: Endoscopic mucosal resection; Endoscopic submucosal dissection; *En bloc* resection; Perforation

Core tip: The recently introduced tissue anchor device has the capability of deploying three spikes into the tissue that allow a reliable fixation of the tissue and facilitate retraction into snare. We demonstrated the efficacy of circumferential endoscopic mucosal resection (EMR)

with a novel tissue-anchoring device in comparison with circumferential EMR using conventional forceps, and endoscopic submucosal dissection.

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INTRODUCTION

Endoscopic mucosal resection (EMR) is widely employed for the local treatment of early superficial cancer and dysplasia. Due to its simplicity and safety, it is one of the most common endoscopic techniques for resecting superficial lesions of the esophagus, stomach or colon. Various techniques of EMR such as ligation-EMR (EMRL), cap-EMR (EMRC), and strip-biopsy EMR (SB-EMR) have been developed. With these conventional techniques, however, the specimen size obtained from a one-piece resection is limited in size, with mean maximum resection sizes in the 10-15 mm range^[1-5]. The precut-EMR (EMR-P) method, in which lesions are resected using a snare after circumferential precutting, allows *en-bloc* resection of lesion with a maximum diameter of 20 mm^[6,7]. This snare technique is not reliable for lesions greater than 20 mm in diameter because of the difficulty of capturing and effectively ligating the significant amount of submucosal tissue in these lesions, even after successful circumferential precutting^[3,8,9]. Endoscopic submucosal dissection (ESD) has a potential for a high rate of *en-bloc* resection, regardless of tumor size, leading to a more precise histological evaluation of the specimen and a lower recurrence rate at long-term follow up^[10,11]. ESD, however, is a technically difficult procedure, and it can frequently cause serious complications such as significant bleeding or perforation. Thus, development of new endoscopic tools and the simplification of endoscopic resection techniques are necessary to enhance safety. Von Renteln and colleagues recently published a pilot study demonstrating the feasibility of grasp-and-snare circumferential EMR using a novel tissue-anchoring device ("Tissue Anchor", Ovesco Endoscopy AG, Tübingen, Germany) for large-sized lesions^[12]. To date, there is no study that compares circumferential EMR with this novel tissue-anchoring device and other resection techniques, including circumferential EMR with a conventional strip-biopsy technique and ESD. Therefore, the aim of this study is to evaluate of the efficacy of these three methods.

MATERIALS AND METHODS

The study was designed as a prospective, randomized, *ex*

vivo study. Fresh *ex vivo* specimens containing esophagus, stomach and duodenum were harvested from adult white Yorkshire pigs weighing 30-50 kg (from a commercial livestock vendor) and used with the EASIE-R simulator platform (Endosim, LLC, Berlin, MA, United States) (Figure 1). Institutional review board (IRB) review for human subject and/or live animal research was not required as there were no human research subjects or live animals involved in the study. A total of 75 procedures were performed by three advanced endoscopists. Prior to the study, the participants each practiced five cases of circumferential EMR using the novel tissue-anchoring device. Each endoscopist then performed eight to nine recorded cases of each: circumferential EMR using the tissue-anchoring device (TA-EMR), forceps precut EMR (FP-EMR), and endoscopic submucosal dissection (ESD).

Creation of lesions

Seventy-five standardized, artificial lesions measuring 3 cm × 3 cm were created by methylene blue tattoo in the mucosa of fresh *ex vivo* stomachs at the anterior and posterior wall in the proximity of the greater curvature (Figure 2). The endoscopists and the type of cutting methods were determined randomly by grouped randomized selection (*i.e.*, each endoscopist performed the same number of each procedure, but the order was randomized).

Tissue resection

A double-channel endoscope (GIF-2T 160; Olympus America Inc, Center Valley, PA, United States) was used for all resections. A normal saline and methylene blue solution was injected to provide tissue separation between the mucosal and submucosal layers. For the circumferential TA-EMR, the tissue anchor was used to grasp the mucosal flap after circumferential cutting. For FP-EMR, a foreign body retrieval forceps (Olympus, Tokyo, Japan) was used to grasp the mucosal flap after circumferential cutting. For ESD, conventional ESD technique was used. All cases of direct circumferential resection were carried out with the hook knife, needle knife and IT knife, after repeated injection of the saline/methylene blue cushion solution (Figure 3A). The separation of the circumferential cutting area was carefully inspected (Figure 3B). The anchor and forceps accessories were used in the left channel of the double-channel endoscope for their respective resection techniques, and a 25 mm standard oval-shaped disposable electrosurgical snare (SD-210U-25, Olympus, Tokyo, Japan) was used in the right channel. Following injection with normal saline solution, the tissue anchor and forceps were then retracted into the endoscope to lift the mucosa, and the snare was placed into the circular pre-cut incision (Figure 4). The snare was subsequently closed and the specimen resected with electrocautery (UES-30 generator, 40 W output; Olympus America Inc, Center Valley, PA, United States) (Figure 5). For conventional ESD, a circular precut was made with the IT knife after an initial incision with the conventional needle knife. The lesion was then resected with a conventional needle



Figure 1 Simulation platform using the EASIE-R simulator with an ex-vivo porcine stomach specimen.

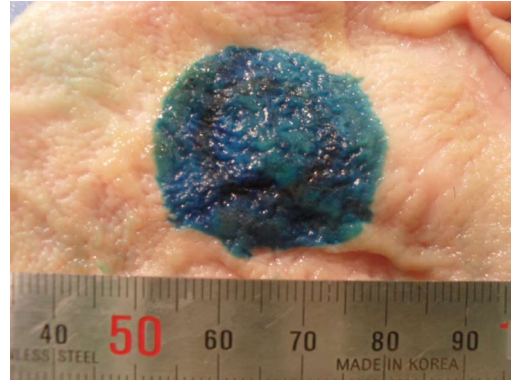


Figure 2 3 cm x 3 cm target lesions created by methylene blue tattoo in the mucosa of fresh ex-vivo stomachs.

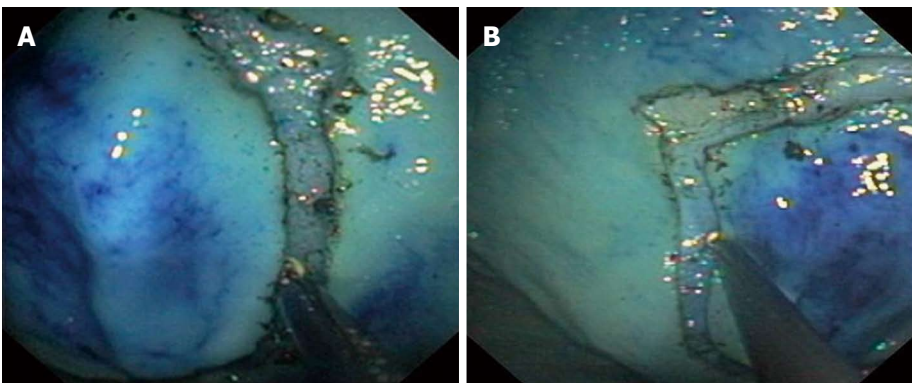


Figure 3 Endoscopic images. A: Circumferential resection with the IT knife after injection; B: The separation of the circumferential cutting area being carefully inspected.

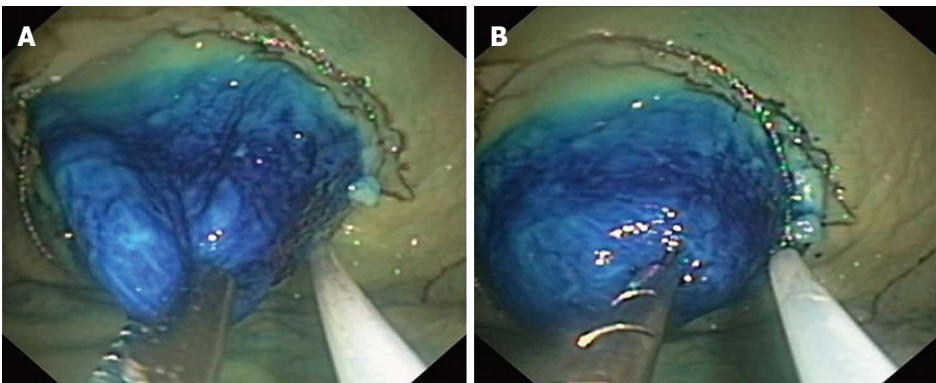


Figure 4 Endoscopic images. A: The mucosal retraction with regular forceps (unipolar traction); B: Mucosal retraction with the tissue-anchoring device (retracting tissue from three anchor points).

knife and hook knife following injection to separate the mucosa and submucosa.

Assessment of complications

Immediately after retrieving the excised specimens, the lesions were spread and pinned on flat cork plates. The length and area of each excision specimen were measured. The resection bed was grossly inspected to determine whether the lesion was resected “*en-bloc*” (defined as no remaining mucosal tattoo remaining on specimen).

The resection bed was also probed for evidence of perforation. The procedural time of circumferential resection, submucosal dissection, and injection frequency were recorded by an independent observer.

Statistical analysis

The sample size was calculated by 10 cases of initial data of each group (TA-EMR: 21.1 ± 6.4 min, FP-EMR: 20.1 ± 7.8 min, and ESD: 35.1 ± 18.5 min). We used the one-Way ANOVA method to estimate sample size, with an

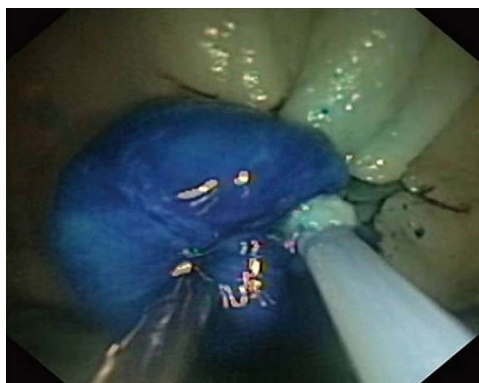


Figure 5 The snare being subsequently closed and the specimen resected by application of electrocautery.

Table 1 Resection results of tissue-anchoring circumferential endoscopic mucosal resection

Endoscopist	Margin (min)	Dissection (min)	Total time (min)	Perforation (rate)	<i>En-bloc</i> (rate)
1 st	7.3 ± 2.4	5.2 ± 3.8	17.8 ± 4.7	1/9 (11.1%)	9/9 (100%)
2 nd	9.0 ± 4.5	6.0 ± 3.7	21.5 ± 6.7	0/8 (0%)	6/8 (75%)
3 rd	5.8 ± 2.2	4.1 ± 2.1	13.2 ± 3.5	1/8 (12.5%)	6/8 (75%)
Total	7.4 ± 3.3	5.1 ± 3.3	17.5 ± 6.0	2/25 (8.0%)	21/25 (84.0%)

alpha of 0.05, a power of 80% and calculated an estimated sample size of 25 cases for each group. Data were analyzed by using SPSS software, version 18.0 (SPSS Inc Headquarters, Chicago, Ill). Statistical comparisons were made between the groups using the One-Way ANOVA test and statistical significance was defined as $P < 0.05$.

RESULTS

All 75 created lesions were successfully resected by three advanced endoscopists using the three techniques. All parameters (procedure time, specimen size, *en-bloc* resection status, and perforation) were successfully recorded by an independent observer for each procedure. The mean ± SD size of resected specimens (long axis) were 39.5 ± 5.6 mm, 36.5 ± 7.3 mm, and 44.6 ± 5.6 mm for the tissue-anchoring circumferential EMR (TA-EMR), forceps pre-cut EMR (FP-EMR), and ESD respectively.

The overall mean total procedure time of TA-EMR was 17.5 ± 6.0 min (circumferential cutting: 7.4 ± 3.3 min, dissection: 5.1 ± 3.3 min) and the *en-bloc* resection rate was 84.0% (21/25) (Table 1).

The overall mean total procedure time of the forceps circumferential EMR was 16.6 ± 6.6 min (circumferential cutting: 7.9 ± 4.0 min, dissection: 3.5 ± 2.0 min) and the *en-bloc* rate was 60.0% (15/25). Two of the piecemeal resections (non *en-bloc*) resulted in 3 and 4 individual resection pieces, respectively (Table 2).

The overall mean total procedure time of the ESD was 28.6 ± 13.9 min (circumferential cutting: 6.9 ± 4.9 min, dissection: 15.8 ± 9.5 min) and the *en-bloc* rate was 100% (25/25). The perforation rate of each technique

Table 2 Resection results of forceps pre-cut endoscopic mucosal resection

Endoscopist	Margin (min)	Dissection (min)	Total time (min)	Perforation (rate)	<i>En-bloc</i> (rate)
1 st	9.6 ± 4.1	3.8 ± 2.4	19.1 ± 9.2	0/8 (0%)	5/8 (62.5%)
2 nd	8.4 ± 2.9	3.6 ± 1.7	18.0 ± 3.8	0/9 (0%)	4/9 (44.4%)
3 rd	5.6 ± 2.3	3.0 ± 2.1	12.6 ± 4.3	2/8 (25%)	6/8 (75%)
Total	7.9 ± 4.0	3.5 ± 2.0	16.6 ± 6.6	2/25 (8.0%)	15/25 (60.0%)

Table 3 Resection results of endoscopic submucosal dissection

Endoscopist	Margin (min)	Dissection (min)	Total time (min)	Perforation (rate)	<i>En-bloc</i> (rate)
1 st	7.2 ± 2.3	16.1 ± 7.0	30.5 ± 9.2	1/8 (12.5%)	8/8 (100%)
2 nd	8.3 ± 6.1	18.7 ± 12.1	33.1 ± 16.6	1/8 (12.5%)	8/8 (100%)
3 rd	5.5 ± 1.9	12.9 ± 7.0	22.9 ± 10.0	0/9 (0%)	9/9 (100%)
Total	6.9 ± 4.9	15.8 ± 9.5	28.6 ± 13.9	2/25 (8.0%)	25/25 (100%)

was 8.0% (2/25) (Table 3). The overall mean dissection time of both the TA-EMR and FP-EMR was significant shorter than ESD (TA-EMR: 5.1 ± 3.3 min, FP-EMR: 3.5 ± 2.0 min *vs* ESD: 15.8 ± 9.5 min, $P < 0.001$, $P < 0.001$) (Figure 6A). The overall mean total procedure time of both the tissue-anchoring and forceps circumferential EMR was significantly shorter than ESD (TA-EMR: 17.5 ± 6.0 min, FP-EMR: 16.6 ± 6.6 min *vs* ESD: 28.6 ± 13.9 min, $P < 0.001$, $P < 0.001$) (Figure 6B).

DISCUSSION

The ability to perform an *en-bloc* endoscopic resection of superficial cancerous and pre-malignant lesions may lead to an improvement of patient outcomes, since it provides an accurate and reliable histopathological evaluation. An inaccurate histopathological assessment from piece-meal resection may result in an inaccurate decision for further treatment and ultimately, local tumor recurrence^[6,13]. EMR is used world-wide as the first-choice therapy for patients with early gastric cancer (EGC) who meet indications for this technique. The appropriate indication for EMR for EGC is considered to be an intramucosal differentiated type adenocarcinoma without ulceration or scarring, that is no more than 15 mm in size, regardless of macroscopic type^[14]. The most common technique for upper gastrointestinal EMR include A) the strip biopsy method, also referred to as grasp-and-pull technique, using a double-channel endoscope, and B) the aspiration mucosectomy technique which uses a clear cap fitted onto the end of the endoscope. Using these techniques, only lesions of up to 10 mm in diameter can be reliably removed *en-bloc* with a sufficiently clear margin^[15-18]. A definite histological diagnosis of the depth of invasion and the tumor margin from these resected specimens is frequently challenging, since the lesions measure only 10 mm or less in size. Circumferential incision with a tool such as the IT-knife, followed by snare resection (EMR-P), has been used to overcome such obstacles. Studies have demonstrated that

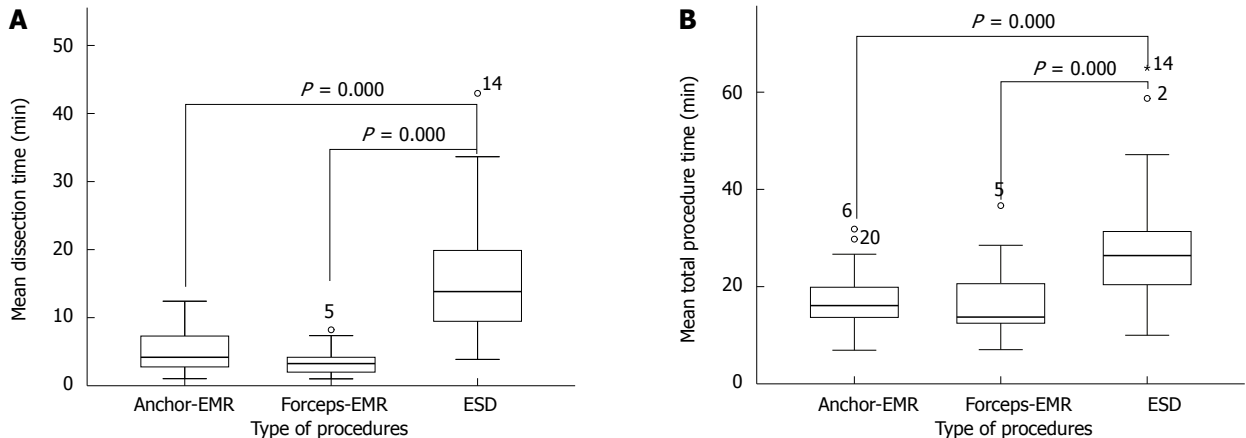


Figure 6 The overall mean total procedure time. A: Overall mean dissection time; B: Mean total procedure time. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.



Figure 7 Detail of the novel tissue-anchoring device.

the *en-bloc* resection rates of the EMR-P technique are 82% for lesions of 10 mm or less, 54%-75% for those between 11 and 20 mm, 14%-38% for those of over 20 mm. They showed that snaring a lesion of over 20 mm using this technique was difficult, even after successful circumferential incision by IT-knife^[3,8,9].

The concept of tissue grasping in combination with snare resection, after circumferential cutting, may enable the performance of EMR to be expanded further. Ovesco's recently introduced tissue anchor device has the capability of deploying three spikes into the tissue (Figure 7) that allow a reliable fixation of the tissue and facilitate retraction into snare. von Renteln *et al*^[12] demonstrated that grasp-and-snare EMR using this tissue anchor, in combination with a 25 mm monofilament snare, is feasible and results in reliable *en-bloc* resections of up to 40 mm × 42 mm specimens. The group achieved 90% (9/10) complete *en-bloc* resections. They demonstrated an improved time-efficiency of this method (average of 32 min) when compared to ESD (average of 78 min). However, the study lacked a control group and allowed no direct comparison between various EMR/ESD methods.

In this study, we compared the efficacy (as defined by *en bloc* resection rate) and efficiency (as defined by time of total procedure) of grasp-and-snare circumferential EMR using a novel tissue-anchoring device in comparison to

circumferential EMR with strip biopsy and direct ESD, using *ex vivo* porcine endoscopy simulator. Our results demonstrated that the overall mean total procedure time of TA-EMR was significantly shorter than ESD. Mean total procedure times of the anchor and forceps circumferential EMR were shorter than ESD. The overall mean total procedure time of TA-EMR was not significantly different from FP-EMR. The perforation rate of both TA-EMR and FP-EMR were comparable. However, the *en-bloc* rate of the TA-EMR (84.0%) was higher than for FP-EMR (60.0%), although this difference did not hold statistical significance ($P = 0.18$).

Based on our experience, the tissue-anchoring device was able to retract the mucosal flap into the snare easier and more efficiently than regular forceps since pulling the tissue with forceps resulted in a triangle shape of the mucosal flap as it only uses one point of traction. However, the tissue anchor is capable of retracting tissue from three anchor points (Figure 7). Therefore, it pulls the mucosal flap more efficiently into the snare thus avoiding a deformity of the lesion from unipolar traction. There is a theoretical potential for the three spikes of the tissue anchor to result in more injury of the resection specimen than the regular forceps since the spikes penetrate into the tissue. We did not, however, observe any injury of the specimens from the tissue anchor in any of the specimens retrieved. We believe that clear circumferential cutting is the most important factor for successful *en-bloc* resection. The operator should examine the adequate separation of the circumferential cutting area carefully before using the tissue-anchoring device for resection. A generous submucosal cushion should be injected and confirmed prior to retraction-assisted resection.

Limitations of this study include the fact that bleeding is not able to be accounted for as a complication in this simulation model. Of course, bleeding is a significant complication that must be managed in ESD and also occasionally in EMR. Furthermore, our study did not compare different sizes of lesions or compare multiple different anatomical resection locations.

In conclusion, the grasp-and-snare EMR using a

novel tissue-anchoring device after circumferential cutting appears to be equivalent in performance to EMR using forceps, with a trend towards increased *en bloc* resection rate. When comparing the EMR techniques, we confirmed a known trade-off between techniques: ESD has more predictably successful *en bloc* resection of specimens, while the EMR techniques were significantly quicker to perform.

COMMENTS

Background

To date, there is no reliable endoscopic mucosal resection (EMR) method for *en-bloc* resection for lesions greater than 20 mm in diameter. Recently, a novel tissue-anchoring device was introduced to improve grasping and retraction of tissue for endoscopic resection.

Research frontiers

This concept of tissue grasping in combination with snare resection after circumferential cutting is not new. However, the recently introduced tissue-anchoring device has the capability of deploying three spikes into the tissue that allow a reliable fixation of the tissue and facilitate retraction into snare. A pilot study demonstrated the feasibility of the grasp-and-snare EMR technique using a tissue-anchoring device for the resection of large-sized lesions.

Innovations and breakthroughs

The pilot study demonstrated that grasp-and-snare EMR using the tissue-anchoring device in combination with a 25 mm monofilament snare is feasible and results in reliable *en-bloc* resections of up to 40 mm x 42 mm specimens. The group achieved 90% complete *en-bloc* resections and time-efficiency of this method (average of 32 min) compared to the endoscopic submucosal dissection (ESD) (average of 78 min).

Applications

This study may represent another strategy for therapeutic intervention in the treatment of patients with large sized early gastric cancer or adenoma.

Terminology

En-bloc was defined as no remaining mucosal tattoo on resected specimen.

Peer review

Grasp-and-snare endoscopic mucosal resection using a novel tissue-anchoring device (TA-EMR) appears to be quicker than ESD, and there was a trend towards improved *en bloc* resection rate with the TA-EMR when compared to the conventional EMR technique.

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Clinical outcomes and risk factors for perforation in gastric endoscopic submucosal dissection: A prospective pilot study

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Abstract

AIM: To evaluate clinical outcomes and risk factors for endoscopic perforation during endoscopic submucosal dissection (ESD) in a prospective study.

METHODS: We investigated the clinical outcomes and risk factors for the development of perforation in 98 consecutive gastric neoplasms undergoing ESD regarding. Demographic and clinical parameters including patient-, tumor-, and treatment-related factors, clinical parameters, and duration of hospital stay were analyzed for risk factors for perforation. In subgroup analysis, we also compared the clinical outcomes between perforation and "silent" free air without endoscopically visible perforation detected only by computed tomography.

RESULTS: Perforation was identified in 8.2% of patients. All patients were managed conservatively by the administration of antibiotics. The mean procedure time was significantly longer in patients with endoscopic perforation than in those without. According to the receiver-operating characteristic analysis, the resulting cutoff value of the procedure time for perforation was 115 min (87.5% sensitivity, 56.7% specificity). Prolonged procedure time (≥ 115 min) was associated with an increased risk of perforation (odds ratio 9.15; 95%CI: 1.08-77.54; $P = 0.04$). Following ESD, body temperature and C-reactive protein level were significantly higher in patients with perforation than in those without ($P = 0.02$), whereas there was no difference between these patient groups on the starting day of oral intake or of hospitalization. In subgroup analysis, the post-ESD clinical course was not different between endoscopic perforation and silent free air.

CONCLUSION: Only prolonged procedure time (≥ 115 min) was significantly associated with perforation. The clinical outcomes of perforation are favorable and are comparable to those of patients with or without silent free air.

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Key words: Gastric cancer; Endoscopic submucosal dissection; Perforation; Risk factors; Treatment outcome

Core tip: There has been little prospective study on the clinical outcomes of endoscopic perforation in endoscopic submucosal dissection for gastric neoplasia. In the current study, we investigated clinical outcomes of perforation during gastric endoscopic submucosal dissection, and analyzed various demographic and clinical parameters for risk factors. The results clearly demonstrated that prolonged procedure time (≥ 115 min),

but not tumor location, was significantly associated with endoscopic perforation. The clinical outcomes of perforation are favorable and comparable to those with or without silent free air without endoscopic perforation as detected only by computed tomography.

Watari J, Tomita T, Toyoshima F, Sakurai J, Kondo T, Asano H, Yamasaki T, Okugawa T, Ikehara H, Oshima T, Fukui H, Miwa H. Clinical outcomes and risk factors for perforation in gastric endoscopic submucosal dissection: A prospective pilot study. *World J Gastrointest Endosc* 2013; 5(6): 281-287 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i6/281.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i6.281>

INTRODUCTION

Endoscopic submucosal dissection (ESD) is indicated for early gastric cancer in Japan, and enables *en bloc* resection regardless of lesion size^[1,2]. Besides its positive outcomes, ESD carries controversial risks, such as perforation, bleeding, aspiration pneumonia, and technical difficulties^[1-6]. According to a recent meta-analysis, although ESD had higher *en bloc* and curative resection rates than endoscopic mucosal resection (EMR), operation time was longer, with higher risks of complications compared to EMR^[7].

Previous reports showed that large tumor size, location of the lesion in an upper region of the stomach, and long procedure time are risk factors for perforation following ESD^[8-13]. Although perforation may be the most serious complication in the ESD procedure, most studies have reported recovery from perforation with conservative management such as endoscopic clipping, fasting, nasogastric aspiration, and broad-spectrum antibiotics^[1,14]. However, the previous reports regarding clinical outcomes of perforation during ESD are retrospective analyses^[5,8,9,13-15]. More recently, prospective studies by Onogi *et al*^[16] and our group^[17] found that “transmural air leak” or “silent” free air without endoscopically visible perforation detected only by computed tomography (CT) did not affect the post-ESD clinical course. In contrast, there has been little prospective research regarding clinical outcomes of perforation during the ESD procedure. In this study, we prospectively evaluated clinical outcomes and factors of endoscopic perforation during ESD.

MATERIALS AND METHODS

Patients

Between November 2010 and January 2012, 94 consecutive patients with a total of 98 gastric adenomas or cancers treated with ESD were enrolled in this study. In patients with multiple gastric neoplasms, each of the lesions was treated separately at an interval of at least 1 mo. The indications for ESD for gastric neoplasms, such as intramucosal gastric cancer and adenoma, include in-

tramucosal differentiated tubular adenocarcinoma of any size without ulceration or signs of submucosal invasion and intramucosal differentiated-type adenocarcinoma of less than 3 cm with an ulcer scar. The histology, tumor location, and depth of invasion fulfilled the criteria of the Japanese Research Society for Gastric Cancer^[18]. The histological criteria for the ESD to be considered curative were as follows: (1) margins negative for a lesion; and (2) an intramucosal lesion or minute submucosal invasion (up to 500 μm invasion into the submucosal layer) without any venous or lymphatic invasion^[16].

All patients were admitted on the day before ESD, and were usually discharged 9 d after the procedure. Oral intake was started 3 d after ESD. The hospital stay for patients without any clinical complications was basically 10 d, in line with the clinical protocol at our hospital (Figure 1).

Written informed consent was obtained from all patients prior to the start of the study, and all patients provided written informed consent for publication of individual clinical details. The study design was approved by the ethics committee of Hyogo College of Medicine.

ESD procedure

The ESD procedure was performed under conscious sedation using midazolam and pethidine with or without propofol. ESD was performed using an insulation-tipped diathermic (IT-2) knife (KD-610L; Olympus Medical Systems, Tokyo, Japan) or FlushKnife BT (Fujifilm, Tokyo, Japan) for *en bloc* resection. We marked the normal mucosa about 5 mm outside the tumor edge with a needle knife (KD-1L-1; Olympus Medical Systems). Saline with adrenaline (1:10000 solution in saline) was injected into the submucosa, and the initial incision was made outside the marked line. Next, the diathermic knife was inserted into the initial incision, and the mucosa 5 mm outside the mark was cut circumferentially using a VIO electrosurgical generator (Erbe, Tübingen, Germany). After tumor resection, all visible vessels in the created ulcer were coagulated using coagulation forceps (Olympus Medical Systems) to reduce the risk of delayed bleeding, according to a report by Takizawa and colleagues^[5]. During the ESD procedure, carbon dioxide (CO₂) insufflation was used.

ESD complications

Endoscopic perforation was diagnosed by direct endoscopic observation of the extramural organ or fat through the muscle layer during ESD. When perforation occurred, the perforation site was immediately closed using endoclips (Olympus Medical Systems). However, endoclips sometimes make it difficult to obtain a sufficient resection margin or perform *en bloc* resection. In such cases, it is desirable to apply clips to perforated areas after an incision has been made or an exfoliation performed and after sufficient space for complete resection has been created. All patients with endoscopic perforation were administered antibiotics. In cases with severe pneumoperitoneum such as that caused respiratory failure, de-

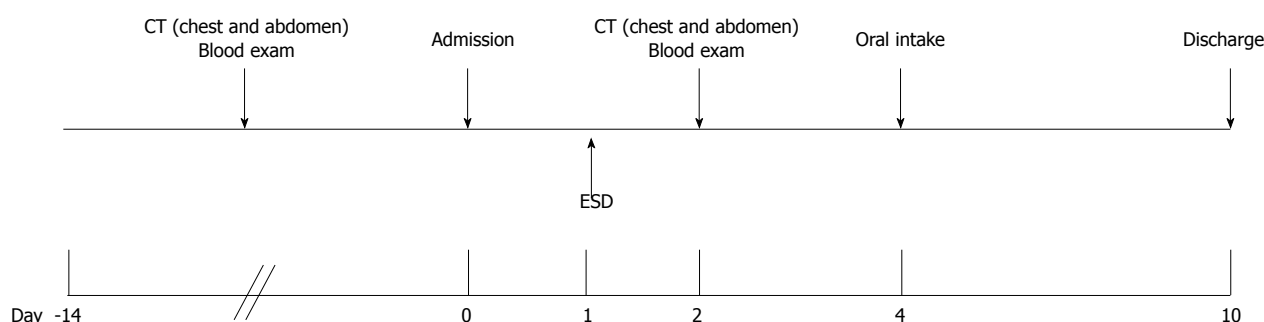


Figure 1 Clinical protocol of endoscopic submucosal dissection. ESD: Endoscopic submucosal dissection; CT: Computed tomography.

creased blood pressure or increased abdominal fullness, after which centesis was performed with an 18-gauge puncture needle to remove air from the abdominal cavity. Patients with this condition received a nasogastric tube for 1 to 2 d. In patients with perforation, oral intake was started once the white blood cell (WBC) count fell to the normal range.

Data analysis

We evaluated the following demographic and clinical parameters: patient-related factors (age, sex, use of alcohol and tobacco, and body mass index), tumor-related factors (macroscopic type, tumor location, presence or absence of scarring in the tumor, invasion depth, and histology), treatment-related factors (operator's skill, mean dimension (cm²) of the resected specimen, and procedure time), clinical parameters (body temperature, WBC count, and serum C-reactive protein (CRP) level at one day before and after ESD), and duration of hospital stay. The procedure time was recorded from the start of the marking around the tumor to the removal of the endoscope.

The operator's skill is thought to affect the total procedure time and the treatment complications of ESD, according to previous reports^[1-6]. Thus, differences in these outcomes between experienced and less-experienced endoscopists should be assessed. Japanese endoscopists receive board certification from the Japan Gastroenterological Endoscopy Society (JGES) after 5 years of training in a JGES-approved educational institution of endoscopy, and must also pass an examination administered by JGES. In the present study, the doctors who were defined as experienced endoscopists had board certification from the JGES and had each performed more than 30 ESD procedures for early gastric cancers^[5,19,20].

Statistical analysis

The data were assessed using the Mann-Whitney *U*-test for comparisons between two independent groups and the χ^2 test or Fisher's exact test for comparisons between two proportions. Patient-, tumor-, and treatment-related factors were included as potential risk factors for endoscopic perforation in univariate analysis. Risk factors with a *P* value of < 0.05 in univariate analysis were included in the multiple logistic regression model and analyzed using the backward approach. Odds ratios (OR) and 95%CI

were calculated for risk factors. The 95%CI of the OR was used to assess statistical significance at the conventional level of 0.05. Statistical analysis was performed using StatView version 5.0 (SAS Institute, Cary, NC, United States).

To identify the ESD procedure time that was associated with the highest diagnostic performance in terms of perforation development, we used receiver operating characteristic (ROC) curve analysis. The ROC curve for procedure time was plotted by using SPSS 11.0 for Windows (SPSS, Chicago, IL, United States). The area under the ROC curve (AUC) was calculated. The point with the largest AUC was defined as the point having the greatest association with perforation. Optimal cutoff points were determined on the basis of maximum values of the Youden index, calculated as [sensitivity + specificity - 1], and the minimum values of the square root of $[(1 - \text{sensitivity})^2 + (1 - \text{specificity})^2]$, which indicates the minimum distance from the upper left corner to the point on the ROC curve^[21].

RESULTS

A total of 98 gastric lesions in 94 patients were evaluated, including 6 adenomas and 92 gastric cancers. The mean age of the patients was 70.9 ± 9.1 years (range, 48-87 years), and women accounted for 24.5% (23 of 94) of the patients. The curative *en bloc* resection rate was 88.8% (87 of 98), and endoscopic perforation during ESD occurred in 8.2% (8 lesions).

Factors predicting development of endoscopic perforation

The mean procedure time was significantly longer in patients with perforation than in those without (controls) (*P* = 0.02), but the tumor location and lesion with scar were not associated with perforation (Table 1). Also, the perforation rate did not differ between experienced and less-experienced operators.

The association between endoscopic perforation and procedure time was evaluated using ROC curve analysis (Figure 2). According to this analysis, cutoff points showing optimal performance were chosen by the distance to the ROC curve and the Youden index for the procedure time. The resulting cutoff value of the procedure time

Table 1 Relationship between perforation and various factors

	Control (<i>n</i> = 90)	Perforation (<i>n</i> = 8)	<i>P</i> value
Patient-related factors			
Age (yr)	70.8 ± 9.2	72.4 ± 7.5	NS
Sex, male/female	69/21	6/2	NS
Active alcohol drinking	40/50	4/4	NS
Positive/negative			
Active smoking	16/74	2/6	NS
Positive/negative			
Body mass index (kg/m ²)	23.2 ± 2.9	23.0 ± 3.3	NS
Tumor-related factors			
Macroscopic type: I / II a/ II b/ II c	9/43/2/36	0/5/0/3	NS
Location: Upper/middle/lower	12/48/30	2/6/0	NS
Scar: Positive/negative	9/81	0/8	NS
Depth of invasion: M/SM and beyond	77/13	5/3	NS
Histology: DAC/poorly DAC/adenoma	5/6/1979	7/1/0	NS
Treatment-related factors			
Operator: Experienced/less-experienced	32/58	2/6	NS
Resected dimensions (cm ²)	9.7 ± 6.0	24.0 ± 24.9	NS
Procedure time (min)	122.5 ± 75.6	203.1 ± 114.3	0.02
Clinical parameters			
Body temperature	36.9 ± 0.5	37.3 ± 0.6	NS
White blood cell (/mL)	10566.9 ± 2903.6	9898.8 ± 3149.4	NS
C-reactive protein (mg/dL)	1.5 ± 1.4	2.4 ± 1.3	0.04
Hospital stay (d)	10.5 ± 2.4	10.9 ± 1.5	NS

Data are expressed as mean ± SD. M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; DAC: Differentiated-type adenocarcinoma; Poorly DAC: Poorly differentiated-type adenocarcinoma; NS: Not significant.

for perforation was 115 min (sensitivity, 87.5%; specificity, 56.7%) for patients who underwent gastric ESD.

Based on the ROC curve analysis and optimal cutoff points of the procedure time of gastric ESD determined above, a procedure time of ≥ 115 min was used in the analyses. We analyzed the strength of the association between perforation development and procedure time (≥ 115 min). As a result, procedure time (≥ 115 min) was significantly associated with increased endoscopic perforation (OR = 9.15, 95%CI: 1.08-77.54; $P = 0.04$).

Clinical course in patients with perforation

Following ESD, only the CRP level was significantly higher in patients with perforation than in those without ($P = 0.04$) (Table 1). The clinical courses of patients with perforation are summarized in Table 2. Four patients with endoscopic perforation received a nasogastric tube for a mean of 1.3 d. None of the patients with this condition required surgery, and there was no perforation-related mortality. Oral intake was started from a mean of 4.0 d after ESD (range, 3-7 d). Patients with perforation were discharged after a mean stay of 10.9 d (9.9 d after ESD); this did not differ significantly from the average stays of patients without perforation (Table 1).

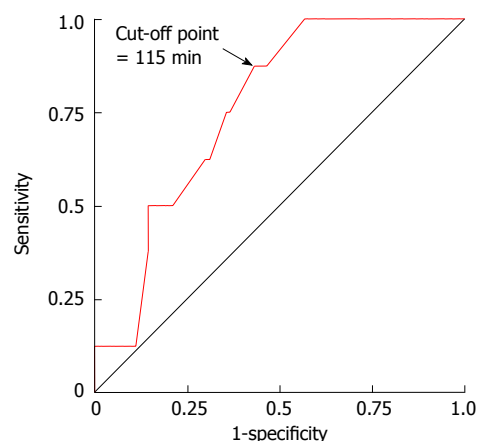


Figure 2 Receiver-operating characteristic curve of perforation development after endoscopic submucosal dissection. The curve is plotted with sensitivity (y-axis) and (1-specificity) (x-axis). The resulting cut-off value of the procedure time for perforation was 115 min (sensitivity, 87.5%; specificity, 56.7%).

Subgroup analysis: Comparison of clinical outcomes between patients with perforation and those with silent free air

All patients underwent plain abdominal CT on the day after ESD. If free air close to the stomach was detected by CT on the day after ESD even though no evidence of endoscopic perforation was seen during ESD and peritonitis, the case was defined as silent free air as reported previously^[17]. We compared the clinical outcomes between patients with perforation and silent free air.

Silent free air was observed in 35.7% (35 lesions) in this period. Body temperature and CRP levels following ESD were significantly higher in patients with endoscopic perforation than in those with silent free air ($P = 0.04$ and $P = 0.03$, respectively) (Table 3). Oral intake was started from 3 d after ESD in all patients with silent free air, as scheduled based on the clinical protocol (Figure 1), but no significant difference in the starting day of oral intake was found between these conditions.

DISCUSSION

Even though ESD is widely accepted and performed worldwide in patients with gastric cancer, perforation is a common and serious complication. In contrast, many retrospective studies show that conservative management by immediate endoscopic closure with endoclips is effective in most patients with perforation^[1,14]. Recently in prospective studies, Onogi *et al.*^[16] and we reported that an “air leak” after gastric ESD, detected only by CT in patients without endoscopically visible perforation, was observed frequently, and this asymptomatic (silent) free air does not affect the post-ESD clinical course. Likewise, the current work, which is based on our recent study^[17], clearly demonstrated that perforation was not associated with clinically significant complications, and showed clinical outcomes similar to those of cases without perfora-

Table 2 Clinical courses after perforation

Age (yr)	Sex	Macroscopic type	Location	Depth of invasion	Scar	Resected dimensions (cm ²)	Procedure time (min)	Nasogastric tube (d)	Beginning of oral intake after ESD (d)	Hospitalization (d)
62	Male	II a	Upper	M	-	69.1	460	1	4	10
63	Male	II c	Middle	M	-	5.5	130	-	3	10
77	Male	II b + II a	Middle	SM	-	18.8	220	1	3	11
71	Male	II a	Middle	M	-	8.2	160	2	3	10
83	Female	II c	Lower	SM	-	56.1	220	-	5	12
72	Female	II a	Middle	M	-	22.0	215	-	3	10
80	Male	II a	Upper	M	-	3.1	100	-	3	10
71	Male	II c	Lower	SM	-	9.4	120	1	7	14

Data are expressed as mean \pm SD. M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; ESD: Endoscopic submucosal dissection.

Table 3 Subgroup analysis: Comparison in various factors between perforation and silent free air

	Perforation (n = 8)	Silent free air on CT (n = 35)	P value
Tumor-related factors			
Location: Upper/middle/lower	2/6/0	9/21/5	NS
Scar: Positive/negative	0/6	5/30	NS
Depth of invasion: M/SM and beyond	5/3	5/30	NS
Treatment-related factors			
Operator: Experienced/less-experienced	2/6	16/19	NS
Resected dimensions (cm ²)	24.0 \pm 24.9	10.4 \pm 7.2	NS
Procedure time (min)	203.1 \pm 114.3	145.1 \pm 76.5	NS
Clinical parameters			
Body temperature	37.3 \pm 0.6	36.8 \pm 0.6	0.04
White blood cell (/mm ³)	9898.8 \pm 3149.4	10658.0 \pm 3119.3	NS
C-reactive protein (mg/dL)	2.4 \pm 1.3	1.4 \pm 1.0	0.03
Oral intake (d)	3.0	4.0 \pm 1.5	NS
Hospital stay (d)	10.9 \pm 1.5	10.7 \pm 2.1	NS

Data are expressed as mean \pm SD. CT: Computed tomography; M: Intramucosal cancer and adenoma; SM: Submucosal invasive cancer; NS: Not significant.

tion. Therefore, perforations might be considered part of the procedure and not as a complication^[22].

In the current study, a procedure time exceeding 115 min was considered to be a reliable marker associated with perforation development by ROC curve analysis. Thus, prolonged procedure time was a highly significant factor for endoscopic perforation; this finding is consistent with those of other studies^[9,11-13,16]. However, tumor location was not related to perforation. In our previous study^[17], tumor location was also not an independent risk factor for silent free air. Previous studies showed that tumor location (the upper portion of the stomach) was a significant and independent predictor of perforation by multivariate analysis^[8-13,16,17]. A possible explanation for the discrepancy may be the difference in the number of patients with perforation investigated between ours and other studies. Indeed, only 8 of the patients in our study had perforation. In reports from Japan and South Korea, perforation was observed in 1.2% to 6.1% of patients^[8-15]. Our perforation rate (8.2%) was slightly higher than in the other studies. Of the 8 cases with endoscopic

perforation, 6 were treated by less-experienced operators. However, operator skill was not associated with either perforation or silent free air (Tables 1 and 2). This was attributed to the fact that more experienced endoscopists were more likely to perform ESD in patients with larger tumors or tumors with scars than were less-experienced endoscopists. Actually, the features of the lesions, *i.e.*, ulcer scarring, tumor size, and tumor location, in addition to technical skill, may be significant risk factors for perforation, as many reports have pointed out.

Silent free air was detected in 35.7% of the cases in this study. Jeon *et al.*^[14] recently reported a similar study, which compared the clinical outcomes of treatment for macro- and micro-perforations with ESD and determined the short-term prognosis after ESD. Those authors defined micro-perforation as a perforation identified by a pneumoperitoneum seen on plain radiographs after ESD. According to their report, a micro-perforation, resembling the silent free air in our study, was observed in only 0.76% (13 of 1711) of the patients undergoing gastric ESD, an extremely lower incidence than we found in our study. The difference may be attributable to different sensitivities between plain radiograph and CT.

With regards to inflammatory markers after ESD, such as body temperature, WBC level, and CRP level, only CRP level was significantly higher in perforation patients than in controls ($P = 0.04$). All the patients with endoscopic perforation were exposed to antibiotics, and 4 patients received a nasogastric tube. By conservative treatments, these patients with perforation were able to start oral intake from a mean of 4 d following ESD; this time to resume oral intake was not significantly different from that in patients with or without silent free air. Furthermore, the hospital stay did not differ according to the presence or absence of perforation or silent free air. These results indicate that immediate closure of the perforation site, intravenous antibiotic therapy, or brief nasogastric tube replacement may be important for favorable outcomes. In our clinical protocol of ESD, the hospital stay was 10 d, and oral intake was started 3 d after ESD; these may be slightly longer than in other hospitals. It remains possible, therefore, that this longer hospitalization in our protocol affected the present results.

In our series, we used CO₂ insufflation during the ESD procedure. It has been reported that ESD with CO₂

insufflation is safe and reduces both abdominal discomfort and the risk of perforation after ESD^[9,23,24]. Hereafter, ESD with CO₂ insufflation should be performed during lengthy endoscopic treatment procedures to avoid complications during and after ESD.

In the present study, there has been no evidence of peritoneal seeding after endoscopic perforation with short follow-up periods by CT or ultrasonography, and this was consistent with previous results^[10,14]. Similarly, Ikehara *et al*^[25] reported that perforation associated with EMR and ESD does not lead to peritoneal dissemination even in the long term (median 53.6 mo, range 7.0-136.6 mo). Further studies are needed before definitive conclusions can be drawn about the risk of peritoneal seeding after perforation or silent free air^[10].

The limitation of this study is the small number of patients with perforation in a single center, limiting our ability to draw conclusions, as mentioned previously^[8,9,13,14]. Our results do not necessarily mean, therefore, that perforation during ESD can be managed conservatively. Seewald *et al*^[22] previously showed an algorithm for endoscopic management of gastrointestinal perforation. Therefore further studies with larger numbers of patients will be needed to clarify the long-term outcomes of patients with endoscopic perforation.

In conclusion, the current prospective pilot study showed that prolonged procedure time (≥ 115 min) was associated with an increased risk of perforation. However, conservative management of perforation was successful and did not affect the post-ESD clinical course. Therefore, clinical outcomes of endoscopic perforation are favorable and comparable to those with or without silent free air.

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COMMENTS

Background

Endoscopic submucosal dissection (ESD) is indicated for early gastric cancer in Japan, and enables *en bloc* resection regardless of lesion size. Besides its positive outcomes, ESD carries controversial risks, such as perforation, bleeding, aspiration pneumonia, and technical difficulties.

Research frontiers

Even though ESD is widely accepted and performed worldwide in patients with gastric cancer, perforation is a common and serious complication. In contrast, many retrospective studies show that conservative management by immediate endoscopic closure with endoclips is effective in most patients with perforation.

Innovations and breakthroughs

There has been little prospective study on the clinical outcomes of endoscopic perforation in endoscopic submucosal dissection for gastric neoplasia. In the current study, authors investigated clinical outcomes of perforation during gastric endoscopic submucosal dissection, and analyzed various demographic and clinical parameters for risk factors.

Applications

The clinical outcomes of perforation are favorable and comparable to those with or without silent free air without endoscopic perforation as detected only by computed tomography.

Peer review

Generally, this is an interesting and well written prospective study about clinical outcomes and risk factors for perforation in gastric ESD. Authors prospectively investigated 98 consecutive gastric neoplasms undergoing ESD regarding the clinical outcomes and risk factors for development of perforation. They clearly showed that prolonged procedure time was associated with an increased risk of perforation.

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Failure of sequential biliary stenting for unsuccessful common bile duct stone removal

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Abstract

AIM: To determine the factors associated with the failure of stone removal by a biliary stenting strategy.

METHODS: We retrospectively reviewed 645 patients with common bile duct (CBD) stones who underwent endoscopic retrograde cholangiography for stone removal in Siriraj GI Endoscopy center, Siriraj Hospital from June 2009 to June 2012. A total of 42 patients with unsuccessful initial removal of large CBD stones that underwent sequential biliary stenting were enrolled in the present study. The demographic data, laboratory results, stone characteristics, procedure details, and clinical outcomes were recorded and analyzed. In addition, the patients were classified into two groups based on outcome, successful or failed sequential biliary stenting, and the above factors were compared.

RESULTS: Among the initial 42 patients with unsuccessful initial removal of large CBD stones, there were 37 successful biliary stenting cases and five failed cases. Complete CBD clearance was achieved in 88.0% of cases. The average number of sessions needed before

complete stone removal was achieved was 2.43 at an average of 25 wk after the first procedure. Complications during the follow-up period occurred in 19.1% of cases, comprising ascending cholangitis (14.3%) and pancreatitis (4.8%). The factors associated with failure of complete CBD stone clearance in the biliary stenting group were unchanged CBD stone size after the first biliary stenting attempt (10.2 wk) and a greater number of endoscopic retrograde cholangio-pancreatography sessions performed (4.2 sessions).

CONCLUSION: The sequential biliary stenting is an effective management strategy for the failure of initial large CBD stone removal.

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Key words: Endoscopic retrograde cholangiography; Common bile duct stone; Biliary stenting; Large common bile duct stone; Biliary stenting failure

Core tip: This study was a retrospective review of 42 patients who underwent sequential biliary stenting following a failed removal of a large common bile duct stone by endoscopic retrograde cholangiopancreatography. Complete common bile duct (CBD) clearance was achieved in 88% of the patients at 25 wk after the first procedure, while 19% reported complications. The common complications were cholangitis and pancreatitis. The factors associated with the failure of this strategy were unchanged CBD stone size at the second biliary stenting attempt, and more endoscopic retrograde cholangio-pancreatography sessions performed.

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INTRODUCTION

Patients with untreated common bile duct (CBD) stones, irrespective of the presence of symptoms, are at high risk of experiencing further symptoms or complications. Given the potentially serious complications of CBD stones such as ascending cholangitis or acute pancreatitis, specific therapy is usually required^[1]. Choledocholithiasis is one of the most common indications for performing therapeutic endoscopic retrograde cholangiography (ERC)^[1].

The majority (80%-90%) of simple CBD stones, specifically those that are < 1 cm, are removed by ERC *via* endoscopic sphincterotomy by using a basket or balloon catheter^[2,3]. However, from references^[4-15], we know that approximately 10%-15% of patients have bile duct stones that cannot be removed using standard techniques. These stones are generally larger than 1-1.5 cm, impacted, located proximal to strictures, or associated with the duodenal diverticulum, and are frequently successfully removed by mechanical lithotripsy or large balloon sphincteroplasty^[16]. However, the removal of large CBD stones is not possible by using these techniques. Therefore, most endoscopists prefer to place a biliary stent as a temporary measure to maintain biliary drainage and prevent stone impaction^[17]. Biliary stenting is an effective method of reducing the size of CBD stones because the stone-stent friction force can lead to stone fragmentation inside the CBD^[18,19]. Therefore, sequential biliary stenting is still the most common technique for large CBD stone removal. However, this technique can be time-consuming for complete stone removal and is associated with a higher complication rate during the follow-up period, particularly from cholangitis. Thorough studies examining the success factors for this treatments strategy are incomplete or lacking^[18-20]. Thus, the aim of this study was to determine the factors that can potentially predict a high failure rate of the first CBD clearance, in turn providing a clearer picture of patients who can be managed conservatively by sequential biliary stenting.

MATERIALS AND METHODS

The medical records and endoscopic reports of patients who underwent ERC for choledocholithiasis from June 2009 to June 2012 were retrospectively reviewed (645 total records). The siriraj institutional review board gave approval for the study. Experienced endoscopists or gastroenterology fellows under the supervision of experienced endoscopists performed all ERC procedures. The inclusion criteria were as follows: (1) large CBD stones (diameter of > 15 mm); (2) failure of complete stone removal during the initial attempt and biliary stent insertion; and (3) follow-up and subsequent ERC procedures performed in our institution. Patients were classified into two groups: group one comprised patients who underwent repeated short-term biliary stenting after failure of CBD clearance (with standard techniques or mechanical lithotripsy or balloon sphincteroplasty) until achieve-

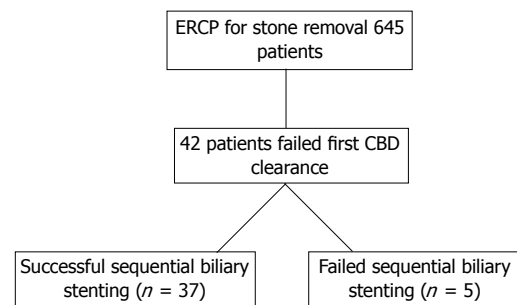


Figure 1 Diagram of the study population. CBD: Common bile duct; ERCP: Endoscopic retrograde cholangio-pancreatography.

ment of complete CBD clearance; group two comprised patients who underwent failed biliary stenting. Patients who were unable to be contacted for a follow-up or who did not undergo further procedures in our institute were excluded. The study design is presented in Figure 1. Five dedicated endoscopists, each performing more than 200 cases annually, performed the ERC procedures with biliary stenting. We used a therapeutic duodenoscope (Olympus TJF-140 or TJF-160; Olympus America, Central Valley, PA, United States) with patients under intravenous sedation or general anesthesia with full anesthetic monitoring. Patients with ascending cholangitis received pre-procedural antibiotics. The first treatment attempt was standard endoscopic sphincterotomy, stone retrieval *via* balloon retrieval catheter or basket extraction catheter, and crushing by mechanical lithotripsy (Soehendra Lithotriptor; Wilson-Cook Medical Inc., Winston-Salem, NC, United States) at the discretion of the endoscopists. After the initial clearance attempts failed, patients underwent biliary stenting and were scheduled for repeated ERC. Straight plastic stents (Cotton-Leung Biliary Endoprosthesis; Wilson-Cook Medical Inc., United States) or double pigtail plastic stents (C-flex Biliary; Boston Scientific, Spencer, IN, United States) were used. The clearance of the biliary tract was documented using a cholangiogram. The success of biliary clearance, cost of the procedures, degree of complications, time interval between the initial attempt and complete CBD clearance of the stones, surgical procedures, and complications during follow-up were assessed. The follow-up period extended to the last recorded medical visit. Descriptive statistics were used to summarize patients' baseline demographics, clinical characteristics, and radiographic data. Continuous variables were reported as means or medians (min, max).

Statistical analysis

The compared data were analyzed using a χ^2 or Mann-Whitney *U* test. A value of $P < 0.05$ was considered significant. All statistical evaluations were performed using SPSS version 11.5 software.

RESULTS

A total of 645 medical records and electronic endoscopy records were retrospectively reviewed, and 42 patients

Table 1 Baseline characteristics and cholangiographic findings of enrolled patients in both groups, including the comparison of procedural details, stone characteristics, and complications *n* (%)

Details	Total (<i>n</i> = 42)	Success group (<i>n</i> = 37)	Failed group (<i>n</i> = 5)	<i>P</i> value
Male sex	34 (81.0)	6 (16.2)	2 (40.0)	NS
Age in years	71.9 ± 14.2	71.9 ± 14.3	72.0 ± 15.5	NS
Indications for ERC				
Cholangitis	22 (52.4)	20 (54.1)	2 (40.0)	NS
Biliary pain	10 (23.8)	8 (21.6)	2 (40.0)	
Obstructive jaundice	4 (9.5)	3 (8.1)	1 (20.0)	
Acute pancreatitis	2 (4.8)	2 (5.4)	0 (0.0)	
Asymptomatic	4 (9.5)	4 (9.5)	0 (0.0)	
CBD size in mm	1.83 ± 0.45	1.80 ± 0.44	2.06 ± 0.56	NS
Stone size in mm	1.86 ± 0.43	1.85 ± 0.41	2.04 ± 0.58	NS
Stone number	1.50 ± 1.06	1.51 ± 1.12	1.40 ± 0.55	NS
Stone fit to CBD	37 (88.1)	32 (86.5)	5 (100)	NS
Stone shape				NS
Irregular		7 (18.9)	1 (20.0)	
Geometric (oval, cube)		30 (81.1)	4 (80.0)	
Stone characteristics				NS
Mixed stone		17 (45.9)	3 (60.0)	
Cholesterol stone		20 (54.1)	2 (40.0)	
Change in stone size				
Decrease		25 (67.6)	1 (20.0)	0.04
Stable		12 (32.4)	4 (80.0)	
Balloon sphincteroplasty		9 (24.3)	3 (60.0)	0.13
Use of mechanical lithotripsy		14 (37.8)	2 (40.0)	NS
Time to successful procedures in weeks		25.42 ± 40.42	None	NA
Sessions carried out		2.43 ± 0.80	2.80 ± 1.30	NS
Average follow-up time in months		13.10 ± 13.79	10.70 ± 8.81	NS
Complications during follow-up period				NS
Ascending cholangitis	6 (14.3)	6 (16.2)	0 (0.0)	
Acute pancreatitis	2 (4.8)	1 (2.7)	1 (20.0)	
None	34 (80.9)	30 (81.1)	4 (80.0)	

CBD: Common bile duct; ERC: Endoscopic retrograde cholangiography; NS: No statistical significance as $P > 0.5$; NA: Not analyzed.

who met the inclusion criteria were enrolled in the study. Thirty-seven patients achieved successful sequential biliary stenting after the failure of initial stone extraction, whereas this strategy failed in five patients. Of the 42 patients were enrolled, 81% were women, and the mean age was 71.9 ± 14.2 years (range: 33-97 years). Almost 90% of patients were symptomatic, presenting with ascending cholangitis, biliary pain, obstructive jaundice, or acute pancreatitis (52.4%, 23.8%, 9.5%, and 4.8%, respectively). The stones were located at the distal, middle, and proximal portions of the CBD in 47.6%, 47.6%, and 4.8% of cases, respectively. Eighty-eight percent were fit to the duct. The mean number of stones per patient was 1.5 ± 1.1 stones (range: 1-6 stones), the mean stone maximum diameter was 1.86 ± 0.43 cm (range: 1.5-3.0 cm), and the average CBD maximum diameter was 1.83 ± 0.45 cm (range: 1.2-3.5 cm). Patients who underwent biliary stenting were followed for an average of 12.8 mo (range: 2-54 mo) after the initial stone removal attempt. Biliary clearance was achieved in 88.0% of cases, with an average time between each attempt of 10.2 wk (range: 5-24 wk), and an average time to complete duct clearance of 26.8 wk (range: 6-216 wk). The average number of sessions for complete biliary clearance was 2.5 ± 0.86 procedures (range: 2-6 procedures). The baseline characteristics of

the patients and procedural details (including cholangiographic findings) are shown in Table 1.

Table 1 compares the clinical characteristics, cholangiographic features, and procedure details between the two groups of patients. Stone shape, size, and characteristics were similar between the groups. For patients with failed sequential biliary stenting, the average time interval after the first endoscopic retrograde cholangio-pancreatography (ERCP) to surgery was 71 wk (range: 28-184 wk), and the average number of sessions performed before surgery was 4.2 sessions (range: 3-6 sessions). The surgical outcomes were satisfactory without significant complications. The patients who underwent successful sequential biliary stenting had an average time interval between the first attempt and complete CBD clearance of 25.4 wk (range: 6-216 wk), and the average number of sessions performed was 2.43 sessions (range: 2-6 sessions). The factors that may be related to the failure of sequential biliary stenting were no reduction of CBD stone size at the second procedure ($P = 0.04$) and a greater number of sessions performed ($P < 0.001$). Another factor that may contribute to the failure of sequential biliary stenting, albeit insignificant in our study ($P = 0.13$), is the failure of balloon sphincteroplasty at the first attempt. A study in a larger cohort may be required to confirm this result.

DISCUSSION

Almost 7% of the patients in this study had large CBD stones that were not completely cleared using standard techniques at the first attempt, which is consistent with reports from other endoscopy centers^[1-3,16,17]. Almost 90% of all patients in this study were symptomatic, and the most common clinical presentation was ascending cholangitis. Stones were located throughout the CBD, but more prominently in the distal and mid portions. The conventional management of large CBD stones that fail to be completely removed at the first attempt is sequential biliary stenting, which reduces stone size by stent-stone friction force. We observed that leaving the stent inside the CBD for an average of 10 wk resulted in stone size reduction in 45% of the cases and complete disappearance in 16% of the enrolled patients. Furthermore, we speculated that the CBD might have been completely cleared in 85.7% of patients by further serial sessions combined with the use of mechanical lithotripsy. Nineteen percent of patients suffered from complications during the follow-up period, which were primarily related to ascending cholangitis. Chan *et al.*^[20] reported on a total of 46 patients with large CBD stones who were treated with plastic stent insertion, among which 28 cases underwent repeated ERC. Stones were extracted after a median of 63 d, and the repeated procedures achieved complete duct clearance in 25 (89%) of the patients. Similar results have also been reported by Maxton *et al.*^[21] and Jain *et al.*^[22]. The most common complications we observed were cholangitis and pancreatitis (14.3% and 4.8%, respectively). This result is in agreement with data reported from a Japanese study in which 13% of patients suffered cholangitis during biliary stenting^[23]. Comparing this with long-term biliary stenting, Ang *et al.*^[24] reported up to 22% mortality among patients treated by long-term biliary stenting for an average of 12 mo (range: 1-54 mo), which accounted for 3.5% of biliary-related mortality. However, there was no mortality in the present study. Therefore, in the majority of patients, sequential biliary stenting was a safer and more effective procedure for treating difficult CBD stones than long-term biliary stenting. However, there were five cases (11.9%) where sequential biliary stenting failed in this study. The factors associated with the failure to achieve complete CBD stone clearance were unchanged CBD stone size at an average of 10 wk after the first biliary stenting attempt and a greater number of sessions performed (particularly for > 4 sessions). In cases presenting these particular factors, the therapeutic strategy should be changed from sequential biliary stenting to other alternative treatments such as intraductal lithotripsy (EHL or laser) or surgery. However, the current study did have some limitations similar to those in the other studies that included a retrospective case series of a limited number of patients. A multicenter study for a larger population should be conducted in the future.

In conclusion, sequential biliary stenting was an effective management strategy for large CBD stones that failed initial complete CBD clearance. The factors associ-

ated with failure were unchanged CBD stone size after the first biliary stenting procedure and a greater number of ERCP sessions performed.

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COMMENTS

Background

Common bile duct (CBD) stones and related complications are one of the most common pancreaticobiliary diseases in daily practice. The treatment of choice for CBD stone removal is endoscopic retrograde cholangiopancreatography (ERCP) with an 85%-90% success rate of complete stone removal. Complete removal is therefore not achieved for 10%-15% of CBD stones-particularly large stones-by the standard technique, and these may be managed conservatively by biliary stenting. The factors associated with the failure of this strategy are not well established.

Research frontiers

Sequential biliary stenting has been used as an option for common bile duct stones that were not completely successfully removed following the first ERCP. The stent-stone friction force could lead to size-reduction or fragmentation of the stone.

Innovations and breakthroughs

The goal of this study was to determine the factors that are associated with the failure of ERCP. These factors will potentially aid endoscopists in making decisions of referring the patient for other treatment options such as laser cholelithotripsy, electrohydraulic lithotripsy or even surgery.

Applications

This study suggested that the treatment strategies should be changed if the size of the CBD stone was not changed at 10 wk after the first procedure or failure of complete stone removal at the second attempt.

Terminology

Sequential biliary stenting was the strategy of insertion the plastic stent over the CBD stone for two major reasons. First to maintain the drainage and second to aid in stone fragmentation after the stent was placed for more than 4-6 wk. The common interval for each procedure was 6-12 wk.

Peer review

The present study demonstrated the parameters associated with the failure of sequential biliary stenting following unsuccessful stone removal from the large common bile duct. The authors found that sequential biliary stenting is an effective management strategy for treating failed initial large CBD stone removal.

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Carcinoma in gut-associated lymphoid tissue in ulcerative colitis: Case report and review of literature

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Abstract

The colorectal mucosa includes two quantitatively, structurally and functionally dissimilar areas: one, built with columnar and goblet cells, covers the vast majority of the mucosa, and the other consists of scattered minute gut-associated lymphoid tissue (GALT). The overwhelming majority of colorectal carcinomas evolve in GALT-free mucosal areas and very rarely in GALT aggregates. Remarkably, the colonic mucosa in patients with ulcerative colitis (UC) displays a high number of newly formed GALT-aggregates. The patient here described is a 68-year-old female with a history of UC since 1984. At surveillance colonoscopy in 2012, one of two detected polyps was a tubular adenoma with high-grade dysplasia. Beneath this adenoma, a well-circumscribed GALT sheltering a carcinoma was found. Serial sections revealed no connection between the villous adenoma

and the GALT-carcinoma. The GALT-carcinoma here reported seems to have evolved in a newly formed, UC-dependent, GALT complex. This notion is substantiated by the fact that 27% or 4 out of the 15 cases of GALT-carcinomas in the colon reported in the literature (including the present case) evolved in patients with UC.

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Key words: Colon; Advanced adenoma; Gut-associated lymphoid tissue; Carcinoma; Ulcerative colitis

Core tip: Of the 15 cases of gut-associated lymphoid tissue (GALT)-carcinomas in the colon reported in the literature (including the present case) 27% ($n = 4$) have evolved in patients with ulcerative colitis. The possibilities that the advanced adenoma on top had invaded the GALT-complex underneath or that the GALT-carcinoma was a metastasis from the adenoma on top were rejected, since serial sections revealed neither continuity between the adenoma and the GALT-carcinoma, nor invasive growth in the adenoma.

Rubio CA, Befrits R, Ericsson J. Carcinoma in gut-associated lymphoid tissue in ulcerative colitis: Case report and review of literature. *World J Gastrointest Endosc* 2013; 5(6): 293-296 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i6/293.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i6.293>

INTRODUCTION

The colorectal mucosa can be divided into two quantitatively, structurally and functionally dissimilar areas^[1]. One comprises the vast majority of the colorectal mucosa: it is built with mucus producing goblet cells and columnar cells exhibiting microvilli covered with glycocalyx. The function of this huge mucosal area is to protect the underlying structures, to allow free passage into the host,

of water and other fluids (encouraged by aquaporin 8, a water channel protein^[2]), ions, vitamins and some nutrients, as well as to produce lysozyme, the innate antibacterial enzyme that annihilates pathogenic bacteria^[3]. The other mucosal area, called gut-associated lymphoid tissue (GALT), is composed of tiny mucosal fractions scattered in the colorectal mucosa. O'Leary *et al*^[4] found only 36 GALT aggregates (also called cryptopatches or lymphoglandular complexes) per colectomy in 27 specimens without ulcerative colitis. A single layer of cubic cells and few or no goblet cells build the epithelium covering GALT aggregates. Electron-microscopic studies show an epithelium with a poorly developed brush border, but clear-cut micro-ridges (thereof the M designation). In addition, invaginations in the surface of M cells create intraepithelial pockets^[5]. The function of M cells is to absorb luminal antigens such as macromolecules and microorganisms *via* clathrin-mediated endocytosis^[6] and to haul these antigens into the underlying collection of gut-indigenous, thymus-independent lymphoid tissue for immediate immunological processing. Hence, the M cell-lymphoid tissue assemblage (that is GALT) is a lympho-epithelial immunological unit that coordinates antigen recognition and processing in the gut mucosa^[5].

Nearly all-colorectal carcinomas (CRC), the third most frequent cancer worldwide^[7], evolve in GALT-free mucosal areas. In contrast, CRC arising in GALT-associated mucosa are very rare.

Patients with extensive ulcerative colitis (UC) are at increased risk of developing a CRC^[7]. It is generally accepted that CRC in UC also originates in GALT-free colorectal mucosa: either from UC-related non-protruding dysplastic crypts (known as dysplasia in flat mucosa^[8]), from protruding, or non-protruding adenomatous lesions, or from age-dependent, UC-unrelated, sporadic adenomas^[9].

Dukes^[10] described in colitic patients a histological lesion, usually in the submucosa, characterized by "misplaced" colonic epithelium surrounded by nodular lymphoid tissue. Dukes^[10] believed that this epithelium was the result of mucosal repair following regeneration of a mucosal ulcer and that the epithelium detached and buried in the submucosa encouraged cancer development. Hultén *et al*^[11] also considered this phenomenon, a precancerous lesion. Their descriptions fit well with the notion of GALT-mucosa.

Searching for a confirmation of the hypothesis of Cuthbert Dukes, we reported and illustrated in 1984, the first case of GALT-carcinoma of the colon in the literature^[12]. In 2002, Rubio and Talbot reported another case of GALT-carcinoma in a patient with UC^[13]. Of note, of the two cases of GALT-carcinoma reported by Stewart *et al*^[14], one occurred in a patient with UC.

de Petris *et al*^[15] reported a case of sporadic GALT-carcinoma in the colon of a patient without UC. Because of its protruding shape, these authors proposed to call it dome carcinoma (DC). Since then, six new cases of sporadic DC in patients without UC appeared in the literature^[14,16-19] (Table 1). In addition 3 DC were found in a

Table 1 Colon carcinomas evolving in gut-associated lymphoid tissue reported in the literature

Ref.	Clinical data	GALT-carcinomas
Rubio ^[12]	UC	1
Rubio <i>et al</i> ^[13]	UC	1
Stewart <i>et al</i> ^[14]	UC (in 1 of 2 cases)	2
De Petris <i>et al</i> ^[15]	HNPCC	1
Jass <i>et al</i> ^[16]		1
Clouston <i>et al</i> ^[17]		2
Asmussen <i>et al</i> ^[18]		2
Rubio <i>et al</i> ^[19]	Lynch	3
Yamada <i>et al</i> ^[20]		1
Present communication	UC	1

UC: Ulcerative colitis; GALT: Gut-associated lymphoid tissue; HNPCC: Hereditary nonpolyposis colon cancer.



Figure 1 Endoscopic image showing a polypoid lesion in the transverse colon.

colectomy specimen in a patient with Lynch syndrome^[20].

The purpose of this communication is to report a new case of GALT-carcinoma in a patient with UC.

CASE REPORT

The patient is a 68-year-old female, with a history of UC since 1984. She has been under colonoscopic-histologic surveillance since 1985. In 2004 one of 11 biopsies exhibited low-grade dysplasia (LGD) in flat mucosa. In 2005, an aggressive breast ductal cancer was diagnosed and treated with surgery and chemotherapy. Despite treatment, the disease progressed, and several skeletal metastases were detected. In September 2011, numerous polyps in the right colon were found at a colonoscopic-histologic séance; two of these polyps were reported as tubular adenomas with LGD. A new colonoscopy in February 2012 revealed two new polyps, this time in the transverse colon (Figure 1).

Biopsies were stained with hematoxylin and eosin (HE), and immuno-histochemically stained with MNF 116, Actin SM (Leica Microsystems AB, Bromma, Sweden), Ki67 (clone MIB1, Leica Microsystems AB, Bromma, Sweden), p53 (BD Products, Franklin Lakes, United States), p21WAF1 (Oncogene Science, Chicago, United States), and histochemically stained with Alcian blue pH 2.5, periodic acid-Schiff (PAS) and PAS-D.

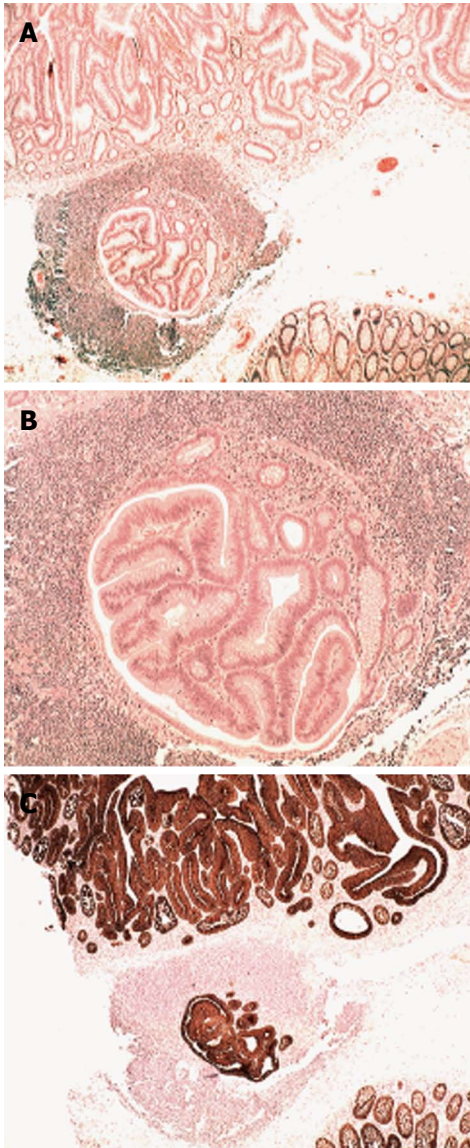


Figure 2 Low-power view. A: A villous adenoma on top of a gut-associated lymphoid tissue (GALT) with carcinoma [hematoxylin and eosin (HE) $\times 4$]; B: Detail showing carcinoma in GALT (HE $\times 10$); C: A villous adenoma on top of a GALT with carcinoma (MNF 116 $\times 4$).

The histological examination showed in one of the two polyps in the transverse colon a GALT-carcinoma roofed by a tubular adenoma with high-grade dysplasia (Figure 2A). Beneath the adenoma, a well-circumscribed GALT-carcinoma was found (Figure 2B). Serial sections revealed no connection between the villous adenoma and the GALT-carcinoma. MNF 116 immunostain labelled all epithelial cells in the villous adenoma on top and in the subjacent GALT-carcinoma (Figure 2C). MIB1 disclosed high cell proliferation in the villous adenoma (Figure 3A); cell proliferation was comparatively lower in the GALT-carcinoma (Figure 3B).

Neither the GALT-carcinoma nor the advanced adenoma expressed p53. The neoplastic cells displayed sialomucins (Alcian blue stain) and mucopolysaccharides (PAS stain) were demonstrated, both in the villous adenoma and in the GALT-carcinoma.

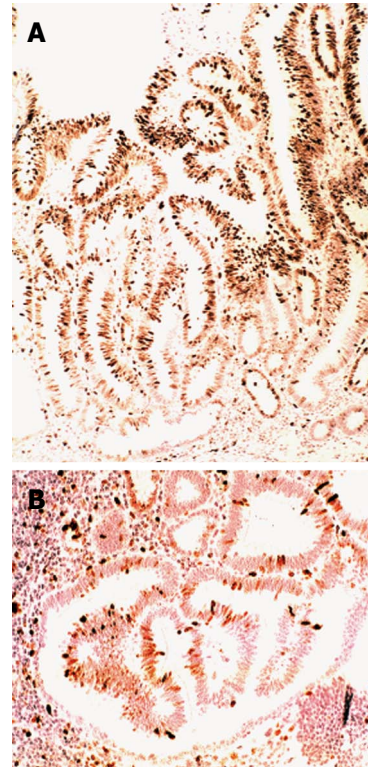


Figure 3 High-power view. A: The villous adenoma showing high cell proliferation (Ki67, clone MIB1 $\times 10$); B: Gut-associated lymphoid tissue with carcinoma showing lower cell proliferation than in the villous adenoma on top (Ki67, clone MIB1 $\times 20$).

DISCUSSION

The lymphoid tissue in the colorectal mucosa is found in three different compartments: in the epithelium, in the lamina propria mucosa, and in GALT aggregates. GALT aggregates may be found as minute lymphoid collections or larger collections of lymphoid tissues, known as Peyer's patches. It goes without saying that the possibility for a neoplasia to evolve in the minute mucosal area that covers a GALT aggregate might be a fortuitous event.

While investigating colorectal neoplasias in Japanese patients^[21] we found GALT aggregates underneath 38% of non-protruding adenomas. Puzzlingly, GALT-carcinomas are a common finding in the colon of rats treated with 1,2-dimethylhydrazine^[22]. Following 27 wk treatment, subjacent lymphoid aggregates were found in as many as 36% of the flat (non-protruding) colon adenomas and early flat adenocarcinomas in rats^[22]. In contrast, only 9% subjacent lymphoid aggregates were found in exophytic (protruding) colon adenomas and early flat adenocarcinomas. When only adenomas were considered, subjacent lymphoid aggregates were present in 50.0% of the flat adenomas, but only in 14.0% of the 50 protruding adenomas^[22]. This is surprising, considering that in these animals, only a mean of 1.9 GALT aggregates per colon was recorded. Thus, it would appear that in humans and in rats, non-protruding colonic adenomas evolve not only in the GALT-free colonic mucosa but also in the GALT-associated mucosa.

Table 1 shows that 27% (4/15) of the reported cases of GALT-carcinoma of the colon evolved in patients with UC. In this context, O'Leary *et al*^[23] found, 36 GALT foci per colectomy in patients without UC, but as many as 168 GALT foci per colectomy in patients with UC that is 4.7 times more frequently. Obviously, in the colon of patients with UC, newly GALTs are being formed. It is therefore not inconceivable that the GALT-carcinoma here reported might have evolved in a newly formed, UC-dependent, GALT complex.

Immunohistochemistry showed that cell proliferation was lower in the GALT-carcinoma than in the villous adenoma on top. These findings are in concert with those obtained by Anjomshoa *et al*^[24]. These authors found decreased tumour proliferation in metastatic lymph nodes from colon carcinomas.

This report is limited by the rarity of these tumors. Notwithstanding, the awareness that colonic carcinomas may evolve in mucosa-associated lymphoid tissue should encourage endoscopists to methodically examine areas with GALT complexes, particularly in patients with UC.

The possibilities that the advanced adenoma on top had invaded the GALT-complex underneath or that the GALT-carcinoma was a metastasis from the adenoma on top were rejected, since serial sections revealed neither continuity between the adenoma and the GALT-carcinoma, nor invasive growth in the adenoma. In light of these considerations it is submitted that the GALT-carcinoma here described evolved in a newly formed GALT aggregate in a patient with UC. A similar conclusion was drawn in 1984, when searching for a confirmation of the hypothesis of Cuthbert Dukes^[10], the first case of GALT-associated carcinoma was detected^[12].

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Use of a novel covered self-expandable metal stent with an anti-migration system for endoscopic ultrasound-guided drainage of a pseudocyst

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Abstract

The development of pseudocysts in patients with chronic pancreatitis has been reported in 23%-60% of cases and drainage is indicated when they become symptomatic. Endoscopic ultrasound-guided drainage with the placement of plastic or metallic stents to create a cystogastric anastomosis has been shown to be a reliable and efficacious maneuver. Metallic stent use appears to be a safe and effective alternative that shortens the length of time of the procedure and maintains a greater diameter in the cystogastric communication. However, important migration rates have been reported. The use of new metallic stents that are specially designed to prevent migration represents a promising development in the treatment of these group of patients that appears to be safe and effective for pseudocyst drainage and could importantly reduce migration

rates, while at the same time having the advantage of a single step procedure and a larger fistula diameter in the endoscopic cystogastric anastomosis.

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Key words: Pancreatic pseudocyst; Metallic stents; Endoscopic ultrasound

Core tip: The use of novel covered self-expanding metallic stents that are specially designed to prevent migration represents a promising development in the treatment of patients with pancreatic pseudocysts that appears to be safe and effective for drainage and could importantly reduce migration rates, while at the same time having the advantage of a single step procedure and a larger fistula diameter in the endoscopic cystogastric anastomosis.

Téllez-Ávila FI, Villalobos-Garita Á, Ramírez-Luna MÁ. Use of a novel covered self-expandable metal stent with an anti-migration system for endoscopic ultrasound-guided drainage of a pseudocyst. *World J Gastrointest Endosc* 2013; 5(6): 297-299 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i6/297.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i6.297>

INTRODUCTION

Standard procedure for endoscopic ultrasound-guided drainage of peripancreatic collections includes the use of various plastic endoprotheses in the same endoscopic procedure and the need for programmed replacement to preclude their dysfunction. The use of completely covered self-expanding metallic stents (CSEMS) has recently been shown to be a safe and effective alternative that reduces the number of procedures^[1]. However, there are

high migration rates (up to 15%)^[1,2]. The use of metallic stents designed to prevent migration are an interesting option in these patients that reduces procedure duration and provides a larger fistula diameter.

CASE REPORT

A 51-year-old man presented with chronic pancreatitis (CP) due to alcohol overuse and had a past 3-year history of obstructive jaundice with a pseudotumor at the level of the pancreatic head, along with common bile duct stricture. Cytology consistent with CP without evidence of cancer was obtained through endoscopic ultrasound-guided fine-needle aspiration biopsy (EUS-FNA). The patient underwent a number of endoscopic treatment sessions for the placement of multiple plastic stents and pneumatic dilatation 4 times a year for 3 years with no adequate response. During the last year of disease progression, he presented with a pseudocyst associated with early postprandial fullness and abdominal pain.

The patient rejected surgical treatment of the pseudocyst and the biliary stricture. Due to symptom persistence, the patient underwent endoscopic placement of a CSEMS in the biliary tract and endoscopic ultrasound-guided drainage of the pseudocyst with the placement of a 3 cm long “NAGI” CSEMS (Taewoong-Medical Co, Seoul, South Korea) with a 10 mm diameter in the center and 20 mm ends, for an endoscopic cystogastric anastomosis (Figure 1).

Biliary diversion

Using a duodenoscope (GIF-140, Olympus America, Melville, NY, United States), endoscopic retrograde cholangiopancreatography (ERCP) was performed. There was evidence of intrapancreatic bile duct stricture and a 6 cm long CSEMS with a 10 mm diameter (Taewoong-Medical Co, Seoul, South Korea) was placed. Pancreatography revealed an area of stricture, at the level of the neck of the pancreas, through which the passage of 0.035”, 0.025”, and 0.018” guidewires (Boston Scientific, Natick, MA, United States) was not possible. The body and tail of the pancreas were dilated and there was contrast medium leakage (Figure 2).

Endoscopic ultrasound-guided pseudocyst drainage

A pseudocyst with a 6 cm × 5 cm diameter was then seen with a GF-UCT140AL5 echo endoscope (Olympus America, Melville, NY, United States). Under endosonographic vision, and after using the Doppler mode to detect blood vessels in the tract, the pseudocyst was punctured through the gastric wall with a 19G-caliber Echotip® needle (Cook Endoscopy, Winston-Salem, NC, United States) followed by the introduction of a 0.035” Hydra Jagwire® (Boston Scientific, Natick, MA, United States). The needle-knife (Boston Scientific, Natick, MA, United States), 6, 7, 8.5, and 10 F Soehendra® catheters (Cook Endoscopy, Winston-Salem, NC, United States), and lastly, a Max Force® balloon dilator (Boston Scientific, Galway, Ireland) were progressively advanced along the guidewire to dilate

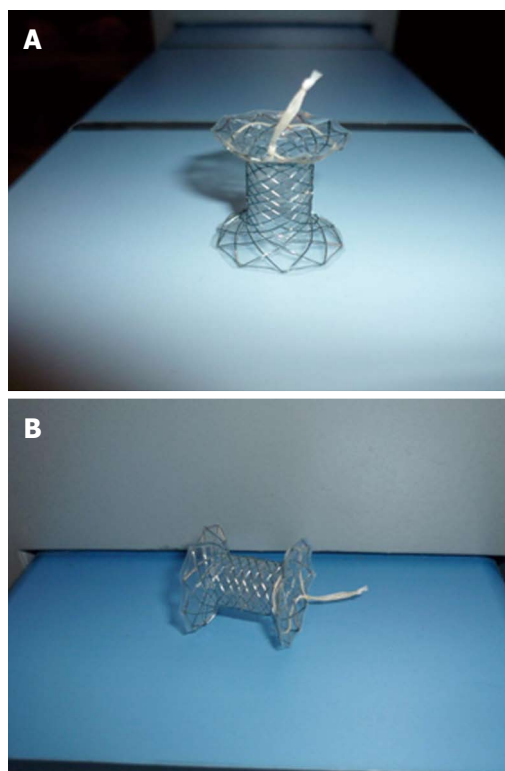


Figure 1 Novel “NAGI” covered self-expanding metallic stents with a 10 mm center and 20 mm ends (A and B).

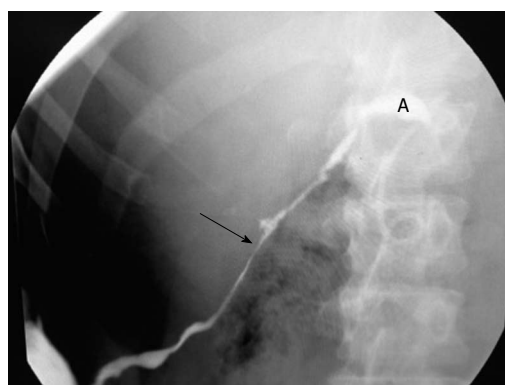


Figure 2 Presence of stenosis (arrow) and leak (A) of the main pancreatic duct.

the puncture tract up to 8 mm. A “NAGI” CSEMS was put in place under fluoroscopic vision to provide support to the cystogastrostomy (Figure 3).

At 6 mo of outpatient evaluation, the patient is asymptomatic and his liver function tests are normal (Table 1).

DISCUSSION

High success rates have been reported for ultrasound-guided pseudocyst drainage since 2001 and this procedure has shown advantages over the surgical option in relation to hospital stay and costs^[3,4].

The placement of multiple plastic stents is technically difficult and so the use of a single CSEMS has been proposed^[1]. Procedure duration and resolution time is lower

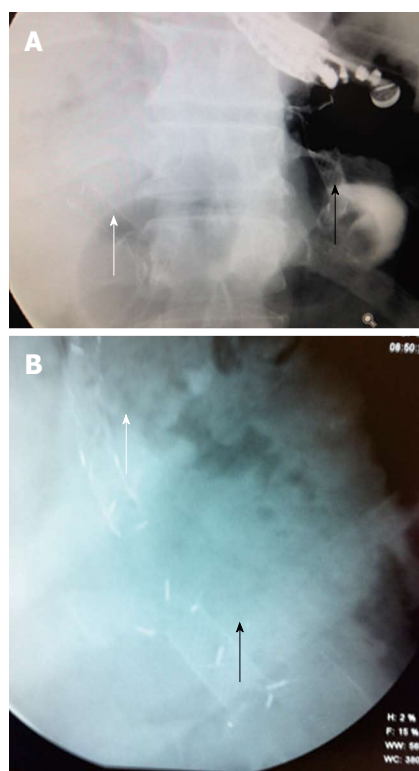


Figure 3 Fluoroscopy image at basal (A) and at after 6 mo (B) of follow-up: Biliary stent (white arrows) and Nagi stent through cystogastrostomy (black arrows).

with CSEMSs and this is probably related to the larger fistula diameter, while the technical success, clinical outcome, and complications are similar^[5]. Nevertheless, the probability of stent migration in 15% of the patients is a concern^[1,2]. In the present case, a stent with a specially designed feature to reduce the high migration rate was used. The design of the “NAGI” stent, with 20 mm large and acute angled flare ends, implies a decrease in the migration rates due to better anchoring in the gastric and pseudocyst extremes. Besides this is fully covered with silicone that prevents leakage and tissue ingrowth and with retrieval string allows for easy removal. With a reduced migration rate, severe complications such as gastrointestinal tract obstruction, impaction, and/or perforation of the gastrointestinal tract wall could be prevented^[6-11].

In conclusion, the use of CSEMSs that are designed with an anti-migration system is an alternative that appears to be safe and effective for pseudocyst drainage and could importantly reduce migration rates, while at the same time having the advantage of a single step procedure and a larger fistula diameter in the endoscopic cystogastric anastomosis.

Table 1 Liver function test before and after procedure

Parameter	Before procedure	12-wk after procedure
Total bilirubin	5.66	0.45
Direct bilirubin	4.09	0.08
ALT	351	49
AST	271	25
ALP	391	112

ALT: Alanine amino transferase; AST: Aspartate amino transferase; ALP: Alkaline phosphatase.

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E-Editor Zhang DN



Youngest case of an early gastric cancer after successful eradication therapy

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No atrophic change or *H. pylori* infection was evident histologically. This is the youngest patient ever reported to have developed a node-positive early gastric cancer after eradication of *H. pylori*.

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Key words: Early gastric cancer; *Helicobacter pylori*; Eradication therapy; Undifferentiated adenocarcinoma; Intestinal-type adenocarcinoma; Point of no return theory

Core tip: Although, earlier eradication of *Helicobacter pylori* (*H. pylori*) is considered to be more effective for prevention of gastric cancer by inhibiting the progression of mucosal atrophy, this youngest case developed an invasive gastric cancer with nodal involvement. From the viewpoint of the "point of no return" theory, future research should focus on the appropriate time of life at which to treat ideal candidates who would benefit from preventive eradication therapy. At present, it appears that cure of *H. pylori* infection still cannot prevent all gastric cancers, clinical studies are needed to clarify how to follow up patients after successful eradication therapy.

Abstract

A 28-year-old woman visited our clinic with a chief complaint of epigastralgia. She had received successful *Helicobacter pylori* (*H. pylori*) eradication therapy 5 years before. We repeated esophagogastroduodenoscopy, and a discolored depressed area with reddish spots and converging folds, 20 mm in size, was detected. No atrophic change including intestinal metaplasia or nodular gastritis was seen endoscopically. Two endoscopic biopsies revealed undifferentiated adenocarcinoma. No *H. pylori* was found, and the ¹³C-urea breath test was also negative. Abdominal computed tomography demonstrated no nodal involvement, distant metastasis or fluid collection. She underwent a laparoscopy-assisted distal gastrectomy. Histologically, the resected specimen revealed an early undifferentiated gastric cancer that had invaded deeply into the submucosal layer. Nodal involvement was histologically confirmed.

Konuma H, Konuma I, Fu K, Yamada S, Suzuki Y, Miyazaki A. Youngest case of an early gastric cancer after successful eradication therapy. *World J Gastrointest Endosc* 2013; 5(6): 300-303 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i6/300.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i6.300>

INTRODUCTION

Helicobacter pylori (*H. pylori*) infection plays an important role in the development of gastric cancer. Therefore, *H. pylori* eradication is considered an important approach for prevention of gastric cancer. *H. pylori* infection has been

shown to induce gastric adenocarcinoma in animal models^[1,2]. Furthermore, a number of studies in humans have demonstrated that *H. pylori* eradication has the potential to prevent gastric cancer^[3-7]. Unfortunately, however, gastric cancers can still arise after *H. pylori* eradication therapy^[8]. We herein report a case of diffuse-type early gastric cancer that developed in a young woman 5 years after successful *H. pylori* eradication.

CASE REPORT

A 28-year-old woman visited our clinic with a chief complaint of epigastralgia that had lasted for 10 d. She had undergone esophagogastroduodenoscopy (EGD) at another outpatient clinic because of epigastralgia 5 years previously. At that time, she had received successful *H. pylori* eradication therapy, as histologic examination of the endoscopic biopsy specimen had revealed *H. pylori* positivity. Her family history included a hepatocellular carcinoma in her father at the age of 31-year-old, a gastric cancer in her grandmother at the age of 67-year-old, and an esophageal squamous cell carcinoma in her grandfather at the age of 76-year-old. We repeated EGD at our clinic for further investigation, and a depressed area, 20 mm in size, was detected at the anterior wall in the greater curvature of the gastric body (Figure 1). The depressed area was discolored with a reddish spot, and converging folds were also evident endoscopically. The endoscopic diagnosis was early-stage undifferentiated adenocarcinoma (submucosal invasive carcinoma). No atrophic change including intestinal metaplasia or nodular gastritis was seen during the first and second endoscopy examinations. Two endoscopic biopsies were performed for histological evaluation, and the specimens revealed undifferentiated adenocarcinoma. However, no *H. pylori* was found, and the ¹³C-urea breath test was also negative. Abdominal computed tomography demonstrated no nodal involvement, distant metastasis or fluid collection suggestive of ascites. A final clinical diagnosis of localized early gastric cancer with undifferentiated histology was established, and the patient was sent for surgical treatment. She underwent a laparoscopy-assisted distal gastrectomy with D2 dissection of lymph nodes. Histologically, the resected specimen revealed an early undifferentiated gastric cancer that had invaded deeply into the submucosal layer, and marked lymphatic permeation (Figures 2, 3). Nodal involvement was histologically confirmed in one out of 24 dissected lymph nodes. No atrophic change or *H. pylori* infection was evident histologically. The pathological staging was T1bN1M0 (stage IB) according to the TNM classification. The postoperative course was uneventful, and no recurrence of gastric cancer was recognized thereafter.

DISCUSSION

To our knowledge, the present patient is the youngest ever reported to have developed a node-positive early gas-

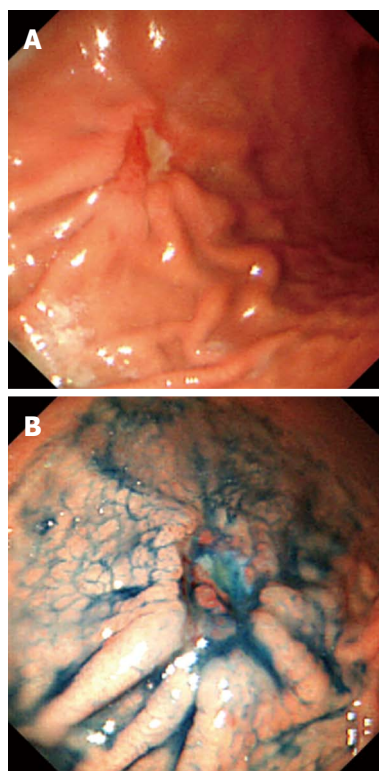


Figure 1 Endoscopic views. A: Conventional endoscopy before dye spraying showed a depressed area, 20 mm in size, was detected at the anterior wall in the greater curvature of the gastric body. The depressed area was discolored with a reddish spot, and converging folds were also evident endoscopically; B: Chromoendoscopy after 0.4% indigo-carmin dye spraying better defined the depressed area.



Figure 2 Surgical specimens obtained by a laparoscopy-assisted distal gastrectomy revealed an depressed cancer with fold convergence (white arrow).

tric cancer after eradication of *H. pylori*. Until now, most reported patients developing gastric cancer after *H. pylori* eradication therapy have been 50 years old or more^[8,9]. Characteristically, such gastric cancers have been discovered at an advanced stage significantly less frequently in Japanese patients than in patients elsewhere^[8]. Most of the Japanese cases were detected at an early stage, had a depressed form, and showed an intestinal-type dominant histology^[8,9]. The risk factors for gastric cancer after *H.*

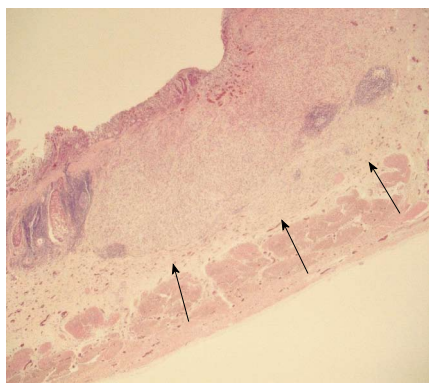


Figure 3 Histologically, it was an early undifferentiated gastric cancer that had invaded deeply into the submucosal layer (black arrow), and marked lymphatic permeation.

pylori eradication therapy are reportedly older age and advanced atrophic change in the gastric corpus, neither of which characterized the present case^[8,10]. In the multistep pathogenesis of intestinal-type gastric cancer, *H. pylori*-induced chronic active gastritis slowly progresses through the premalignant stages of atrophic gastritis, intestinal metaplasia, and dysplasia to gastric adenocarcinoma. No similar sequence has been described for the diffuse type. Theoretically, *H. pylori* eradication stops the natural progression of premalignant lesions, and thus stabilizes the risk of gastric cancer. In the present young female patient, however, an early diffuse-type gastric cancer was detected even after *H. pylori* had been eradicated. The incidence of *H. pylori*-negative gastric cancer is extremely low (less than 1%)^[10]. Recently, a prospective study reported that infection with *H. pylori* is associated with the development of both intestinal- and diffuse-type gastric cancer^[4]. Furthermore, a close relationship between *H. pylori* and diffuse-type cancer has also been described, especially in younger individuals^[11].

Previous reports have indicated that *H. pylori* eradication does not prevent the development of gastric cancer in all patients during long-term follow-up^[12]. The risk of developing gastric cancer reportedly depends on the level of severity and extent of atrophic gastritis and gastric atrophy at the time of eradication. In a study from China, a beneficial effect of *H. pylori* eradication was seen only among those with a low baseline risk (without atrophy), and it was concluded that the chemopreventive effect of eradication is achieved during the earlier phases of carcinogenesis, before preneoplastic lesions have developed^[13]. Therefore, earlier eradication of *H. pylori* is considered to be more effective for prevention of gastric cancer by inhibiting the progression of mucosal atrophy. Despite undergoing successful eradication therapy in her early 20s in the absence of any premalignant lesions such as mucosal atrophy or intestinal metaplasia identified endoscopically and histologically, this young woman unfortunately developed an invasive gastric cancer with nodal involvement. From the viewpoint of the “point of no return” theory (when the development of gastric cancer can no

longer be prevented by *H. pylori* eradication), future clinical research should focus on the appropriate time of life at which to treat ideal candidates who would benefit from preventive eradication therapy. At the present time, however, it appears that cure of *H. pylori* infection still cannot prevent the development of gastric cancer in all patients. More data such as the optimal interval for surveillance endoscopy are needed for patients even after successful eradication of *H. pylori*.

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Incarceration of a colonoscope in an inguinal hernia: Case report and literature review

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Author contributions: Tan VP performed the endoscopy, literature review and wrote the manuscript; Lee YT reviewed and edited the manuscript; Poon JTC performed the endoscopy and reviewed the manuscript.

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Key words: Colonoscopy; Inguinal hernia; Fluoroscopy

Core tip: Incarceration of a colonoscope in an inguinal hernia is likely an under reported occurrence. The authors present a case report and literature review of incarceration of a colonoscope in an inguinal hernia and a suggested management algorithm.

Tan VP, Lee YT, Poon JTC. Incarceration of a colonoscope in an inguinal hernia: Case report and literature review. *World J Gastrointest Endosc* 2013; 5(6): 304-307 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i6/304.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i6.304>

Abstract

Incarceration of an endoscope in an inguinal hernia may occur during the course of routine colonoscopy. The incarceration may occur on insertion or withdrawal and frequently the hernia is not suspected prior to the colonoscopy. Most commonly, a left sided inguinal hernia is involved, however right inguinal hernias may be implicated in subjects with altered anatomy post abdominal surgery. Incarceration of an endoscope in an inguinal hernia has been seldom reported in the literature which is likely to be related to under reporting. A range of techniques have been suggested by various authors over the last four decades to manage this unusual complication of colonoscopy. These techniques include utilizing fluoroscopy, manual external pressure and/or the fitting of a cap onto the tip of the colonoscope to facilitate colonoscopic navigation. The authors present a case report of incarceration of the colonoscope on withdrawal in an unsuspected left inguinal hernia with a review of the literature on the management of this colonoscopic complication. A management strategy is suggested.

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INTRODUCTION

A 76-year-old man presented for colonoscopy for follow up of previously diagnosed colonic polyps. A colonoscopy had been performed one month prior where a significant 1.2 cm sessile polyp was found in the mid transverse colon, however at that juncture given the patient's comorbid conditions and the lack of recent clotting profile and platelet count, the decision was made to repeat the colonoscopy with polypectomy after relevant blood work was performed. During the original colonoscopy no complications were encountered and the patient did not require much sedation (midazolam 4 mg and pethidine 37.5 mg).

CASE REPORT

The colonoscope was inserted without difficulty or significant abdominal discomfort to the terminal ileum at 100 cm. The procedure was performed under conscious sedation and the patient had received 2 mg of midazolam and 25 mg of pethidine at this juncture. Multiple polyps in the caecum, hepatic flexure and transverse colon had

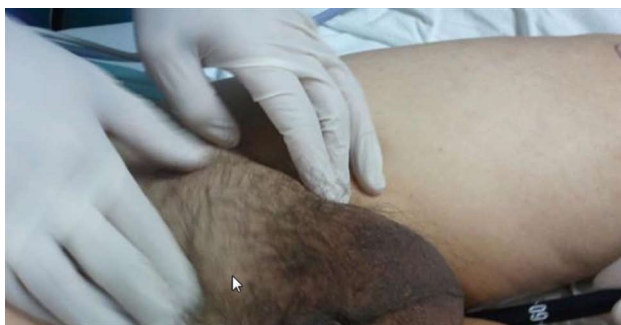


Figure 1 Incarcerated colonoscope bulging into the left inguinal hernia during colonoscopy.

been noted on insertion and were removed on with snare polypectomy on withdrawal. In the mid transverse colon at 60 cm the colonoscope could not longer be withdrawn and appeared to be “frozen” in position, although the patient did not experience significant discomfort. Despite clockwise and counter clockwise rotation with gentle traction as well as positioning the patient into the supine position the colonoscope was unable to be withdrawn. During these manoeuvres the lumen of the transverse colon could be clearly seen. An examination of the patient's left inguinal hernia orifice revealed a bulge in the left scrotum consistent with incarceration of the colonoscope in the inguinal hernia sac (Figure 1).

The patient was given further midazolam and pethidine to a total of 5 mg and 62.5 mg, respectively, to ensure adequate analgesia and the incarcerated colonoscope was attempted to be reduced manually through external manual pressure and clockwise and counter clockwise torque with gentle traction. This was unsuccessful and the patient was immediately wheeled into the fluoroscopy suite and under direct radiographic guidance, the loop in the hernial sac was minimized and the colonoscope withdrawn by gentle traction without complication (Figure 2). The patient remained well throughout the reduction of the incarcerated colonoscope. On further withdrawal of the endoscope, a large 1-1.5 cm flat polyp was seen in the mid transverse colon which had been seen at the original endoscopy. A saline lift was attempted but the lesion did not lift the polyp which suggested sub-mucosal infiltration. Biopsies were taken, the lesion tattooed and the colonoscope withdrawn without complication. The histopathology of the lesion returned adenocarcinoma of the transverse colon. The patient was subsequently referred to the surgeons for a right hemi-colectomy and left inguinal hernia repair. An examination of the patient post colonoscopy indicated that the patient had a large sliding indirect inguinal hernia. We now present a review of the literature regarding the complication of incarceration of the colonoscope within an inguinal hernia.

DISCUSSION

Due to under reporting, the occurrence of colonoscope incarceration in an abdominal hernia is probably un-

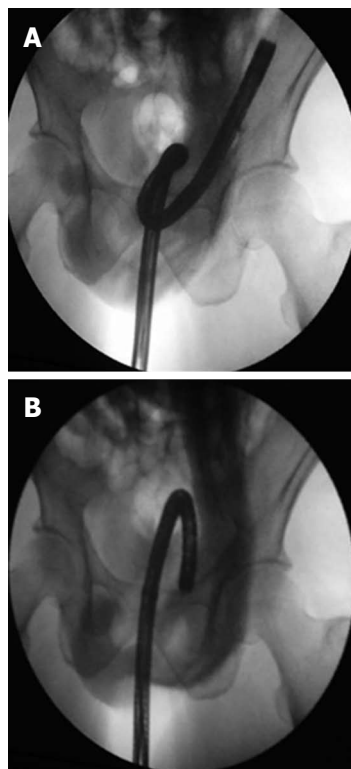


Figure 2 Colonoscopic loop in the process reduction under fluoroscopic guidance and fluoroscopic image of complete reduction of colonoscopic loop respectively. A: Fluoroscopic image of incarcerated colonoscope in left inguinal hernia; B: Fluoroscopic image of incarcerated colonoscope post reduction.

derestimated as evidenced by the scant number of case reports published in the English language. A total of 12 case reports involving 15 cases have been identified by the authors published to date (Table 1). The incarceration occurs both on insertion and withdrawal, usually when the endoscope is 60-80 cm from the anal verge and involves left inguinal hernias exclusively. One exception was a case published by Koltun *et al*^[1], where the incarceration occurred in the right inguinal hernia however the patient had slightly altered abdominal anatomy due to a prior right hemi-colectomy. In only four of the cases were the presence of an inguinal hernia known prior to colonoscopy.

The neck of an indirect inguinal hernia is usually the site of obstruction when loops of bowel become incarcerated. In cases where the colonoscope becomes unable to progress on insertion, this is likely to occur due to three scenarios, firstly, a loop of bowel has become incarcerated in an inguinal hernial sac which has a small neck, the aperture of which is insufficient to permit the entry of the colonoscope^[2]. In this specific scenario the hernia may only be suspected on imaging, in this case, a barium enema revealed a constriction at the level of the sigmoid colon. The second scenario occurs in patients with moderate sized inguinal hernias sufficient to permit the entry of the colonoscope into the hernial sac but not simultaneous entry and exit of the colonoscope side by side^[3]. In this scenario, the tip of the colonoscope enters the

Table 1 Published case reports of incarcerated colonoscopes in inguinal hernia and strategy utilized to remove the scope

Ref.	No. of cases	Inguinal hernia (side)	Method of scope removal	Distance from anus at obstruction	Obstruction on insertion <i>vs</i> withdrawal
Waye ^[5]	1	Unknown	NA	NA	NA
Leichtmann <i>et al</i> ^[6]	3	× 2 Unknown × 1 Known	× 2 Manual reduction × 1 Hernial reduction before and maintenance during procedure	NA	NA
Fulp <i>et al</i> ^[7]	1	Known, Left	Withdrawal of endoscope	Sigmoid colon	Insertion
Leisser <i>et al</i> ^[8]	1	Unknown, Left	Manual reduction	60 cm	Insertion
Koltun <i>et al</i> ^[11]	2	Known, Right	Failed fluoroscopic reduction Manual reduction utilizing "Pulley" technique	NA	Withdrawal
Yamamoto <i>et al</i> ^[4]	1	Unknown, Left	Failed manual reduction, Reduction under fluoroscopic guidance	70cm	Insertion
Saunders ^[9]	1	Unknown	NA	NA	NA
Punnam <i>et al</i> ^[10]	1	Known, Left	Failed manual reduction Surgical Dissection of Hernial Sac	NA	Withdrawal
Lee <i>et al</i> ^[2]	1	Unknown, Left	Manual reduction	NA	Insertion
Iser <i>et al</i> ^[11]	1	Unknown, Left	Manual reduction under deep sedation	NA	NA
Fan <i>et al</i> ^[3]	1	Unknown, Left	Reduction under fluoroscopy and external manual pressure	60 cm	Withdrawal
Kume <i>et al</i> ^[12]	1	Unknown, Left	Reduction under fluoroscopy	60 cm	Withdrawal

NA: Not available.

hernial sac very easily but when the colonoscope forms a loop and attempts to exit the hernial sac it becomes obstructed with bulging and pain in the lower abdomen/scrotum. In the third scenario, the hernial sac is sufficiently wide enough to accommodate both the entry and exit of the two segments of colonoscope, however further insertion creates a large loop in the scrotum resulting in pain, "freezing" of the scope and inability to progress the examination^[4]. For the first two scenarios, should it be necessary to proceed with the colonoscopy, use of a cap attached to the tip of the colonoscope may facilitate passage of colonoscope through the loop of bowel which has prolapsed into the hernia (unpublished data). In the third scenario, manual pressure externally may enable the colonoscopy to be completed.

However, in half of the published case studies, incarceration of the colonoscope occurs during withdrawal. Here, during the advancement phase of the colonoscope a loop forms bulging into the hernial sac. The hernial orifice is sufficiently wide to comfortably permit the entry and exit of the two segments of colonoscope, with prolapse of the colonoscope and colon into the scrotum. It is only on withdrawal of the colonoscope that a tight loop, usually a gamma loop, is formed which becomes incarcerated if the maximum diameter of the loop exceeds that of the hernial orifice, which occurred in our case.

A variety of methods have been published to reduce the incarcerated colonoscope which included manual reduction after deepened sedation, a "pulley" method of manual reduction, reduction under direct fluoroscopic guidance, surgical reduction or some combination of the aforementioned methods^[1,3,4]. The authors suggest that in the event of an incarcerated colonoscope in an inguinal hernia, clinicians should proceed directly to fluoroscopic guidance if available. The benefits of fluo-

roscopic guidance includes the ability to minimize the colonoscope loop in the scrotal sac and an estimation of the hernial orifice to determine if removal of an incarcerated colonoscope with a loop *in situ* is feasible. After the retraction of the loop from the scrotal sac, fluoroscopy can enable the straightening of the colonoscope before the procedure is completed^[3]. Simultaneous gentle manual pressure to encourage the loop through the hernial orifice is recommended. Failing this, the authors suggest trying the "pulley" method if the hernial orifice is so small it will not permit the exit of the smallest loop feasible with the colonoscope^[1]. Should this fail surgery is most likely indicated.

Some clinicians have suggested the presence of a large inguinal hernia is a relative contra-indication to colonoscopy^[1]. We suggest that in the event a colonoscopy is clinically necessary prior to repair of moderate to large inguinal hernia, the option of computerized tomography colonoscopy be explored. Should a colonoscopy still be necessary, the authors suggest that the risk of incarceration may be reduced by reducing the hernia prior to colonoscopy and maintaining reduction manually whilst the scope is advanced. The use of cap assisted colonoscopy may also aid the negotiation of the endoscope through the herniated bowel loop (unpublished data). However as most of these case studies demonstrate, most cases of incarcerated colonoscopes are the first presentation of the patient with an inguinal hernia.

In summary, incarcerated colonoscopes in an inguinal hernia are, thankfully, a rare event. In patients with known inguinal hernias, consideration must be given to computed tomography colonoscopy and in the event the colonoscopy must proceed, strategies employed to reduce the risk of complication. However as our literature review has demonstrated the incarcerated scope is usually

the first sign of an inguinal hernia in a patient and in this situation should be reduced under direct fluoroscopic guidance with gentle manual pressure and adequate sedation, followed by an attempt at the “pulley” system and finally, surgery, if all else fails.

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Endoscopic treatments for chronic radiation proctitis

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Abstract

Chronic radiation proctitis is a complication that occurs in patients who receive radiation therapy for pelvic malignancies. The common presentation is with rectal bleeding, but also rectal pain, diarrhea, tenesmus and even passage of mucus can occur. The optimal treatment of bleeding due to radiation proctitis remains unclear. Among various therapeutic options, medical management is generally ineffective and surgical intervention has a high incidence of morbidity. Promising advances have been made in endoscopic therapy, including argon plasma coagulation (APC), formalin application as well as new techniques such as radiofrequency ablation and cryoablation. APC is a safe, highly effective and long-lasting therapy in patients with rectal bleeding associated with radiation proctitis. It has been shown that several sessions of APC reduce the rate of bleeding and therefore the blood transfusion requirements. Moreover, the effect of treatment is long lasting. However, best results are achieved in patients with mild to moderate radiation proctitis, leaving space for alternative treatments for patients with more severe disease. In patients with severe or refractory

radiation proctitis intra rectal formalin application is an appropriate treatment option. Radiofrequency ablation and cryoablation have shown efficacy as alternative methods in a limited number of patients with refractory chronic radiation proctitis.

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Key words: Radiation proctitis; Endoscopic treatment; Argon plasma coagulation; Formalin application; Cryoablation; Radiofrequency ablation

Core tip: Chronic radiation proctitis presents with rectal bleeding, pain, diarrhea, tenesmus and passage of mucus. Among other therapeutic options, endoscopic therapy with argon plasma coagulation (APC) is a safe and highly effective in patients with rectal bleeding associated with radiation proctitis. Although best results are achieved in patients with mild to moderate lesions, APC therapy reduces the rate of bleeding and blood transfusion requirements and its effect last for long. In patients with severe or refractory radiation proctitis intra rectal formalin application, radiofrequency ablation and cryoablation have shown efficacy in a limited number of patients.

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INTRODUCTION

The rectum is often injured during pelvic radiation due to its fixed position and its anatomical proximity to the radiated target organ such as prostate and cervix. Radiation proctitis, usually mild, is a complication that occurs in up to 15% of patients who receive radiation therapy for pelvic malignancies. Radiation damage may occur in

acute or chronic form. Acute complications are seen during or up to 6 wk after radiotherapy, whereas late radiation injury usually occurs in the first 2-3 years after treatment^[1-3]. A change in the treatment practices has recently occurred toward escalating radiation doses with improved local control. Conformal radiotherapy of pelvic tumors focuses on reducing irradiation of organs at risk such as rectum^[4,5]. Although the incidence of complications has been reduced using this new technology, rectal wall damage continues to be an important side effect of pelvic radiotherapy^[6-9].

CLINICAL FEATURES AND TREATMENT OPTIONS

The common presentation of radiation proctitis is with rectal bleeding, but also rectal pain, diarrhea, tenesmus and even passage of mucus can occur. In approximately 35% of patients the symptoms are mild and settle spontaneously over several months without any treatment. However, rectal bleeding due to chronic radiation proctitis may lead to anemia and necessitate repeated blood transfusions. Medical treatment with salicylates, sucralfate or corticosteroids enemas is usually not beneficial^[10-14]. Thus, alternative treatments including endoscopic ones have been used. Among endoscopic treatments, argon plasma coagulation (APC), a nontouch thermo ablative therapy, is increasingly recommended as first line treatment for patients with radiation proctitis.

APC

For evaluation of endoscopic severity of radiation proctitis, a scoring system with measurement of three independent factors (telangiectasia distribution, surface area involved and the presence of fresh blood) was proposed^[15] (Table 1). A cumulative score was calculated and three categories of endoscopic severity of radiation proctitis were derived: grade A (mild, 2 points), grade B (moderate, 3 points), and grade C (severe 4/5 points).

Recently, we prospectively investigated in a large number of patients the effectiveness of APC in treating patients with various endoscopic grading of radiation proctitis (mild, moderate, and severe) using a modified scoring system with measurement of two independent factors for evaluation of endoscopic severity: telangiectasia distribution and surface area involved^[16]. For APC application, an ERBE APC 300 (ERBE Elektromedizin, Tübingen, Germany) argon delivery unit and a 2.3 mm diameter front-firing APC probe inserted through the working channel of the flexible sigmoidoscopy were used. The argon flow rate and the electrical power were set at 2.0 L/min and 40 W, respectively.

Our results showed that APC was successful in all patients with mild and in almost all patients with moderate radiation proctitis. In contrary, in the presence of severe mucosal damage APC failed in 50% of patients. Patients with mild proctitis required 1-2 sessions of APC,

Table 1 Endoscopic classification of radiation proctitis

Distribution of telangiectasias	Surface area covered by telangiectasias	Presence of fresh blood
Distal rectum (within 10 cm from anal verge): 1 point	Less than 50%: 1 point	No fresh blood: 0 points
Entire rectum +/- sigmoid (more than 10 cm from anal verge): 2 points	More than 50%: 2 points	Fresh blood: 1 point

while patients with moderately to severe form required a statistically significantly higher number of APC sessions. Our results were in accordance with the existing literature; APC is the preferred method in patients with rectal bleeding associated with mild to moderate radiation proctitis, while in cases of severe and diffuse involvement of the rectum multiple treatments sessions are required and success is less certain^[17-26]. We also presented long-term follow up of patients successfully treated with APC and showed that during a follow-up of a mean of 17.9 mo (range 6-33 mo) about 90% of these patients remain in clinical remission.

APC parameters: Number of APC sessions

Till now there is no consensus for the optimal APC settings (power and gas flow rate) for successful and safe coagulation. In the literature the power setting for APC ranged from 25-80 W and for the argon flow rate ranged from 0.6-2 L/min^[21]. In our study low-power settings (argon flow rate and electrical power were set at 2.0 L/min and 40 W, respectively) were used. Although these settings were among the lowest reported in the literature seemed adequate for successful coagulation and also carried low rate of complications.

The optimal number of treatment sessions is still unknown. APC is traditionally not applied in 1 treatment session, particularly in patients with severe disease, because of the concern regarding strictures formation. For therapeutic success, the median number of sessions per patient was ranged from 1 to 3.7^[27]. Similarly to previous reports, multiple sessions of APC were performed in our patients with a maximum of eight sessions in a patient with severe radiation proctitis.

FORMALIN APPLICATION

In severe cases of radiation proctitis and in cases resistant to other treatment modalities intra-rectal formalin is a useful strategy^[28]. Formalin is a mixture of methanol and formaldehyde which covalently binds to proteins, and causes cell necrosis. It acts as a haemostatic agent causing chemical cauterization to control bleeding from telangiectatic mucosal and submucosal vessels. Most used 4% dilute formalin applied to the rectum mucosa either by direct application of formalin-soaked gauze or by 'instilling' the solution in single or multiple aliquots down the operating channel of a colonoscope. Various volumes of formalin and different mucosal contact time were re-

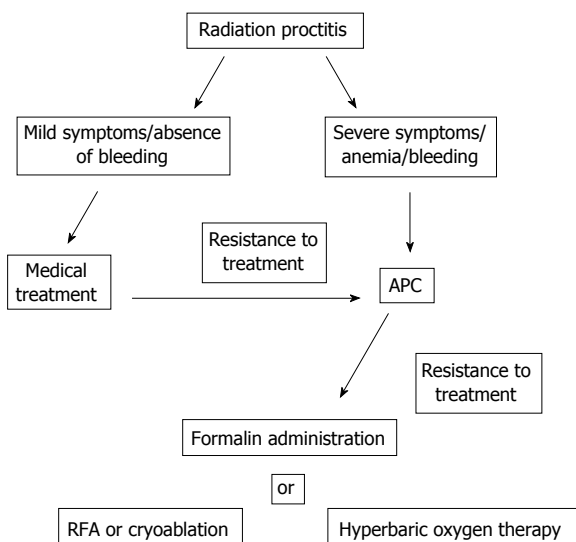


Figure 1 Treatment options for patients with radiation proctitis. APC: Argon plasma coagulation; RFA: Radiofrequency ablation.

ported. Mean number of treatment ranged from 1.1-3.4 per patient. Cessation of bleeding occurred in most studies in the range of 60%-100%^[28-38]. Median follow ups to a period of two years have shown only a minimal relapse among responders. Reported side effects include anal stenosis, fissures, fecal incontinence and ulceration of mucosa.

RADIOFREQUENCY ABLATION

The theoretical benefits of radiofrequency ablation are extrapolated are studies treating gastric antral vascular ectasia and Barrett's esophagus. Effective control of lower gastrointestinal bleeding in patients with refractory chronic radiation proctitis using radiofrequency ablation (RFA) with the Halo90 system has been recently reported^[39-41]. RFA was performed in an outpatient practice using a single use Halo90 electrode catheter that was fit on the distal end of a standard flexible sigmoidoscope. An energy density of 12 J/cm² at a power density of 40 W/cm² was chosen based on previous studies performed, which showed no transmural injury at these settings. In all cases, the procedure was well tolerated and hemostasis was achieved after 1 or 2 RFA sessions. Re-epithelialization of squamous mucosa was observed over areas of prior hemorrhage. Patients were symptom free on follow-up up to 19 mo after treatment.

CRYOABLATION

Cryoablation involves noncontact application of liquid nitrogen or carbon dioxide gas to tissue for superficial ablation^[42]. Cryospray ablation has been used to treat esophageal high-grade dysplasia and early cancer. In two recent studies endoscopic cryoablation was performed in 20 patients with hemorrhagic radiation proctitis^[43,44]. Endoscopic severity and subjective clinical scores im-

proved in all patients. Cryoablation was performed with a catheter placed through the endoscope under direct endoscopic visualization to approximately 0.5 to 1.0 cm from the tip of the endoscope. The spray was applied for 5 s and the treatment area was then allowed to thaw no less than 45 s before initiating subsequent cryospray applications. Required sessions ranged from one to four and endoscopic score significantly improved, as well as, rectal pain and rectal bleeding. Although patients tolerated the procedure well, one patient experienced a cecal perforation^[43] after therapy probably due to over insufflation during the procedure.

ALTERNATIVE TREATMENT OPTIONS (HYPERBARIC OXYGEN THERAPY)

Hyperbaric oxygen therapy (HBOT) is the use of 100% oxygen at pressures greater than atmospheric pressure. The patient breathes 100% oxygen intermittently, while the pressure of the treatment chamber is increased to greater than 1 atmosphere absolute. HBOT promotes angiogenesis and hyperoxygenation to the irradiated tissues. Increasing the oxygen content to the surrounding tissues markedly increases the overall oxygen gradient between these tissues and the central hypoxic area. The increased oxygen gradient is the essential catalytic factor for angiogenesis^[45].

Unfortunately, the research into the use of HBOT in radiation proctitis is heterogeneous in terms of duration of treatment, number of treatments and pressures of HBOT used. Warren *et al*^[46] reported a response rate of 64%, with complete symptomatic resolution in 57%, in 14 cases of radiation proctitis treated with varying doses of HBOT. Girnius *et al*^[47] reported nine patients with refractory haemorrhagic proctitis who had failed previous therapy; all patients had some response to HBOT and seven had complete resolution of their rectal bleeding. Jones *et al*^[48] also found that 8 out of 10 patients with refractory radiation proctitis responded to HBOT. Dall'Era *et al*^[49] found that a total of 48% of 27 patients with treatment-resistant radiation proctitis had complete resolution of bleeding and 28% of them had significantly fewer bleeding episodes. Similarly, a recent study reported that HBOT significantly improved the healing responses in patients with refractory radiation proctitis, generating an absolute risk reduction of 32% (number needed to treat of 3)^[50]. Although HBOT appears to be of value for refractory radiation proctitis, the quality of current data is poor with marked variability between studies. Moreover, the cost of HBO is high enough, and it is not widely applicable.

CONCLUSION

Based on currently data, APC is the favored treatment for bleeding from chronic radiation proctitis. APC is a safe, highly effective and long-lasting therapy in patients with rectal bleeding associated with endoscopic mild

radiation proctitis. In severe radiation proctitis multiple APC applications are usually required and success is likely to be more limited. In these patients other treatment options such as intra rectal formalin application should be considered. New therapeutic endoscopic modalities, including radiofrequency ablation and cryoablation, showed effective control of lower gastrointestinal bleeding in patients with refractory chronic radiation proctitis. As the number of patients treated with these new modalities was limited, further studies are needed to identify their safety and efficacy. Figure 1 summarized the treatment modalities available for patients with radiation proctitis.

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Implementation of a polling protocol for predicting celiac disease in videocapsule analysis

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Abstract

AIM: To investigate the presence of small intestinal villous atrophy in celiac disease patients from quantitative analysis of videocapsule image sequences.

METHODS: Nine celiac patient data with biopsy-proven villous atrophy and seven control patient data lacking villous atrophy were used for analysis. Celiacs had biopsy-proven disease with scores of Marsh II-III C except in the case of one hemophiliac patient. At four small intestinal levels (duodenal bulb, distal duodenum, jejunum, and ileum), video clips of length 200 frames (100 s) were analyzed. Twenty-four measurements were used for image characterization. These measurements were determined by quantitatively processing the videocapsule images *via* techniques for texture analysis, motility estimation, volumetric reconstruc-

tion using shape-from-shading principles, and image transformation. Each automated measurement method, or automaton, was polled as to whether or not villous atrophy was present in the small intestine, indicating celiac disease. Each automaton's vote was determined based upon an optimized parameter threshold level, with the threshold levels being determined from prior data. A prediction of villous atrophy was made if it received the majority of votes (≥ 13), while no prediction was made for tie votes (12-12). Thus each set of images was classified as being from either a celiac disease patient or from a control patient.

RESULTS: Separated by intestinal level, the overall sensitivity of automata polling for predicting villous atrophy and hence celiac disease was 83.9%, while the specificity was 92.9%, and the overall accuracy of automata-based polling was 88.1%. The method of image transformation yielded the highest sensitivity at 93.8%, while the method of texture analysis using subbands had the highest specificity at 76.0%. Similar results of prediction were observed at all four small intestinal locations, but there were more tie votes at location 4 (ileum). Incorrect prediction which reduced sensitivity occurred for two celiac patients with Marsh type II pattern, which is characterized by crypt hyperplasia, but normal villous architecture. Pooled from all levels, there was a mean of 14.31 ± 3.28 automaton votes for celiac *vs* 9.67 ± 3.31 automaton votes for control when celiac patient data was analyzed ($P < 0.001$). Pooled from all levels, there was a mean of 9.71 ± 2.8128 automaton votes for celiac *vs* 14.32 ± 2.7931 automaton votes for control when control patient data was analyzed ($P < 0.001$).

CONCLUSION: Automata-based polling may be useful to indicate presence of mucosal atrophy, indicative of celiac disease, across the entire small bowel, though this must be confirmed in a larger patient set. Since the method is quantitative and automated, it can potentially eliminate observer bias and enable the detection

of subtle abnormality in patients lacking a clear diagnosis. Our paradigm was found to be more efficacious at proximal small intestinal locations, which may suggest a greater presence and severity of villous atrophy at proximal as compared with distal locations.

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Key words: Automata; Celiac disease; Small intestine; Videocapsule; Villous atrophy

Core tip: Videocapsule endoscopy images from celiac disease patients and controls were extracted from video clips and compared using image processing. The image processor consists of 24 automated measurements, or automata. The values of these automata were polled for yes or no vote, which depended on a predetermined threshold value set for each measurement. The polling process predicted whether the patient had celiac disease, based on majority vote from the 24 automata. Celiac patients with even subtle villous atrophy were distinguished from controls by this method. For 16 patients, the overall sensitivity, specificity, and accuracy of the method was 83.9%, 92.9%, and 88.1%, respectively.

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INTRODUCTION

Videocapsule endoscopy has been used in clinical practice for over 10 years as a way to visualize the entire small intestine in patients with known or suspected celiac disease, inflammatory bowel disease, and other diseases where lesions are likely to be present in this region^[1-5]. The capsule is swallowed and then provides two high resolution images per second from all regions of the gastrointestinal system, including distal areas where standard endoscopy cannot be used. Based on findings that show the videocapsule to be helpful in the identification of abnormalities consistent with celiac disease^[6-9], there is increasing use in clinical practice.

When villous atrophy is present in the small intestine, as confirmed using standard endoscopy with biopsy, abnormalities are often evident in the endoscopic images including fissuring, mosaic pattern, and scalloping of mucosal folds^[10-14]. These abnormalities are often patchy in location, being interspersed with more normal-appearing mucosal surface. We have developed quantitative analyses of videocapsule endoscopy images^[15-19]. In these studies, it was hypothesized that patchy small intestinal abnormality would result in quantitative differences in the digital images. In patient image sequences with substantial

heterogeneity, caused by visually evident abnormalities including fissuring, mosaic pattern, and scalloping of mucosal folds in celiac patients, the image texture, which is the pixel-to-pixel variability in brightness level, would be expected to increase. Furthermore, it was hypothesized that in celiac patients, small bowel regions with villous atrophy may have abnormal motility, manifested as changes in oscillations in videocapsule image brightness. These hypotheses were validated in our initial studies^[15-19], and it was determined that patients with active celiac disease vs controls could be classified using threshold levels of the quantitative parameters used to measure image texture and oscillations in image brightness levels.

Although in prior work, classification of celiac vs control image sequences was done using several variables and multidimensional nonlinear discriminant functions^[15-19], development of such functions without user intervention is computationally intensive. Herein, a means to automatically classify celiac vs control image sequences using quantitative texture and oscillation variables is described using automata-based polling^[20].

MATERIALS AND METHODS

Clinical procedure and data acquisition

Retrospective videocapsule endoscopy data was obtained from 9 celiac patients and 7 control patients. In all except one patient, six biopsy specimens were obtained during endoscopy and then analyzed using light microscopy. In one hemophiliac patient, biopsies were not obtained. The celiac patients had recently begun a gluten-free diet, except for one patient with hemophilia and positive anti-endomysial antibody who had not yet started the diet. These patients had a diagnostic biopsy with Marsh grade II-IIIc lesions, and positive serology for celiac disease upon diagnosis. These patients were still considered to have active celiac disease due to the fact that a period of months is often needed for the diet to cause a reduction in small intestinal villous atrophy^[1-4].

For the videocapsule endoscopy study, informed consent was obtained. Exclusion criteria were age under 18 years, history of or suspected small bowel obstruction, dysphagia, presence of electromedical implants, previous gastrointestinal surgery, pregnancy, or nonsteroidal anti-inflammatory drug use during the previous month. For analysis, only complete videocapsule endoscopy studies, reaching the colon, were used. The study was approved by the Internal Review Board at Columbia University Medical Center, with all patients being evaluated from May 1, 2008 to July 31, 2009.

The PillCam videocapsule (ver. SB2, 2007, Given Imaging, Yoqneam, Israel)^[21] was used for imaging. The device includes a recorder unit, battery pack, wireless interface, and real-time viewer. The capsule acquires digital image frames at a 2/second rate, with a resolution of 576 × 576 pixels, and it is a single-use pill-sized device^[21]. For each patient undergoing the procedure, abdominal leads were placed on the upper, mid, and lower abdomen, and a belt containing the data recorder was positioned at waist

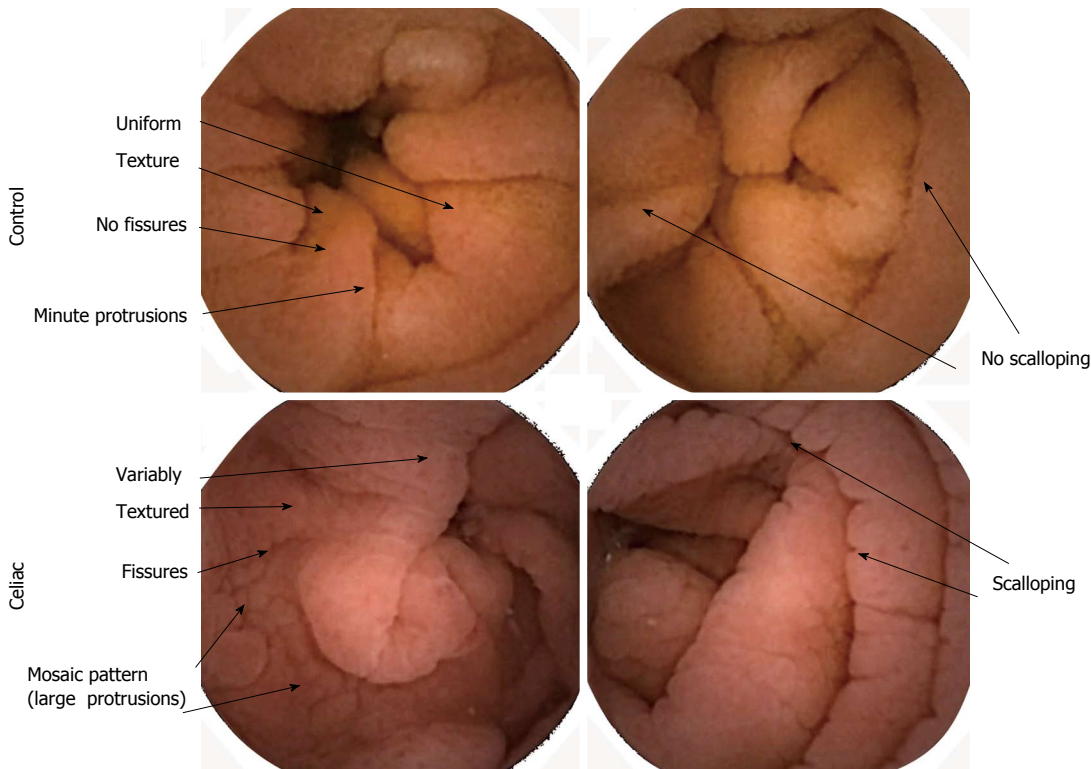


Figure 1 Color images from videocapsule device. Differences in celiac images where villous atrophy is present are shown vs control. Control images have a more uniform texture at the mucosal surfaces. Celiac surfaces have a rougher appearance, with more fissuring, large protrusions, and scalloping along the folds.

level. All subjects swallowed the videocapsule with radio transmitter in the early morning with approximately 200 cc's of water and 80 mg simethicone after an overnight fast without bowel preparation. Subjects were allowed to drink water two hours after capsule ingestion, and to eat a light meal four hours after capsule ingestion. The recorder was then removed, and the data downloaded to a HIPAA-compliant PC-based computer console equipped with RAPID software (ver. 5, 2008, Given Imaging, Yonqneam, Israel). The RAPID software was used for review and clinical report generation during the videocapsule endoscopy studies. Videos were interpreted by three experienced gastroenterologists. Selected video clips, 200 image frames in length (100 s of data), were exported to external media without patient identifiers for quantitative analysis. Images were acquired immediately distal to the pylorus corresponding to the proximal duodenum (location 1). The total small bowel transit time of the videocapsule was divided into tertiles. Video clips were also acquired from each of the three tertiles for each patient (locations 2, 3, and 4, roughly corresponding to the distal duodenum, the jejunum, and the proximal ileum, respectively).

Data preprocessing

From each color videoclip, 200 grayscale images (*i.e.*, 256 brightness levels, 0 = black, 255 = white) were extracted using Matlab Ver. 7.7, 2008 (The MathWorks, Natick, MA, United States). The image data were ported into software created by the authors, which was coded using the Intel Visual Fortran Compiler (ver. 9.0, 2005, Intel

Corporation, Santa Clara, CA, United States).

Implementation of automata-based polling

A procedure termed automata-based polling^[20] was implemented for analysis of videocapsule images. Automata are defined as functional nodes in a computational network, and they are used for quantitative analysis of a physiological system. At each node, a calculation is done based on a predefined set of rules and equations. Quantitative measurements devised previously were used to develop the network of automata for polling^[15-19]. The following methods were used:

Texture analysis: Texture analysis^[15] is based on measurement in 10×10 subimage regions from each 576×576 pixel image in the sequence, excluding edge pixels. Texture was defined by the measurement of standard deviation in pixel grayscale level in each subimage. The average grayscale level (brightness) and the standard deviation in grayscale level (image texture) of each subimage were averaged for all subimages in each image. The mean in brightness and texture over 200 frames (100 s) were used as automata measurements. It was expected that brightness would decrease with increase in abnormal features due to villous atrophy in active celiac images. Similarly, it was expected that texture would increase in celiac patient images due to heterogeneity in the mucosal surface characteristics. In Figure 1 are shown examples of control and celiac images in color. The control images have uniform texture, no fissures, and minute protrusions. There are few folds and no scalloping of folds. In

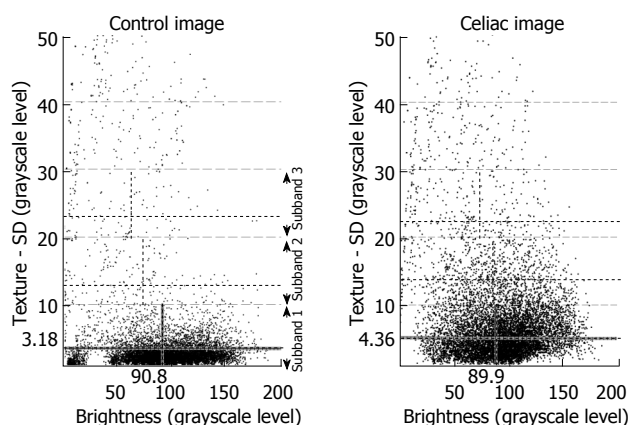


Figure 2 The method of using subbands in the standard deviation of image texture. Subbands are shown to the right of the control scatterplot. Mean values for each of the two variables are noted as hatched lines in each subband. The subband characteristics differ in celiac vs control videoclip series. In the control scatterplot the points are concentrated at low values of standard deviation in texture. In the celiac scatterplot the points are concentrated at higher values of standard deviation in texture. Thus the celiac image data has a greater variability of pixel gray level, which can be used to distinguish it from the control image data.

contrast, the celiac images have variable texture, presence of fissuring, and a mosaic pattern of large protrusions. There are more folds and scalloping of folds.

A third parameter was derived from the variability in frame-to-frame mean image brightness over the sequence of 200 images. The largest peak in the frequency spectrum of this measurement is termed the dominant frequency^[15]. Its inverse, the dominant period, was used as a third automaton measurement, and it is reflective of oscillations in image brightness over the 200 image sequence. Thus three automata were developed from the texture analysis method. Mean values for celiac and control from the prior study^[15] were used to develop threshold levels for classification. The threshold levels used were the midpoints between celiac and control data. An input videoclip sequence with a measured value closer to the celiac mean as compared with the threshold level would be counted as a vote for celiac. An input videoclip sequence with a measurement value closer to the control mean as compared with the threshold level would be counted as a vote for control.

Extraction from texture subbands: These measurements are made by plotting the brightness and texture of individual subimages. In the scatterplot, subimage values for all 200 images are included. The scatterplot is then divided into subbands. This is shown in Figure 2. Subband 1 is defined as including those subimages having a texture of 0-10 as measured by the standard deviation in pixel brightness. The average texture and the average brightness level within this subband, shown as hatched lines in the figure, along with the number of subimage values contained in the subband, are used as measurement values. This is repeated for subband 2 (texture of 10-20 as measured by the standard deviation in pixel brightness)

and subband 3 (texture of 20-30 as measured by the standard deviation in pixel brightness). Thus there are 9 measurements in all, 8 of which were used for automata. The texture for subband 3 was not used as an automaton, since the mean values from previous data for celiac and controls overlapped. Threshold levels for classification of celiacs vs controls were determined from previous data^[16]. The scatterplots of Figure 2 suggest that celiacs tend to have greater texture in the 0-10 subband, which is the subband consisting of most of the subimages. Also, as shown in Figure 2, celiacs tend to have less total pixels in the 0-10 subband but more total pixels in the 10-20 and 20-30 subbands, suggesting that celiac subimages have greater texture variability (their presence is at the higher variability subbands) as compared with controls.

Motility estimation: The darkest 10000 pixels per image were selected as an approximation of the view along the luminal axis of the small intestine. Variation in the centroid of this region (mean pixel location along the x and y axes), and variation in the maximum width of the region, were used as estimates of motility. The threshold values for the three automata to distinguish celiac from control data were based on a prior study^[17]. In the prior study it was found that celiacs tend to have more variability in the x and y position of the lumen, perhaps due to irregular motility.

Volumetric method: Two-dimensional images were converted to three dimensions using shape-from-shading principles^[18]. The third dimension is formed according to the grayscale level of each pixel. The principle is shown in Figure 3. Darker pixels and darker image regions are at greater depth along the z-axis in the three-dimensional representation at right, while brighter pixels and image regions are at shallower depth. Examples of corresponding locations in two and three dimensions are noted by asterisks. The text at left in the two-dimensional image is shown for reference in the three-dimensional representation. Based on the three-dimensional structure, a syntax was developed to detect and measure luminal wall protrusions. Protrusions were quantified according to their height, width, and number per image. Means and standard deviations for each 200 image sequence were used as automata values. Threshold values for polling were obtained from a prior study^[18]. In this study it was shown that active celiac patients tend to have less protrusions per image, and that these protrusions are greater in width and height, and in the standard deviation, or variability, in the width and height dimensions^[18]. This may be due the blunted and perhaps clumped nature of villi when there is atrophy.

Image transformation to basis images: Transformed images contain salient features from the sequence of original videocapsule images and are termed basis images^[19]. The purpose of transformation is to retain repetitive components in the sequence of images, while

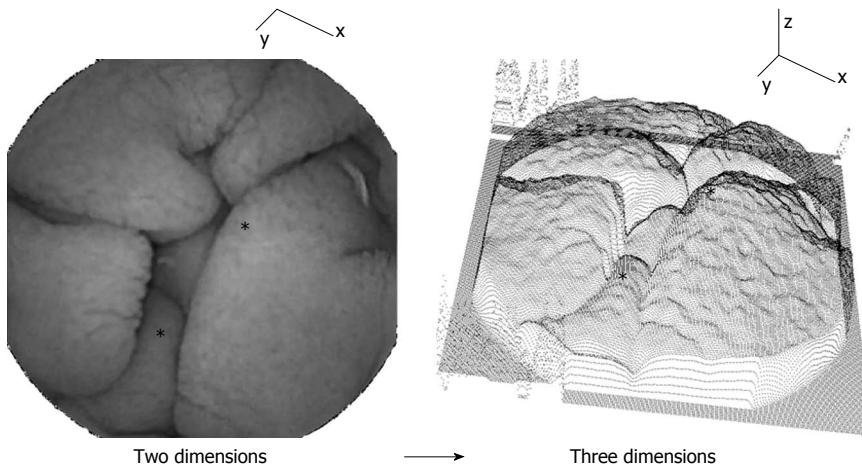


Figure 3 Image transformation from two to three dimensions. Coordinate axes are shown for reference. Examples of corresponding landmark locations are noted by asterisks. The gray levels of the two-dimensional endoscopic image at left are converted to a depth along the z axis in the three-dimensional projection at right. The characteristics of the surface protrusions in the three-dimensional image are used for distinguishing celiac from control patient data.

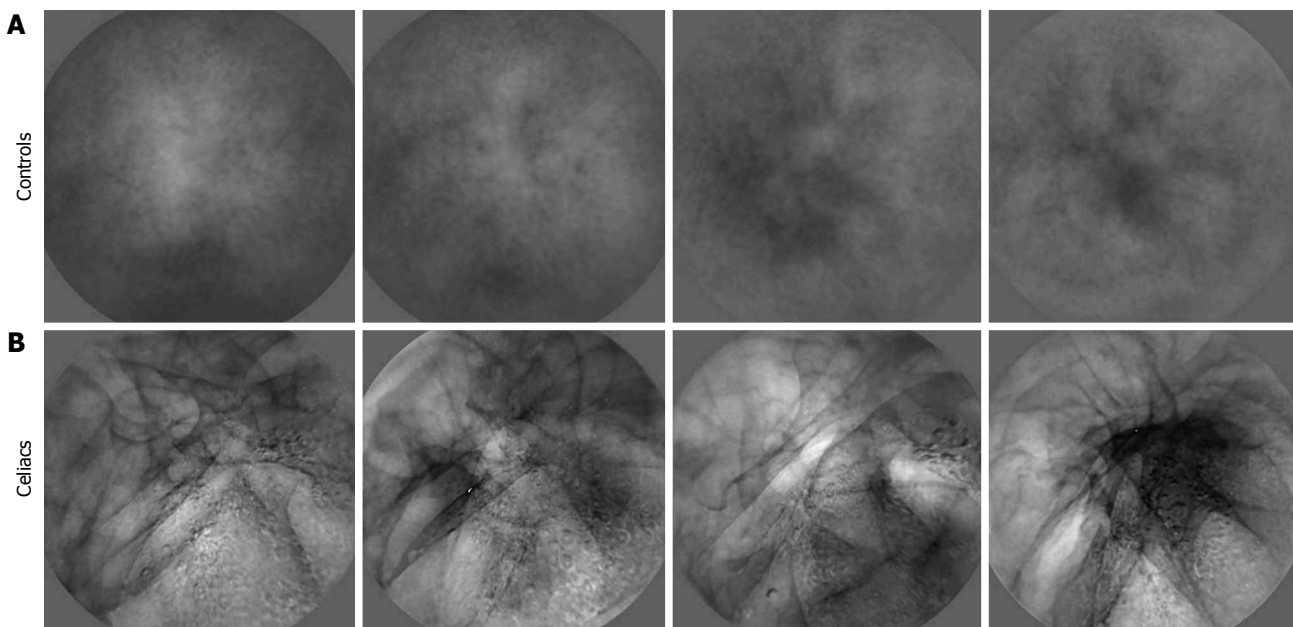


Figure 4 Examples of basis images derived from celiac vs control videoclip series. A: Control; B: Celiacs. The celiac basis has more heterogeneous structure. There are dark lines running through the celiac basis images as well as black and white blotches. In contrast, the control basis images are mostly uniform, with only diffuse features being evident.

removing noise and extraneous substances such as air bubbles and opaque fluids^[19]. Analysis of basis images rather than the original images makes the measurements more robust to features that were not a part of the actual luminal surface. Examples of basis images are shown in Figure 4. Note that the control basis images appear smoother and with less change in content as compared with the celiac basis images. The control basis contains more uniform homogeneous structure. The celiac basis images vary substantially in content and brightness. These basis images are indicative of the original salient content in each series of images. The parameters measured from basis images were the mean texture and standard deviation in brightness over the basis image series. The domi-

nant period was also measured, as calculated from the original 200 image sequence. A separate spectrum was constructed for each x, y pixel location (576×576 pixels in total)^[19]. These separate spectra were then averaged to form a mean spectrum from which the dominant period was determined. An example is shown in Figure 5. Control spectra generated from image series acquired from locations 3 and 4 have highest peak (dominant period) at 4.0-4.5 s. Celiac spectra generated from image series acquired from locations 3 and 4 have highest peak (dominant period) at 6-8.5 s. This was typical of all spectra-celiacs tended to have longer dominant periods, perhaps due to an increase in motility at areas of injury. The threshold values for vote-casting to classify the data were

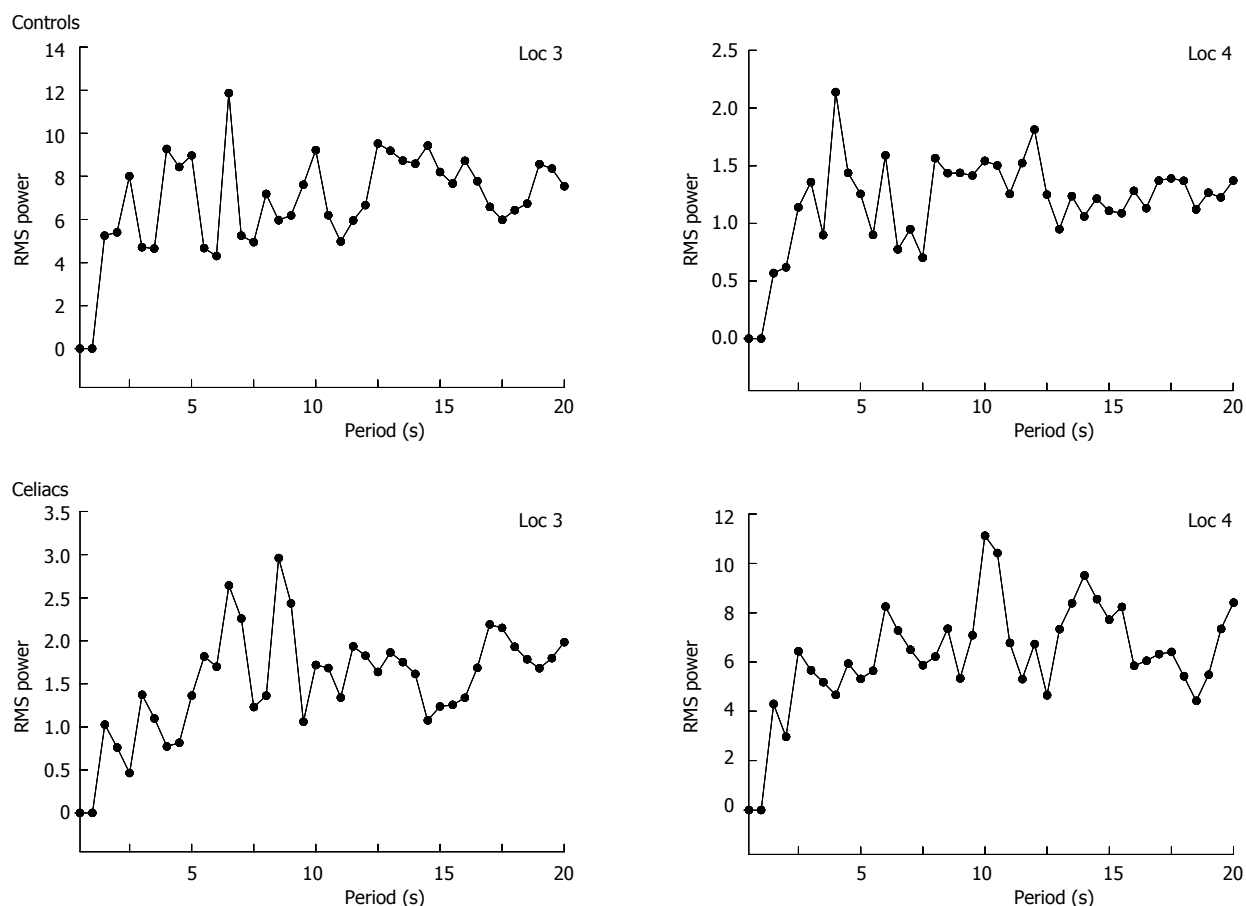


Figure 5 Examples of frequency spectra for celiac vs control. The dominant period (DP) is the highest peak in the physiologic range, taken as 1-20 s per oscillation. The graphs are shown for locations 3 and 4 in the small intestine. In the control patient the DP is 6 and 5 s for location 3 and 4, respectively. In the celiac patient the DP is 9 and 10 s for location 3 and 4, respectively. Thus the DP is higher for the celiac patient.

again midpoints between means for celiacs and controls from prior data^[19].

Overall a total of 24 automata from the five measurement methods outlined above were incorporated as functional nodes into the computational network. Each automaton was given one vote, and all automata were then polled to decide whether the sequences of images being analyzed was acquired from a patient with active celiac disease or not. Thus there were 24 vote-casting nodes, each having equal weight.

Statistical analysis

Votes for celiac and for control were tallied at all four intestinal levels for both celiac and control video clips. Summary results in terms of the number of votes cast were also expressed as mean \pm SD, and the statistical significance based on the unpaired *t*-test was determined for each small intestinal level (SigmaPlot 2004, ver. 9.01, Systat Software, Chicago, IL, United States). The sensitivity, specificity, and accuracy of the method was then determined. The sensitivity was defined as the number of videoclip image sequences determined to be celiac out of the total number of actual celiac video clips that were classified. The sensitivity was defined as the number of video clips determined to be controls out of the total

number of actual control videoclip sequences that were classified. The accuracy was defined as the total number of correct classifications out of the total number of video clips classified. Video clips that were not classified by the automata-based polling protocol were not included in the sensitivity, specificity, and accuracy statistical calculations. The statistical calculations were done separately for each of the small intestinal locations 1-4, and also for all four locations combined.

RESULTS

Automata-based voting and prediction are summarized in Table 1 for celiac and control patients. Votes are shown for locations 1 to 4, and by patient. More votes in the celiac as compared with the non-celiac column are predictive of a celiac patient, while more votes for non-celiac is predictive of a control patient. A tie indicates that no prediction was made. For most locations and patients, prediction by the automata-based polling protocol was correct. All predictions were correct for Marsh type IIIc celiac patients. However for the two celiac patients with Marsh type II pathology, prediction was incorrect at two locations, there was no prediction at location 4, and at only one location out of four was the prediction correct.

Table 1 Number of votes cast by automata, celiac patient data

Mar	C1	N1	Vote	C2	N2	Vote	C3	N3	Vote	C4	N4	Vote
Celiac patients												
III C	13	11	C	13	11	C	20	4	C	18	6	C
III C	13	11	C	16	6	C	17	7	C	16	8	C
III C	13	11	C	21	3	C	13	11	C	15	9	C
III A	17	7	C	16	8	C	19	5	C	14	10	C
III A	16	8	C	16	8	C	14	10	C	12	12	-
ND	16	8	C	17	7	C	16	9	C	12	12	-
III A	14	10	C	15	9	C	9	15	N	12	12	-
II	10	14	N	14	10	C	9	15	N	12	12	-
II	19	5	C	10	14	N	6	18	N	12	12	-
Mean \pm SD	14.56 \pm 2.70	9.44 \pm 2.70	$P = 0.022$	15.33 \pm 3.00	8.44 \pm 3.13	$P = 0.009$	13.67 \pm 4.85	10.44 \pm 4.80	$P = 0.345$	13.67 \pm 2.24	10.33 \pm 2.24	$P = 0.056$
Control patients												
0	9	15	N	11	13	N	5	19	N	8	16	N
0	9	15	N	8	16	N	6	18	N	8	16	N
0	10	14	N	12	13	N	9	15	N	9	15	N
0	11	13	N	10	14	N	4	20	N	11	13	N
0	16	8	C	10	14	N	9	15	N	6	18	N
0	16	8	C	11	13	N	10	14	N	9	15	N
0	10	14	N	10	14	N	10	14	N	15	9	C
Mean \pm SD	11.57 \pm 3.10	12.43 \pm 3.10	$P = 0.727$	10.29 \pm 1.25	13.86 \pm 1.07	$P = 0.006$	7.57 \pm 2.51	16.43 \pm 2.51	$P = 0.003$	9.43 \pm 2.88	14.57 \pm 2.88	$P = 0.056$

Automata vote tallies for celiac (C) and non-celiac controls (N). The number of votes for each are shown for small intestinal levels 1, 2, 3, and 4. Vote = the overall vote for celiac, non-celiac, or tie (-) based on the tally for each. The vote tallies for celiac patients with villous atrophy and control patients lacking villous atrophy confirmed by intestinal biopsy. The Marsh score based on the intestinal biopsy is given (Mar) except in one patient who was a hemophiliac it was not determined (ND). Means and standard deviations are provided in the lower two rows, with significances based on the paired *t*-test shown.

For two of the Marsh type IIIA celiac patients, and for the patient lacking biopsy, no prediction was also made at location 4, suggesting that images acquired from this location (ileum) are more difficult to evaluate, or that there is a lesser degree of villous atrophy, as compared with more proximal small intestinal locations. The results for control patients are shown in Table 1. In 4/7 control patients, predictions at all four levels were correct, indicating no celiac disease. In 3/7 control patients, prediction at three of the four locations was correct.

The mean and standard deviations for number of votes cast by automata are noted in the last row of each portion of the table. The significance of the difference based upon the paired *t*-test is also provided. At intestinal levels 1 and 2, there is significance for all but level 1 of control patients. At intestinal levels 3 and 4, there is significance only at level 1 of control patients. Thus there is a tendency for greater significance in the automated classification procedure at more proximate levels of the small intestine as compared to distal levels. When the data of Table 1 was pooled from all levels, for actual celiacs there was a mean of 14.31 ± 3.28 celiac votes cast, *vs* 9.67 ± 3.31 control votes cast ($P < 0.001$). When the data of Table 1 was pooled from all levels, for actual controls there was a mean of 9.71 ± 2.81 celiac votes cast *vs* 14.32 ± 2.79 control votes cast ($P < 0.001$).

The sensitivity, specificity, and accuracy of the automata-based polling protocol described in this study are shown in Table 2. At top are the results for sensitivity. Provided are the values for each method type alone and also based on location, as well as the value for data pooled from all locations. The method of first transform-

ing the data into a series of basis vectors had the highest sensitivity at 93.8% (Table 2), while textural measurement without transformation being the second most sensitive method, at 77.8%. The other methods had approximately the same sensitivity. Values for specificity are also shown in Table 2. For data pooled from all locations, the subband method is the most specific at 76.0%. The transformation into basis vectors is least specific at 27.8%. The accuracy of the methods are also shown in Table 2. The transformation into basis vectors method is the most accurate at 70.8% for pooled data. The texture, subband, and volume methods have approximately equal accuracy overall.

In Table 2 at the bottom is shown the overall sensitivity, specificity, and accuracy of the automata-based polling protocol. Similar efficacy is evident at each small intestinal location. For pooled values from all locations, the overall sensitivity of vote-casting was 83.9%, the specificity was 92.9%, and the accuracy was 88.1%.

DISCUSSION

Videocapsule data was acquired from the small intestine of celiac patients with biopsy-proven active disease, and from control patients without mucosal lesions. Using an automata-based polling protocol to classify celiac *vs* control video clips, the overall specificity and accuracy were 92.9% and 88.1%, with the sensitivity being 83.9%. The method of transformation to basis vectors had the best overall sensitivity and accuracy for prediction, although the specificity using this method was reduced. Several tie votes were cast at location 4 (ileum) suggesting that

Table 2 Statistics of automata polling to correctly classify videocapsule data

Sensitivity	1 st	2 nd	3 rd	4 th	All locations
Sensitivity					
Texture	88.9	88.9	55.6	77.8	77.8
Subband	55.6	50.0	42.9	83.3	56.7
Motility	42.9	100.0	50.0	37.5	84.2
Volume	44.4	77.8	55.6	44.4	55.6
Basis	100.0	100.0	75.0	100.0	93.3
Specificity					
Texture	0.0	42.9	71.4	71.4	46.4
Subband	80.0	83.3	71.4	71.4	76.0
Motility	100.0	25.0	83.3	60.0	64.7
Volume	71.4	85.7	85.7	71.4	78.6
Basis	0.0	33.3	100.0	40.0	27.8
Accuracy					
Texture	50.0	68.8	62.5	75.0	64.1
Subband	64.3	64.3	57.1	76.9	65.4
Motility	55.6	70.0	64.3	46.2	58.7
Volume	56.3	81.3	68.8	56.3	64.1
Basis	50.0	80.0	81.8	76.9	70.8
Overall					
Sensitivity	88.9	88.9	66.7	100.0	83.9
Specificity	85.7	100.0	100.0	85.7	92.9
Accuracy	87.5	93.8	81.3	90.9	88.1

The sensitivity, specificity, and accuracy of the method at locations, and for all locations combined, separated by the measurement type (texture, subband coding, motility, volumetric analysis, and reconstruction using basis vectors).

videocapsule images acquired from this region are less differentiable as being active celiac or control data. Prediction using the automata-based polling protocol is an improved technique because votes are polled from many independent automata. Although extraneous features and random and phasic noise may degrade quantitative comparisons of videocapsule data, the methodology has been shown to be relatively robust to these external influences^[22,23].

As compared to prior analyses^[15-19], the automata-based polling protocol tended to improve prediction. Although the methods as introduced previously tended to be quite predictive of celiac and control patients, they made use of nonlinear discriminant functions which were specifically tailored to the data at hand. This previous methodology was computationally intensive and was developed for a specific data set. The texture method, the subband method, and the motility method by themselves all make use of manually-derived three-dimensional classifiers and nonlinear discriminant functions^[15-17]. In contrast, the automata-based polling protocol described in this study does not use three-dimensional classifiers nor complex nonlinear discriminant functions. Rather, each measurement method is used independently for calculation. The threshold for determining whether the measurement is likely to have been from data acquired from an active celiac or a control patient was based on a predetermined threshold level from data analyzed previously. Pooled voting from all measurements was used for prediction, making the method robust to outliers in the

individual measurements.

Other measurement methods may be useful to incorporate into the automata polling procedure for improved efficacy. These include texture-based methods^[24-28]. Yet equally important will be the need for advances in videocapsule technology^[29-32] and image resolution^[33-36].

Limitations

The number of video clips analyzed was relatively small, and validation should be done in a prospective double-blinded study with larger data set. Our results suggest in part that classification of celiacs *vs* controls can be used for dynamic estimates of wall motility. Inclusion of a control group with severe intestinal motility disorders would be helpful for validation. The number of automata used for classification was 24. Classification accuracy may increase with a larger computational network, the subject of future study. The technique presented in the study presumed that camera angle and distance to the mucosal surface is uniform, and that coverage of the surface area of the small intestinal lumen is relatively constant during transit of the videocapsule. However, continual variation in these parameters actually occurs. These variations may act as random and phasic noise to reduce accuracy in quantitatively comparing celiac *vs* control videoclip images. Yet, these quantitative methods have been shown to be relatively robust to additive random and phasic noise^[22]. Removal of extraneous image features prior to analysis^[23] can potentially improve efficacy further. Capsule motion may also be erratic, further limiting analysis. The study was also performed with only one type of capsule endoscope and it is unclear if these results would be different with the use of a different capsule endoscopy system. Since there was no gold standard of biopsy specimen for levels 3 and 4 analysis, villous atrophy may have been absent from these regions in celiac patients, which would result in classification error. The findings were determined with a relatively small patient population, and should be confirmed in a larger study.

In conclusion, video clips from four small intestinal locations in the duodenum, jejunum, and ileum can be used to differentiate data acquired from active celiacs from controls. Several methods that were introduced previously, namely texture-based analysis, use of subbands, syntactic analysis of volumetric properties, estimation of motility, and use of transformed basis vectors to extract salient information, were all found to be useful for prediction. The system was implemented as an automata-based polling protocol, with pooling of the votes cast from a network of 24 automata. The findings of this study suggest that the technique may be useful for discerning images of celiac patients with villous atrophy from images of control patients lacking atrophy, though this must be confirmed with a larger data set that includes different Marsh grades of intestinal damage. The sensitivity of the method was less accurate due to the fact that Marsh type II celiac patients were not as readily discerned by the quantitative analysis.

COMMENTS

Background

In celiac disease patients and in other patients with gastrointestinal malady there may be atrophy of the small intestinal villi. Changes in the villi and other abnormalities of the intestinal mucosa may be detectable by quantitative analysis of videocapsule images.

Research frontiers

Quantitative biomedical image processing is becoming an important means to assist gastroenterologists during their evaluation of videocapsule images for the detection of gastrointestinal abnormalities.

Innovations and breakthroughs

In this study an automated, unbiased method was developed to quantify changes in videocapsule images of the small intestine. The method was found useful to distinguish images of celiac disease patients with biopsy-proven villous atrophy, vs control patients lacking villous atrophy.

Applications

The method is potentially useful as a real-time analysis tool during videocapsule image acquisition and playback at the clinical analysis console. The degree of abnormality can be posted on-screen with each image in the set of patient data.

Terminology

The method determines the degree of abnormality in videocapsule imagery by polling of specialized measurement automata. Each automaton is an independent measurement that is calculated without user intervention. By referring to threshold values from prior analysis, each automaton casts a vote as to whether their particular measurement value is indicative of abnormality, and the votes are tallied, or pooled. Classification as to whether villous atrophy is present or not at each small intestinal level is determined by which of the two classes garners the greater number of votes.

Peer review

This study outlines an approach for analysis of videocapsule endoscopy data to assess patients with celiac disease. In particular, the benefit of automated quantitative analysis is investigated. It is concluded from the findings that the method is useful in the detection of villous atrophy, especially in proximal locations of the small intestine.

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Reliability in endoscopic diagnosis of portal hypertensive gastropathy

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Abstract

AIM: To analyze reliability among endoscopists in diagnosing portal hypertensive gastropathy (PHG) and to determine which criteria from the most utilized classifications are the most suitable.

METHODS: From January to July 2009, in an academic quaternary referral center at Santa Casa of São Paulo Endoscopy Service, Brazil, we performed this single-center prospective study. In this period, we included 100 patients, including 50 sequential patients who had portal hypertension of various etiologies; who were previously diagnosed based on clinical, laboratory and imaging exams; and who presented with esophageal varices. In addition, our study included 50 sequential

patients who had dyspeptic symptoms and were referred for upper digestive endoscopy without portal hypertension. All subjects underwent upper digestive endoscopy, and the images of the exam were digitally recorded. Five endoscopists with more than 15 years of experience answered an electronic questionnaire, which included endoscopic criteria from the 3 most commonly used Portal Hypertensive Gastropathy classifications (McCormack, NIEC and Baveno) and the presence of elevated or flat antral erosive gastritis. All five endoscopists were blinded to the patients' clinical information, and all images of varices were deliberately excluded for the analysis.

RESULTS: The three most common etiologies of portal hypertension were schistosomiasis (36%), alcoholic cirrhosis (20%) and viral cirrhosis (14%). Of the 50 patients with portal hypertension, 84% were Child A, 12% were Child B, 4% were Child C, 64% exhibited previous variceal bleeding and 66% were previously endoscopic treated. The endoscopic parameters, presence or absence of mosaic-like pattern, red point lesions and cherry-red spots were associated with high inter-observer reliability and high specificity for diagnosing Portal Hypertensive Gastropathy. Sensitivity, specificity and reliability for the diagnosis of PHG (%) were as follows: mosaic-like pattern (100; 92.21; High); fine pink speckling (56; 76.62; Unsatisfactory); superficial reddening (69.57; 66.23; Unsatisfactory); red-point lesions (47.83; 90.91; High); cherry-red spots (39.13; 96.10; High); isolated red marks (43.48; 88.31; High); and confluent red marks (21.74; 100; Unsatisfactory). Antral elevated erosive gastritis exhibited high reliability and high specificity with respect to the presence of portal hypertension (92%) and the diagnosis of portal hypertensive gastropathy (88.31%).

CONCLUSION: The most suitable endoscopic criteria for the diagnosis of PHG were mosaic-like pattern, red-point lesions and cherry-red spots with no subdivisions,

which were associated with a high rate of inter-observer reliability.

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Key words: Endoscopy; Cirrhosis; Portal hypertension; Portal hypertensive gastropathy; Stomach

Core tip: This article proposes a simplified approach for the diagnosis of portal hypertensive gastropathy, considering the presence or the absence of mosaic-like pattern, red point lesions and cherry-red spots, without subdivisions, as those criteria exhibit high agreement among observers and high specificity. This simplified approach is useful for future research on the natural history of this disease and its related factors, thus helping to clarify some of the current controversies due to the lack of homogeneity on the diagnostic criteria of portal hypertensive gastropathy.

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INTRODUCTION

Portal hypertensive gastropathy (PHG) is characterized by an alteration in gastric mucosa that causes digestive hemorrhage in patients with portal hypertension (PH) of any etiology. Its incidence varies in the medical literature from 4% to 80% owing to a lack of consensus on endoscopic criteria for diagnosis^[1-6].

PHG is histologically characterized by the dilation and tortuosity of the sub mucosal vessels, the thinning of the vascular wall and the increased areas of gastric mucosa occupied by vessels^[7-11]. These alterations stem from hemodynamic modifications caused by portal hypertension syndrome and are not related to inflammatory infiltration^[7-18].

McCormack *et al*^[7] first described PHG in 1985 and proposed the first classification, attributing a risk of bleeding of 38% to 62% for severe forms and 3.5% to 31% for mild forms of PHG. Although simplified, this classification is problematic for grading intermediate endoscopic findings.

In 1994, the New Italian Endoscopy Club (NIEC) proposed an alternative classification including a moderate aspect of PHG for grading intermediate endoscopic findings^[19].

Shortly after, in 1996, the Baveno Consensus, a scoring system for the most relevant aspects of PHG (the Baveno Score System), was developed and attributed a higher risk of bleeding in patients with the severe form of PHG and an odds ratio of 2.56^[20].

The medical literature is not in agreement regarding the best classification and endoscopic criteria for diagnosing PHG, nor is there a consensus on its therapeutic management^[21-28].

The purpose of this study was to analyze reliability among endoscopists in diagnosing PHG and to determine which endoscopic criteria, from the most utilized classifications (McCormack, NIEC and Baveno), are most suitable for diagnosing PHG.

MATERIALS AND METHODS

In a prospective study, a total of 100 patients were selected from those undergoing upper digestive endoscopy between January and July 2009 at the Endoscopy Service - Santa Casa School of Medical Sciences (Santa Casa de São Paulo Medical School), São Paulo, Brazil. This study was approved by the local Research Ethics Committee, and patients were included only after signing informed consent forms.

Fifty sequential patients with portal hypertension of various etiologies previously diagnosed based on clinical, laboratory and imaging exams who presented with esophageal varices were selected (Table 1). All patients with clinical or endoscopic signs of upper hemorrhage were included in this study. A control group was formed, consisting of 50 sequential patients with dyspeptic symptoms referred for upper digestive endoscopy without portal hypertension or a previous history of hepatopathy or congestive cardiopathy, abdominal ultrasounds disclosing normal liver and spleen, and a portal vein caliber of less than 12 mm.

Exams were performed under sedation and digitally recorded. Six images were selected from recordings, consisting of two from the antrum, two from the gastric body and two from the gastric fundus (not showing varices). The images were then analyzed by five independent expert endoscopists with over 15 years of experience in our service. First, the examiners were familiarized with the standards used in this trial and subsequently evaluated the selected images of each patient while blinded to patients' clinical information. The varices were deliberately excluded from the images that were presented in sequential order to each endoscopist. The endoscopists were also blinded to each other's comments and evaluations.

An electronic questionnaire, which included endoscopic criteria from PHG classifications (McCormack, NIEC and Baveno) and recorded the presence or otherwise of elevated or flat antral erosive gastritis, was used to collect and collate the results (Figure 1). The results were independently analyzed to determine their relationship with PHG.

Figures 2-4 compare endoscopic aspects with their classifications.

Due to inconsistencies in the medical literature on the role of histological analysis of standard endoscopic biopsies for diagnosing PHG, we decided not to perform

Table 1 Group with portal hypertension and esophageal varices *n* (%)

Character	<i>n</i> = 50
Mean age (52.7 yr)	
Sex	
Male	28 (56)
Female	22 (44)
Etiology	
Alcohol	10 (20)
Schistosomiasis	18 (36)
Hepatitis B	2 (4)
Hepatitis C	5 (10)
Alcohol and schistosomiasis	1 (2)
Alcohol, schistosomiasis and Hepatitis B	1 (2)
Autoimmune hepatitis	1 (2)
Portal vein thrombosis	1 (2)
Non-alcoholic hepatic steatosis	1 (2)
Budd-Chiari Syndrome	1 (2)
Biliary cirrhosis	1 (2)
Idiopathic or not yet identified	8 (16)
Child-pugh classification	
A	42 (84)
B	6 (12)
C	2 (4)
Previous digestive bleeding	32 (64)
Previous endoscopic treatment	33 (66)
Using propanolol	25 (50)

biopsies in this study^[29-31]. Due to the absence of an established gold standard for diagnosing PHG, the statistical analysis was performed in two stages. The first stage verified the correlation between each endoscopic criterion and the presence of PH, with the group of 50 patients without PH serving as a control. The second stage determined the correlation between each endoscopic criterion and the diagnosis of PHG. The establishment of a relationship between the endoscopic criterion and the presence of PH was a prerequisite for the potential correlation between the same criterion and PHG. If any criterion demonstrated an apparent relationship with PHG but not with PH, then it was deemed logically false.

The Statistical Package for Social Sciences version 17.0 was utilized for statistical analysis, adopting a 5% level of significance on Fisher's Exact Test. Cronbach's alpha was used to determine reliability among the five endoscopists, with values between 0 and 0.60 considered Unsatisfactory, values between 0.60 to 0.69 as Satisfactory, and values between 0.70 to 1.00 as a High degree of reliability.

RESULTS

For criteria from the McCormack classification (Table 2), the mosaic-like pattern was associated with high reliability, specificity (90%) and positive predictive value (82.76%) for the presence of PH, as well as sensitivity and negative predictive values of 100% for the diagnosis of PHG. Fine pink speckling and superficial reddening both exhibited unsatisfactory reliability, as well as low specificity (86%) and high false positive values (7%) for the presence of PH. In addition, these criteria exhibited

low specificity (76.62%) and high false positive values (18%) for the diagnosis of PHG.

On the NIEC classification (Table 3), pink and red mosaic-like patterns were associated with unsatisfactory reliability, but red center mosaic-like patterns exhibited high reliability, thus defining PHG as moderate.

For criteria from the Baveno classification (Table 4), only red marks demonstrated high reliability and specificity (92%) for the presence of PH and high reliability for the diagnosis of PHG.

Table 5 depicts the results of the statistical analysis of antral erosive gastritis and its variations, flat and elevated, in relation to the presence of portal hypertension and the diagnosis of portal hypertensive gastropathy. Antral elevated erosive gastritis exhibited high reliability and high specificity with respect to the presence of PH (92%) and the diagnosis of PHG (88.31%).

DISCUSSION

The analyzed classifications (McCormack, NIEC and BAVENO) comprise several common endoscopic aspects, albeit aspects that are occasionally analyzed from different perspectives, thereby affecting the level of agreement among the observers. Others classifications have been published, including pre- and post-treatment evaluations, but these classifications have been reported without exclusive diagnostic aspects^[21-22].

The presence of any mosaic-like pattern, defined as polygonal areas with whitish reticular borders, is utilized in all three classifications studied. The McCormack Classification considers only its presence or absence but not variations in its inner polygonal area. In the present study, the mosaic-like pattern was associated with high reliability, specificity and positive predictive value for the presence of PH, as well as sensitivity and negative predictive values of 100% for the diagnosis of PHG, where its absence almost excluded this diagnosis. This finding corroborates the results of the study by Stewart *et al*^[24] in which, out of the 100 patients diagnosed with PHG, 96 exhibited mosaic-like patterns.

Based on the NIEC classification, the mosaic-like pattern is subdivided into three and classified according to the color of the inner polygonal area as either pink, red center or red. In the present study, pink and red mosaic-like patterns were associated with unsatisfactory reliability, whereas a red center mosaic-like pattern had high reliability, defining PHG as moderate. Nevertheless, the red center may also be considered a red-point lesion or a cherry-red spot, characterizing the PHG as severe, thereby rendering this stratification of the pattern ambiguous and the NIEC classification inconsistent.

The Baveno Score System subdivides the mosaic-like pattern into two aspects: mild, corresponding to a pink mosaic-like pattern, and severe, which corresponds to a red mosaic-like pattern, which as mentioned above, was found to exhibit Unsatisfactory reliability and thus low agreement among observers. Although Stewart *et al*^[24]

Figure 1 Electronic questionnaire.

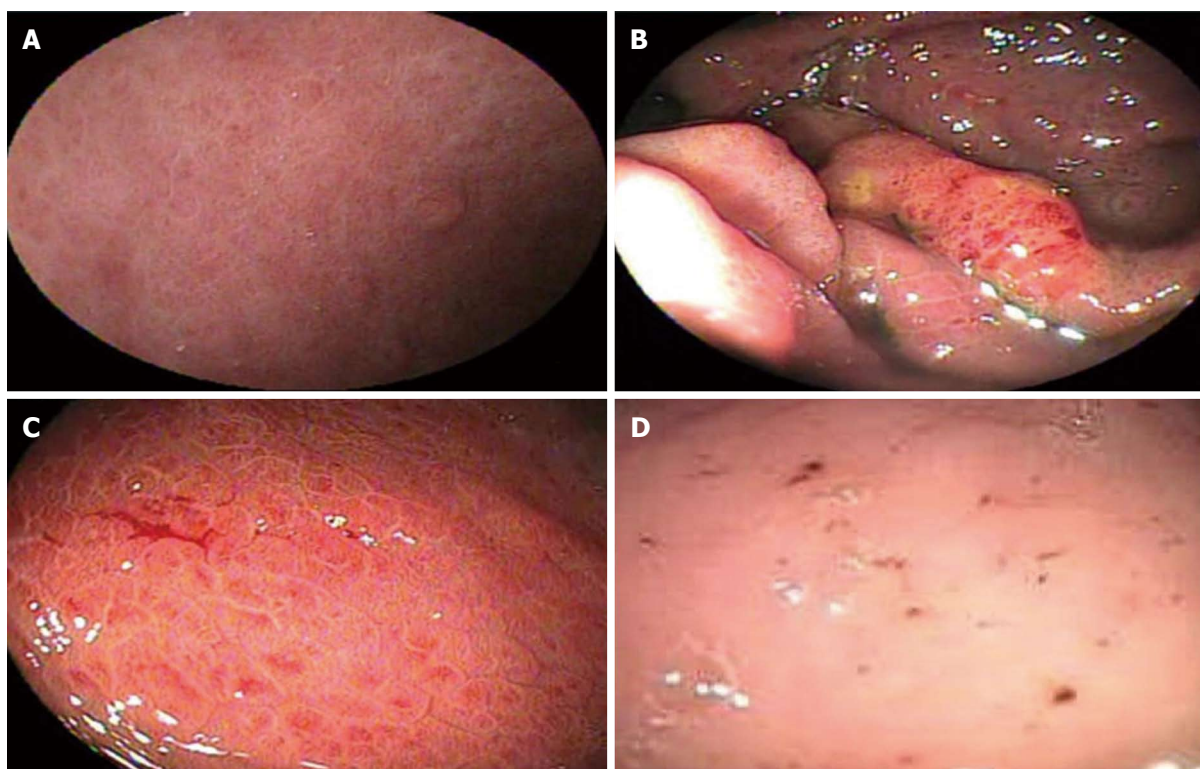


Figure 2 Endoscopic aspects of portal hypertensive gastropathy considered in the study and their corresponding classifications. A: Fine pink speckling - McCormack; B: Superficial reddening - McCormack; C: Diffuse hemorrhagic lesion - McCormack; D: Black brown spots - New Italian Endoscopy Club.

also demonstrated agreement among observers analyzing the presence or absence of the mosaic-like pattern, with a Kappa Index of greater than 0.75, concordance

decreased when this aspect was subdivided according to variation in the inner polygonal area.

The present results demonstrated that fine pink

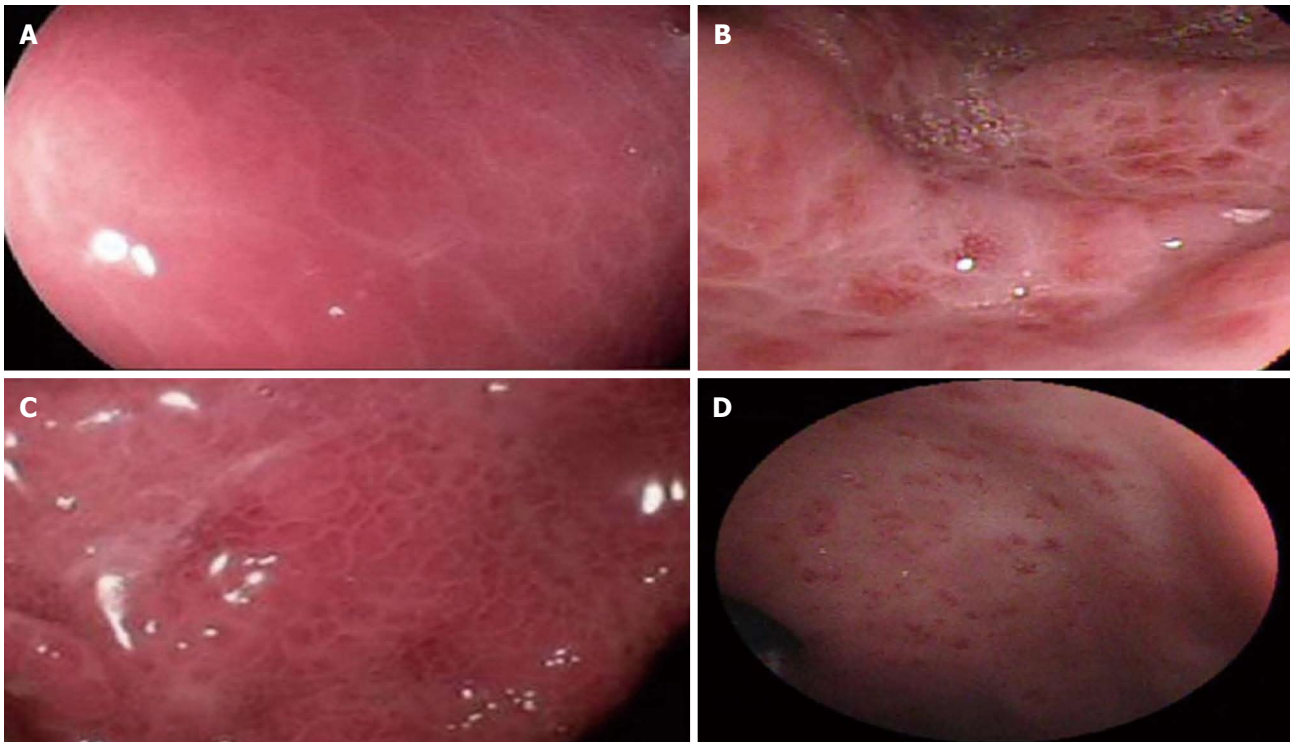


Figure 3 Endoscopic aspects of portal hypertensive gastropathy considered in the study and their corresponding classifications. A: Corresponds to “mosaic-like pattern” with different nomenclature in each classification as follows: mosaic-like pattern - McCormack; mild mosaic-like pattern - New Italian Endoscopy Club (NIEC); mild mosaic-like pattern - Baveno; B: Corresponds to “mosaic-like pattern” with different nomenclature in each classification as follows: red center mosaic-like pattern - McCormack; moderate mosaic-like pattern - NIEC; C: Corresponds to “mosaic-like pattern” with different nomenclature in each classification as follows: mosaic-like pattern - McCormack; severe mosaic-like pattern - NIEC; severe mosaic-like pattern - Baveno; D: GAVE - Baveno.

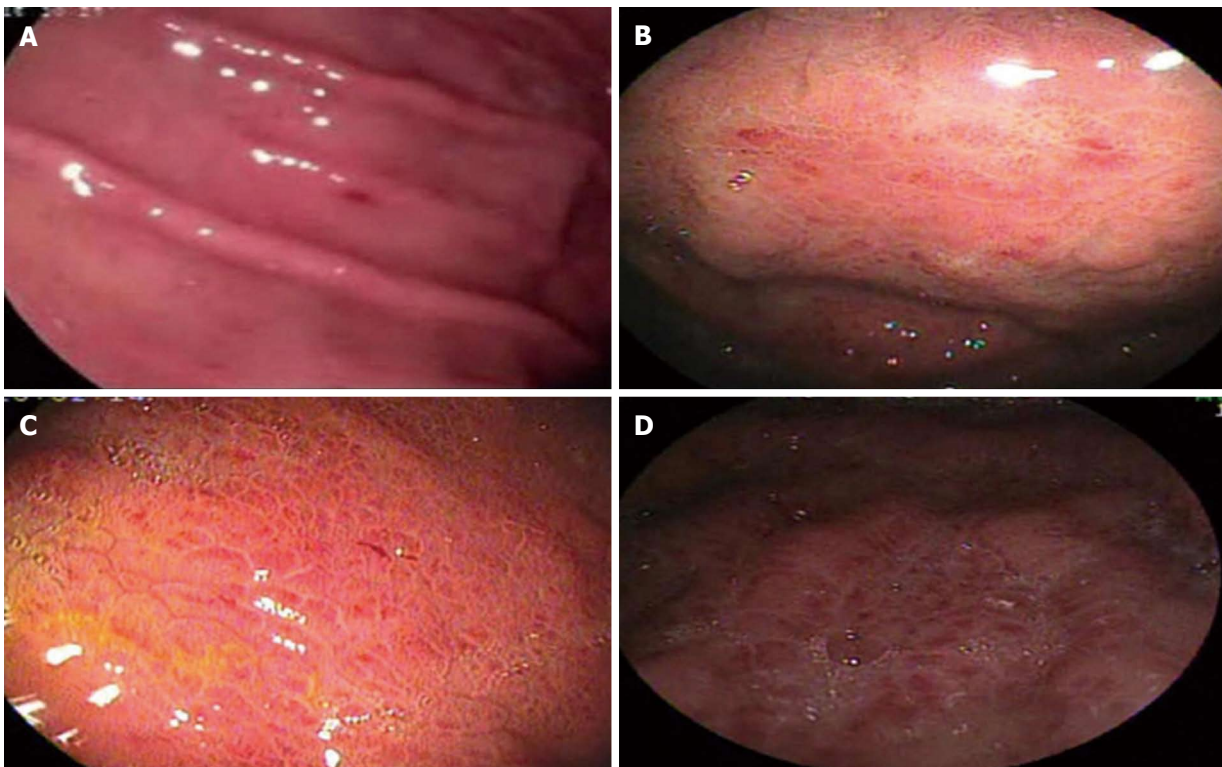


Figure 4 Endoscopic aspects of portal hypertensive gastropathy considered in the study and their corresponding classifications. A: Corresponds to “cherry-red spots” with different nomenclature in each classification as follows: discrete red spots - McCormack; cherry-red spots - New Italian Endoscopy Club (NIEC); B: Red-point lesions - NIEC; C: Isolated red marks - Baveno; D: Confluent red marks - Baveno.

Table 2 Analysis of the criteria from the McCormack classification for the presence of portal hypertension and portal hypertensive gastropathy

	Fine pink speckling		Superficial reddening		Mosaic-like pattern		Cherry-red spots		Diffuse hemorrhagic lesion	
Diagnosis	PH	PHG	PH	PHG	PH	PHG	PH	PHG	PH	PHG
Sensitivity	48.00%	56.52%	64.00%	69.57%	48.00%	100.00%	22.00%	39.13%	8.00%	17.39%
Specificity	86.00%	76.62%	80.00%	66.23%	90.00%	92.21%	98.00%	96.10%	100.00%	100.00%
PPV	77.42%	41.94%	76.19%	38.10%	82.76%	79.31%	91.67%	75.00%	100.00%	100.00%
NPV	62.32%	85.51%	68.97%	87.93%	63.38%	100.00%	55.68%	84.09%	52.08%	80.21%
Accuracy	67.00%	72.00%	72.00%	67.00%	69.00%	94.00%	60.00%	83.00%	54.00%	81.00%
False negative	26.00%	10.00%	18.00%	7.00%	26.00%	0.00%	39.00%	14.00%	46.00%	19.00%
False positive	7.00%	18.00%	10.00%	26.00%	5.00%	6.00%	1.00%	3.00%	0.00%	0.00%
Significance	$P < 0.001$	$P = 0.03$	$P < 0.001$	$P = 0.002$	$P < 0.001$	$P < 0.001$	$P = 0.002$	$P < 0.001$	$P = 0.059$	$P = 0.002$
Reliability (α)	0.430 ¹	0.430 ¹	0.532 ¹	0.532 ¹	0.799 ²	0.799 ²	0.753 ²	0.753 ²	0.574 ¹	0.574 ¹

¹Unsatisfactory; ²High. PPV: Positive predictive value; NPV: Negative predictive value; PH: Portal hypertension; PHG: Portal hypertensive gastropathy.

Table 3 Analysis of the criteria from the New Italian Endoscopy Club classification for the presence of portal hypertension and portal hypertensive gastropathy

	Pink mosaic-like pattern		Red center mosaic-like pattern		Red mosaic-like pattern		Red-point lesions		Cherry-red spots		Black-brown spots	
Diagnosis	PH	PHG	PH	PHG	PH	PHG	PH	PHG	PH	PHG	PH	PHG
Sensitivity	26.00%	52.17%	16.00%	34.78%	6.00%	13.04%	28.00%	47.83%	22.00%	39.13%	2.00%	4.35%
Specificity	90.00%	92.21%	100.00%	100.00%	100.00%	100.00%	92.00%	90.91%	98.00%	96.10%	98.00%	98.70%
PPV	72.22%	66.67%	100.00%	100.00%	100.00%	100.00%	77.78%	61.11%	91.67%	75.00%	50.00%	50.00%
NPV	54.88%	86.59%	54.35%	83.70%	51.55%	79.38%	56.10%	85.37%	55.68%	84.09%	50.00%	77.55%
Accuracy	58.00%	83.00%	58.00%	85.00%	53.00%	80.00%	60.00%	81.00%	60.00%	83.00%	50.00%	77.00%
False negative	37.00%	11.00%	42.00%	15.00%	47.00%	20.00%	36.00%	12.00%	39.00%	14.00%	49.00%	22.00%
False positive	5.00%	6.00%	0.00%	0.00%	0.00%	0.00%	4.00%	7.00%	1.00%	3.00%	1.00%	1.00%
Significance	$P = 0.033$	$P < 0.001$	$P = 0.003$	$P < 0.001$	$P = 0.121$	$P = 0.011$	$P = 0.009$	$P < 0.001$	$P = 0.002$	$P < 0.001$	$P = 0.753$	$P = 0.358$
Reliability (α)	0.569 ¹	0.569 ¹	0.727 ²	0.727 ²	0.079 ²	0.079 ²	0.752 ²	0.752 ²	0.753 ²	0.753 ²	0.408 ¹	0.408 ¹

¹Unsatisfactory; ²High. PPV: Positive predictive value; NPV: Negative predictive value; PH: Portal hypertension; PHG: Portal hypertensive gastropathy.

speckling and superficial reddening from the McCormack classification were associated with unsatisfactory reliability and, thus, the low agreement among observers. These criteria also exhibited low specificity and high false positive values for the presence of PH, as well as low specificity and high false positive values for the diagnosis of PHG. This result indicated that fine pink speckling and superficial reddening also occurred in the group without PH, possibly corresponding to enanthematous mucosal alterations unrelated to portal hypertension. McCormack *et al*^[7], in his original article, emphasized that with the exception of the cherry-red spots, the endoscopic aspects he described for the diagnosis now called PHG were indistinguishable from gastritis.

PHG is classified according to its tendency to bleed. Nonetheless, diffuse hemorrhagic lesions and black brown spots (old mucosal hemorrhage) are utilized in the McCormack and NIEC classifications. This use reveals incoherence because these aspects are, concomitantly, both a cause (PHG) and a consequence (hemorrhage). Additionally, these parameters exhibited unsatisfactory reliability in the present study due to low inter-observer agreement. Occasionally, these tenuous hemorrhages may exhibit discrete clinical manifestations^[2,18]. In our study, patients with suspected digestive bleeding were excluded. The exclusion of these cases may partly explain the low

statistical significance of these criteria.

Mucosal delimited red alterations are utilized in all three classifications. Red-point lesions are employed in the NIEC classification whereas cherry-red spots are used in both the McCormack (called discrete red spots) and NIEC classification. The Baveno score system groups red-point lesions and cherry-red spots together under red marks. We found that the presence or absence of red alterations was associated with high reliability due to high agreement among the endoscopists, high specificity and high positive predictive value in relation to the presence of PH and the diagnosis of PHG (Tables 2-4), thus demonstrating that these endoscopic aspects are related to PH and PHG.

The Baveno score system splits these parameters by grouping the alterations as either isolated or confluent. Nevertheless, there is no definition of the confluence criterion, thus leading to subjective interpretation and unsatisfactory reliability in the present study. Stewart *et al*^[24] studying patients with PHG, demonstrated high inter-observer agreement in relation to the presence or absence of red marks and a kappa index of greater than 0.75, indicating desirable agreement. However, this level became unsatisfactory when used with the confluence criterion, splitting the red marks of the endoscopic aspect into isolated and confluent categories.

Table 4 Analysis of the criteria from the Baveno classification for the presence of portal hypertension and portal hypertensive gastropathy

	Pink mosaic-like pattern		Red mosaic-like pattern		Isolated red marks		Confluent red marks		GAVE	
Diagnosis	PH	PHG	PH	PHG	PH	PHG	PH	PHG	PH	PHG
Sensitivity	26.00%	52.17%	6.00%	13.04%	30.00%	43.48%	10.00%	21.74%	8.00%	4.35%
Specificity	90.00%	92.21%	100.00%	100.00%	92.00%	88.31%	100.00%	100.00%	100.00%	96.10%
PPV	72.22%	66.67%	100.00%	100.00%	78.95%	52.63%	100.00%	100.00%	100.00%	25.00%
NPV	54.88%	86.59%	51.55%	79.38%	56.79%	83.95%	52.63%	81.05%	52.08%	77.08%
Accuracy	58.00%	83.00%	53.00%	80.00%	61.00%	78.00%	55.00%	82.00%	54.00%	75.00%
False negative	37.00%	11.00%	47.00%	20.00%	35.00%	13.00%	45.00%	18.00%	46.00%	22.00%
False positive	5.00%	6.00%	0.00%	0.00%	4.00%	9.00%	0.00%	0.00%	0.00%	3.00%
Significance	$P = 0.033$	$P < 0.001$	$P = 0.121$	$P = 0.011$	$P = 0.005$	$P = 0.0014$	$P = 0.028$	$P < 0.001$	$P = 0.059$	$P = 0.429$
Reliability (α)	0.569 ¹	0.569 ¹	0.079 ¹	0.079 ¹	0.753 ²	0.753 ²	0.558 ¹	0.558 ¹	0.514 ¹	0.514 ¹

¹Unsatisfactory; ²High. PPV: Positive predictive value; NPV: Negative predictive value; PH: Portal hypertension; PHG: Portal hypertensive gastropathy.

Table 5 Analysis of antral erosive gastritis in the presence of portal hypertension and portal hypertensive gastropathy

	Antral erosive gastritis		Antral elevated erosive gastritis		Antral flat erosive gastritis	
Diagnosis	PH	PHG	PH	PHG	PH	PHG
Sensitivity	34.00%	39.13%	26.00%	34.78%	8.00%	4.35%
Specificity	84.00%	79.22%	92.00%	88.31%	92.00%	90.91%
PPV	68.00%	36.00%	76.47%	47.06%	50.00%	12.50%
NPV	56.00%	81.33%	55.42%	81.93%	50.00%	76.09%
Accuracy	59.00%	70.00%	59.00%	76.00%	50.00%	71.00%
False negative	33.00%	14.00%	37.00%	15.00%	46.00%	22.00%
False positive	8.00%	16.00%	4.00%	9.00%	4.00%	7.00%
Significance	$P = 0.032$	$P = 0.046$	$P = 0.016$	$P = 0.012$	$P = 0.643$	$P = 0.297$
Reliability (α)	0.840 ²	0.840 ²	0.862 ²	0.862 ²	0.641 ¹	0.641 ¹

¹Satisfactory; ²High. PPV: Positive predictive value; NPV: Negative predictive value; PH: Portal hypertension; PHG: Portal hypertensive gastropathy.

Although the current study demonstrated that GAVE (Baveno score system) exhibited 100% specificity and 0% false positive results, suggesting a strong association with portal hypertension and PHG, this relationship failed to reach statistical significance. Some authors claim that PHG and GAVE are distinct entities with no correlations between them^[32-34].

Analysis of antral erosive gastritis and its variations, flat and elevated, revealed that antral elevated erosive gastritis exhibited high reliability and high specificity with relation to the presence of PH and the diagnosis of PHG, thereby suggesting an association with PHG. Assef *et al*^[35] observed a 37.5% rate of antral elevated erosive gastritis in patients with PHG. Using multivariate analysis, Auroux *et al*^[36] demonstrated that 31.2% of patients with portal hypertension had gastric erosions related to PHG and not to the presence of *Helicobacter pylori*, alcohol abuse, Child classification or the severity of esophageal varices. Further studies including histological analyses are warranted to confirm this association.

All endoscopic parameters analyzed exhibited low accuracy for the presence of PH (Tables 2-4). This low accuracy is due to the low negative predictive values of each separate parameter. Therefore, it is important to analyze all of the endoscopic parameters in conjunction with PH.

Regarding criteria for the diagnosis of PHG, the mosaic-like pattern, pink mosaic-like pattern, mosaic-

like pattern with red center, cherry-red spots and red-point lesions showed accuracies of 94%, 83%, 85%, 83% and 81%, respectively. Of these criteria, only the mosaic-like-pattern offered high sensitivity (100%). As explained earlier, the subdivision of the mosaic-like pattern leads to low inter-observer agreement, whereas the mosaic-like pattern with red center is an incoherent subdivision, at the same time representing a mosaic-like pattern and a red point lesion or cherry red spot.

The unsatisfactory reliability and low inter-observer agreement of the analyzed classifications corroborate the findings reported in other studies. Yoo *et al*^[25] analyzed McCormack and NIEC classifications and observed low kappa indices of 0.52 and 0.44, respectively, indicating low inter-observer agreement given that a desirable Kappa index is greater than 0.75. Stewart *et al*^[24] analyzing the Baveno classification, found an unsatisfactory rate of agreement when mosaic-like patterns and red marks were subdivided.

It is clear that all three investigated classifications have inadequate endoscopic parameters. Nevertheless, analyzing binary criteria such as the presence or the absence of the mosaic-like pattern, red-point lesions and cherry-red spots, the diagnosis of PHG yields high inter-observer agreement and high specificity. This approach can prove useful for future research on the natural history of this disease and related factors, thus helping to clarify some of the current controversies, including studies with his-

tologic findings and comparisons with the endoscopic criteria of the classifications that we have already begun.

In conclusion, the most suitable endoscopic criteria for the diagnosis of portal hypertensive gastropathy were mosaic-like pattern, red-point lesions and cherry-red spots (without subdivisions), all of which were associated with a high rate of inter-observer reliability.

COMMENTS

Background

Portal hypertensive gastropathy (PHG) is an alteration of gastric mucosa causing occult and sometimes massive digestive hemorrhage in patients with portal hypertension of any etiology.

Research frontiers

PHG remains an endoscopic diagnosis, and there are many endoscopic classifications. No histologic correspondence was proven, leading to an individual observer opinion in diagnosis and grading, with a low level of reliability among endoscopists.

Innovations and breakthroughs

The most used classifications of PHG comprise several common endoscopic aspects, albeit aspects that are sometimes analyzed from different perspectives, thereby affecting the level of agreement among observers and leading to no consensus on endoscopic diagnosis and grading.

Applications

By separating the most suitable endoscopic criteria for the diagnosis of PHG, authors found that mosaic-like pattern, red-point lesions and cherry-red spots (without subdivisions) were associated with high inter-observer reliability and should be used to simplify and standardize the PHG diagnosis and severity.

Peer review

PHG is frequently observed on an upper gastrointestinal endoscopy in patients of portal hypertension. However, there are no objective criteria to diagnose PHG, and there is no consensus on the best classification and endoscopic criteria in the medical literature. The authors have attempted to analyze the data regarding reliability of various endoscopic morphological features among different endoscopists based on the criteria of McCormack, New Italian Endoscopy Club and Baveno. The authors concluded that most suitable endoscopic criteria for the diagnosis of PHG are mosaic-like pattern, red point lesions and cherry red spot.

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Evaluation of fully covered self-expanding metal stents in benign biliary strictures and bile leaks

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Abstract

AIM: To investigate the use of fully covered metal stents in benign biliary strictures (BBS) and bile leaks.

METHODS: We studied 17 patients, at Harbor-UCLA Medical center (Los Angeles), with BBS ($n = 12$) and bile leaks ($n = 5$) from July 2007 to February 2012 that had received placement of fully covered self-expanding metal stents (FCSEMS). Fourteen patients had endoscopic placement of VIABIL[®] (Conmed, Utica, New York, United States) stents and three had Wallflex[®] (Boston Scientific, Mass) stents. FCSEMS were 8 mm or 10 mm in diameter and 4 cm to 10 cm in length. Patients were followed at regular intervals to evaluate for symptoms and liver function tests. FCSEMS were removed after 4 or more weeks. Resolution of BBS and leak was documented cholangiographically following stent removal. Stent patency can be defined as adequate bile and contrast flow from the stent and into the ampulla during endoscopic retrograde cholangiopancreatography (ERCP) without clinical signs and/or symptoms of biliary obstruction. Criterion for bile leak resolution at ERCP is defined as absence of contrast extravasation from the common bile duct, cystic duct remanent, or gall bladder fossa.

Rate of complications such as migration, and in-stent occlusion were recorded. Failure of endoscopic therapy was defined as persistent biliary stenosis or continuous biliary leakage after 12 mo of stent placement.

RESULTS: All 17 patients underwent successful FCSEMS placement and removal. Etiologies of BBS included: cholecystectomies ($n = 8$), cholelithiasis ($n = 2$), hepatic artery compression ($n = 1$), pancreatitis ($n = 2$), and Whipple procedure ($n = 1$). All bile leaks occurred following cholecystectomy. The anatomic location of BBS varied: distal common bile duct ($n = 7$), common hepatic duct ($n = 1$), hepaticojejunal anastomosis ($n = 2$), right intrahepatic duct ($n = 1$), and choledochoduodenal anastomatic junction ($n = 1$). All bile leaks were found to be at the cystic duct. Twelve of 17 patients had failed prior stent placement or exchange. Resolution of the biliary strictures and bile leaks was achieved in 16 of 17 patients (94%). The overall median stent time was 63 d (range 27-251 d). The median stent time for the BBS group and bile leak group was 62 ± 58 d (range 27-199 d) and 92 ± 81 d (range 48-251 d), respectively. All 17 patients underwent successful FCSEMS removal. Long term follow-up was obtained for a median of 575 d (range 28-1435 d). Complications occurred in 5 of 17 patients (29%) and included: migration ($n = 2$), stent clogging ($n = 1$), cholangitis ($n = 1$), and sepsis with hepatic abscess ($n = 1$).

CONCLUSION: Placement of fully covered self-expanding metal stents may be used in the management of benign biliary strictures and bile leaks with a low rate of complications.

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Key words: Bile leaks; Benign biliary stricture; Fully covered metal stents; Biliary disease

Core tip: We studied 17 patients with Benign Biliary

Strictures (BBS) ($n = 12$) and bile leaks ($n = 5$) from July 2007 to February 2012 that had fully covered self-expanding metal stents (FCSEMs) placed. Twelve of 17 patients had failed prior stent placement or exchange. After a median stent time of 63 d, we found 16 of 17 patients (94%) had complete resolution of biliary strictures and bile leaks. We reported complications in 5 of 17 patients (29%) which included: migration ($n = 2$), stent clogging ($n = 1$), cholangitis ($n = 1$), and sepsis with hepatic abscess ($n = 1$).

Lalezari D, Singh I, Reicher S, Eysselein VE. Evaluation of fully covered self-expanding metal stents in benign biliary strictures and bile leaks. *World J Gastrointest Endosc* 2013; 5(7): 332-339 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i7/332.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i7.332>

INTRODUCTION

Benign biliary diseases, including benign biliary strictures (BBS) and bile duct leaks, are common and management can be potentially challenging. BBS may occur as a result of chronic pancreatitis, postoperative anastomotic strictures following cholecystectomy and liver transplantation, choledocholithiasis, sclerosing cholangitis and other cholangiopathies^[1-3]. Complications of biliary strictures include cholangitis, secondary biliary cirrhosis and end stage liver disease (ESLD). Because of the severity of these complications urgent decompression of strictures is required.

Bile leaks occur after abdominal surgery classically following cholecystectomy, traumatic injury^[4], liver transplantation or hepatic resection^[5,6]. The most common location of bile leaks is the cystic duct stump followed by the duct of Luschka^[6]. Many of these patients require external biliary drainage or develop an internal biliary leak resulting in a biloma, peritonitis or abscess formation^[6]. The first-line intervention in treatment of bile leaks involves placement of transpapillary biliary plastic stents and/or sphincterotomy^[7,8]. Stent placement has been effective in the closure of 70%-100% of postcholecystectomy bile leaks^[8].

Complex leaks are defined as those that are refractory to endoscopic intervention with biliary sphincterotomy or plastic stent placement, bile leaks following orthotopic liver transplantation or complicated cholecystectomy with large leaks. Previous studies have shown single large diameter or multiple stents across the site of the leak are superior in complex leaks^[6,8]. Bile leaks can further be classified by endoscopic retrograde cholangiography (ERC) into low grade (leak identified only after intrahepatic opacification) or high grade (leak observed before intrahepatic opacification)^[8]. In a study by Sandha *et al*^[8] of 204 patients with bile leaks, transpapillary biliary stenting was found to be more effective than sphincterotomy alone in patients with high grade leaks.

Management of BBS includes decompression by endoscopic retrograde cholangiopancreatography (ERCP)

with sphincterotomy and stent placement, and ultimately choledochojejunostomy. Recent studies have shown that therapeutic ERC with stent placement in BBS is a potential, although not equivalent, alternative to surgery. Compared with surgery, stent placement has lower rates of stricture recurrence, lower cost, and lower overall morbidity and mortality^[9]. The standard of care for repairing bile leaks involves placement of transpapillary biliary stents with or without sphincterotomy.

Currently, plastic stents are the only Food and Drug Administration (FDA) approved therapy used in benign biliary conditions to treat biliary strictures and bile leaks. Plastic stent patency, usually 3-4 mo in malignant strictures, has been limited secondary to occlusion due to deposition of a bacterial biofilm within the stent lumen^[10,11]. Self-expanding metal stents (SEMS) provide prolonged stent patency of up to 9 mo and can be deployed from a small diameter delivery system that can expand to a large diameter (10 mm) permitting improved biliary drainage. Initially, SEMS were bare metal (uncovered) meaning they had no coating material covering the metal stent. A major challenge with uncovered SEMS was in-stent epithelial hyperplasia accounting for the difficult removability of the stents and poor long term patency^[2]. Partially covered self-expanding metal stents (PCSEMS) have had some success in BBS and bile leaks but were limited by the susceptibility to in-stent hyperplasia, migration, and difficulty in extraction due to mucosal hyperplasia at the uncovered proximal ends^[11,12]. Advances in the development of endoprosthesis led to Fully Covered SEMS (FCSEMS) which are coated circumferentially with a material that prevents stent occlusion and imbedding due to bacterial colonization, tissue hyperplasia, and tumor ingrowth thereby increasing the duration of stent patency and permitting easier stent retrieval. Moreover, FCSEMS use in BBS and bile leaks may result in fewer endoscopic sessions and not require placement of multiple plastic stents^[12]. Previous studies have shown successful outcomes of FCSEMS used in malignant biliary strictures however the data for use in benign biliary disease remains limited and conflicting (Table 1). Our studies primary aim was to evaluate the efficacy, patency and rate of complications with placement of FCSEMS for BBS and bile leaks.

MATERIALS AND METHODS

From July 2007 and February 2012, seventeen patients diagnosed at Harbor-UCLA Medical center with BBS and bile leaks who had undergone endoscopic placement of a FCSEMS were included in this study. Twelve patients were females and five patients were males; the mean age was 50.5 ± 16.5 years (range 27-77 years). Patient records were reviewed retrospectively. The most common presenting symptom among patients was abdominal pain. All strictures had brushings and biopsies to rule out malignancy. Fourteen patients had endoscopic placement of VIABIL[®] (Conmed, Utica, New York, United States) stents and three had Wallflex[®] (Boston Scientific,

Table 1 Studies reporting placement of covered metal stent in benign biliary strictures and bile leaks

Ref.	No. of patients/ No. stents	BBS or bile leaks	Etiology	Stent type	Time to removal	Results (success rate)	Complications
Benign biliary strictures							
Deviere <i>et al</i> ^[18]	20/20	BBS	CP	Wallstent FCSEMS	NA ¹	90%	Epithelial hyperplasia (2)
Cantù <i>et al</i> ^[19]	14/14	BBS	CP	pCSEMS	21 mo (median)	37.5% at 30-mo fu	Cholestasis (7), cholangitis (5), duodenal migration (2), cholecystitis (1)
Kuo <i>et al</i> ^[20]	3/4	BBS	OLT	FCSEMS	32 d (median)	100%	Septicemia (1), misplacement (1)
Kahaleh <i>et al</i> ^[21]	79/79	BBS	CP, OLT, BC, INF, surgical	pCSEMS	4 mo (median)	90% ITT 75%	Migrations (11)
Cahen <i>et al</i> ^[22]	6/6	BBS	CP	FCSEMS	3-6 mo (median)	66%	Migration (2), recurrent stricture (1)
Mahajan ^[3]	44/44	BBS	CP, gallstone related, OLT, AP, PSC	FCSEMS	3.3 mo (median)s	83% 77% ITT (3 patients died)	Post ERCP pancreatitis (1), mucousal ulceration and bleeding (1)
Garcia-Cano ^[22]	20/20	BBS	Biliary fistula, perforation of papilla, to remove uncovered stents, benign strictures, CBD stones	Wallstent FCSEMS	132 d (median)	70%	Pancreatitis (3)
Sauer <i>et al</i> ^[23]	19/19	BBS and bile leaks	Liver transplant	Wallflex	11.7 wk (mean)	79%	Proximal migration (1), distal migration (5), occlusion (1), <i>de novo</i> stricture (2)
Bile leaks							
Wang <i>et al</i> ^[24]	13	Complex bile leaks	Chole and OLT	Viabil FCSEMS	103 d	85% ITT	Mucousal ulcerations (4), <i>de novo</i> choledocholithiasis/ luminal debris (10), strictures (2)
Sandha <i>et al</i> ^[8]	97	High grade leaks	Chole	FCSEMS	42 d	100%	Post ERCP pancreatitis (2), duodenal perforation (1)
Kahaleh <i>et al</i> ^[11]	16/16	Bile leaks	Chole, OLT	Wallstent FCSEMS	3 mo	93%	Stent migration (2)
Sauer <i>et al</i> ^[23]	19/19	BBS and bile leaks	Liver transplant	Wallflex	11.7 wk (mean)	79%	Proximal migration (1), distal migration (5), occlusion (1), <i>de novo</i> stricture (2)

¹Stents not extracted in the study. OLT: Orthotopic liver transplant; Chole: Cholecystectomy; AP: Autoimmune pancreatitis; PSC: Primary sclerosing cholangitis; ITT: Intent to treat; pCSEMS: Partially covered self-expanding metal stent; FCSEMS: Fully covered self-expanding metal stent; BBS: Benign biliary strictures; CP: Cholangiopancreatography.

Mass) stents. An 8 or 10 mm diameter FCSEM Viabil[®] (Conmed, Utica, New York, United States) or Wallflex[®] (Boston Scientific, Mass) was deployed over a guidewire under endoscopic and fluoroscopic visualization across the biliary stricture or bile leak. The length of the stents varied ranging from 4 to 10 cm. When the gallbladder was present FCSEMS were placed below the cystic duct to avoid cholecystitis. All patients had undergone a biliary sphincterotomy prior to placement of FCSEMS.

Stent patency can be defined as adequate bile and contrast flow from the stent and into the ampulla during ERCP without clinical signs and/or symptoms of biliary obstruction (*e.g.*, RUQ pain/tenderness, elevated alkaline phosphatase \pm bilirubin, *ect.*). Stent placement was confirmed fluoroscopically and endoscopically. Repeat cholangiogram after stent deployment revealed the absence of a leak. Criterion for bile leak resolution at ERCP is defined as absence of contrast extravasation from the CBD, cystic duct remanent, or gall bladder fossa.

Stents were removed after at least a month, only after

liver function test (LFT) normalization and resolution of symptoms, using rat-tooth forceps or a snare. After stent removal, a cholangiogram was performed to document resolution of BBS and sealed leaks. In time of follow-up, LFTs were reviewed after stent extraction and routinely during follow up course. Stent duration was expressed as median \pm SD. All patients were contacted by a physician after stent removal, as a follow-up to evaluate for biliary pain and jaundice. Any patients who developed signs of biliary obstruction underwent follow-up ERCP to re-evaluate for stricture re-occurrence. Failure of endoscopic therapy was defined as persistent biliary stenosis or continuous biliary leakage after 12 mo of stent placement. Patients who failed stent therapy were referred for surgical intervention.

RESULTS

From July 2007 to February 2012, seventeen patients with BBS (12 patients) or bile leaks (5 patients) under-

Table 2 Patient characteristics and demographics

Case No.	Age, yr	Sex	Etiology	Location	FCSEMS (mm), type	Complications	Duration of stenting (d)	Follow-up after removal (d)	Results
Benign biliary strictures									
1	47	M	Biliary anastomosis/ Whipple	Choledocho-duodenal anastomosis	10 mm × 0 mm Viabil	None	89	1435	Patent
2	77	F	Cholecystectomy	Distal CBD	10 mm × 10 cm wallstent	None	92	1210	Patent
3	36	F	Cholelithiasis	Distal CBD	10 mm × 6 cm Viabil	None	37	1138	Patent
4	51	F	Cholelithiasis	Distal CBD	10 mm × 6 cm Viabil	None	161	1131	Patent
5	73	M	Cholecystectomy	Right intrahepatic duct	10 mm × 10 cm Viabil	Solid debris in lumen	160	1112	Patent
6	76	F	Cholecystectomy	H-J anastomosis	8 mm × 6 cm Viabil	None	29	55	Patent
7	27	F	Cholecystectomy	H-J anastomosis	10 mm × 4 cm Viabil	None	42	176	Patent
8	47	F	Compression by hepatic artery	CHD	80 mm × 8 cm wallstent	None	35	302	Patent
9	36	F	Cholecystectomy	CBD	10 mm × 80 mm Viabil	Migration	27	463	Not patent
10	45	F	Chronic pancreatitis/ cholecystectomy	Distal CBD	10 mm × 10 cm Viabil	None	63	36	Patent
11	42	F	Pancreatitis and pancreatic head necrosis	Distal CBD	10 mm × 6 cm wallstent	Recurrent cholangitis (<i>n</i> = 2), migration	199	122	Patent
12	35	M	Cholecystectomy	Distal CBD	10 mm × 8 cm Viabil	Abd pain following day of stent placement; repeat ERCP showed residual bile duct stones	57	41	Patent
Bile leaks									
13	75	F	Cholecystectomy	Bile leak (high grade); complex	10 mm × 80 mm Viabil	None	99	1364	Sealed
14	49	F	Cholecystectomy	Bile Leak (high grade)	10 mm × 10 cm Viabil	None	92	1294	Sealed
15	30	F	Cholecystectomy	Bile leak (low grade); complex	10 mm × 80 mm Viabil	Occluded stent after lost to follow-up (eight and a half months)	251	1007	Sealed
16	64	M	Cholecystectomy	Bile leak (high grade)	8 mm × 8 cm Viabil	None	62	575	Sealed
17	50	M	Cholecystectomy	Bile leak (low grade)	10 mm × 80 mm Viabil	Hepatic abscess and Sepsis	48	28	Sealed

M: Male; F: Female; FCSEMS: Fully covered self-expandible metallic stents; Chole: Cholecystectomy; CBD: Common bile duct; H-J: Hepaticojejunostomy; CHD: Common hepatic duct; ERCP: Endoscopic retrograde cholangiopancreatography.

went successful placement of FCSEMS. Etiologies of BBS included: cholecystectomies (*n* = 8), cholelithiasis (*n* = 2), hepatic artery compression (*n* = 1), pancreatitis (*n* = 2), and Whipple procedure (*n* = 1). All bile leaks occurred following cholecystectomy. Etiologies of BBS and bile leaks are shown in Table 2. The anatomic location of BBS varied: distal common bile duct (*n* = 7), common hepatic duct (*n* = 1), hepaticojejunal anastomosis (*n* = 2), right intrahepatic duct (*n* = 1), and choledochoduodenal anastomatic junction (*n* = 1). All bile leaks were found to be at the cystic duct. One patient was had a previous ERCP with intraductal ultrasonography (IDUS) showing possible hepatic artery compression leading to the common hepatic duct stricture. A repeat ERCP with IDUS for stent placement demonstrated a normal hepatic artery. Twelve of 17 patients had failed prior stent placement or exchange with plastic and/or metal stents (seven having multiple stents). Because several of our subjects

were referred to us who had stents placed at other facilities we were unable to determine the length of previous stenting. In patients with hepaticojejunal anastomotic strictures stents were placed percutaneously.

The median stent time was for all subjects was 63 d (mean 90.7 ± 65 d; range 27-199 d). The median stent time for the BBS group and bile leak group was 62 ± 58 d (range 27-199 d) and 92 ± 81 d (range 48-251 d), respectively. All 17 patients underwent successful FCSEMS removal. Resolution of biliary strictures and bile leaks was achieved in 16 of 17 patients (94%) (Figure 1). One patient with a bile leak did not have her stent removed until eight and a half months after placement due to loss of follow-up. An ERCP showed a sealed bile leak but an occluded stent which was extracted. One patient who failed stent therapy for BBS was referred to surgery. Long term follow-up, which included labs and symptom assessment, was obtained for a median of 575 d (range 28-1435

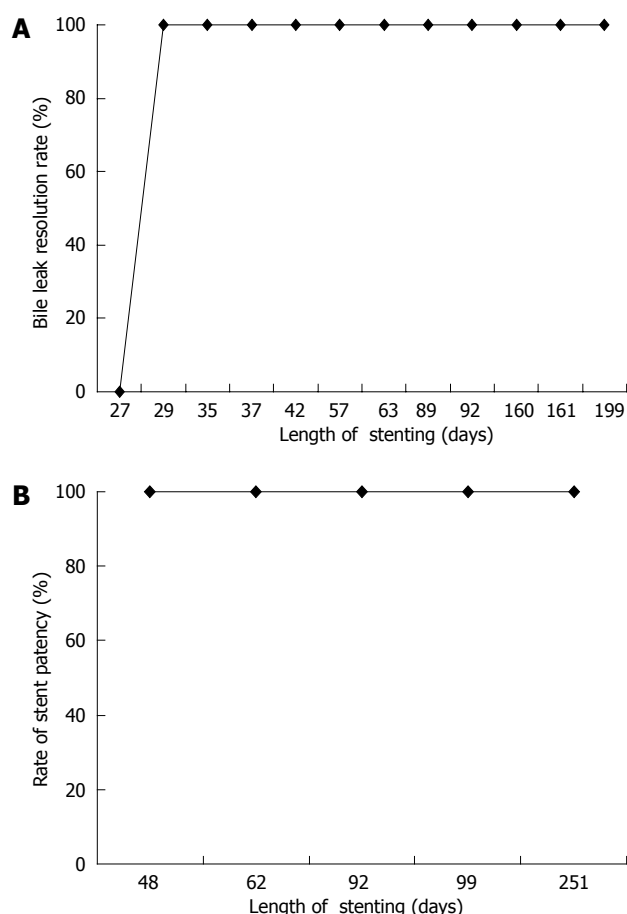


Figure 1 Stent patency rate (%) in patients with benign biliary strictures after insertion of fully covered self-expanding metal stents plotted against stent duration (d). A: Stent patency rate (%) in 12 patients with benign biliary strictures after insertion of fully covered self-expanding metal stents plotted against stent duration; B: Bile leak resolution rate (%) in 5 patients with bile leaks after insertion of fully covered self-expanding metal stents plotted against stent duration (d).

d). Follow-up was longer than one year in 10 cases (58%). No patients reported recurrent biliary pain or jaundice on follow-up. All patients liver function tests normalized. Figure 2 demonstrate stent placement for BBS and bile leaks.

FCSEMS related complications

Complications occurred in 5 of 17 patients (29%). Two patients were found to have proximal stent migration. The first was a Viabil metal stent seen to have migrated proximally. The time elapsed from stent placement to migration of FCSEMS was 27 d. Using rat-toothed forceps the migrated stent was grasped at the distal end and removed. Prior to removal of the stent because the stent had migrated inwards, dilation of the sphincterotomy site was performed after which the distal end of the stent could be seen. The CBD stricture had resolved at the time of extraction. The second migration involved a Wallstent that migrated proximally. The time elapsed from the stent placement to migration was 66 d. A second Wallstent was placed into a migrated Wallstent. Both Wallstents were removed after 133 d.

Two additional patients had stent occlusion caused by intraluminal debris and bile duct stones. The time elapsed from stent placement to occlusion caused by intraluminal debris and bile duct stones were 160 and 251 d, respectively.

One patient developed recurrent cholangitis due to stent occlusion. One patient was found to have a hepatic abscess of the right liver lobe after stent placement for a bile leak. He later developed sepsis and was transferred to the intensive care unit (ICU). Overall, two patients had *de novo* choledocholithiasis and/or lumen debris that required multiple balloon sweeps and irrigation of the bile duct.

DISCUSSION

Placement of plastic stents with or without sphincterotomy is the most popular and accepted therapy for treatment of BBS and bile leaks in most centers. Short-term patency rates, limited stent diameter and requirement of multiple endoscopic sessions with stenting have led to the development of SEMS^[13-15].

The overall success rate in our study for BBS and bile leaks was 94% (16/17). In the subset of patients with only BBS the success rate was 92% (11/12) (Figure 1A). Our results compare favorably to past results including a case series by Mahajan *et al*^[5] of 44 patients with BBS who were treated with FCSEMS (Viabil, Conmed) and demonstrated a success rate of 83% (34/41) after median stent time of 3.3 mo (Table 1).

In our study, FCSEMS were removed only when all criteria described earlier in methods were met. All stents were able to be removed without any difficulty with median duration of 89 d (range 29-428 d). Although there is no consensus on the optimal duration of biliary stenting some advocate for no longer than 6 mo^[2]. Several randomized trials have shown that FCSEMS remained patent for up to a median of 9 mo^[16,17]. Our stricture recurrence rate was 0% after a median follow-up of 575 d. Dumonceau *et al*^[5] reported a stricture recurrence was 19% on 36 patients who underwent plastic stent placement for BBS during a mean follow-up period of 44 mo.

Patients presenting with bile leaks had placement of Viabil FCSEMS. Viabil stents (Conmed, Utica, NY) are entirely covered with polytetrafluoroethylene and fluorinated ethylene propylene (ePTFE/FEP) liner that acts as a barrier to tissue ingrowth permitting long stent duration and easier extraction. Moreover, the anchoring fins placed on each tail end aid in prevent stent migration. Although our results are limited by the small sample size we were able to achieve 100% success rate in resolution of biliary leaks with temporary placement of FCSEMS for a mean of 110 ± 81 d (range, 48-251 d) (Figure 1B). The overall success rate for the subset of patients with bile leaks was 100%. Our results again compare favorably to past studies (Table 1). Three of 5 patients had high grade leaks and two of 5 patients had complex bile leaks refractory to previous stenting (Table 2). One patient had a biloma

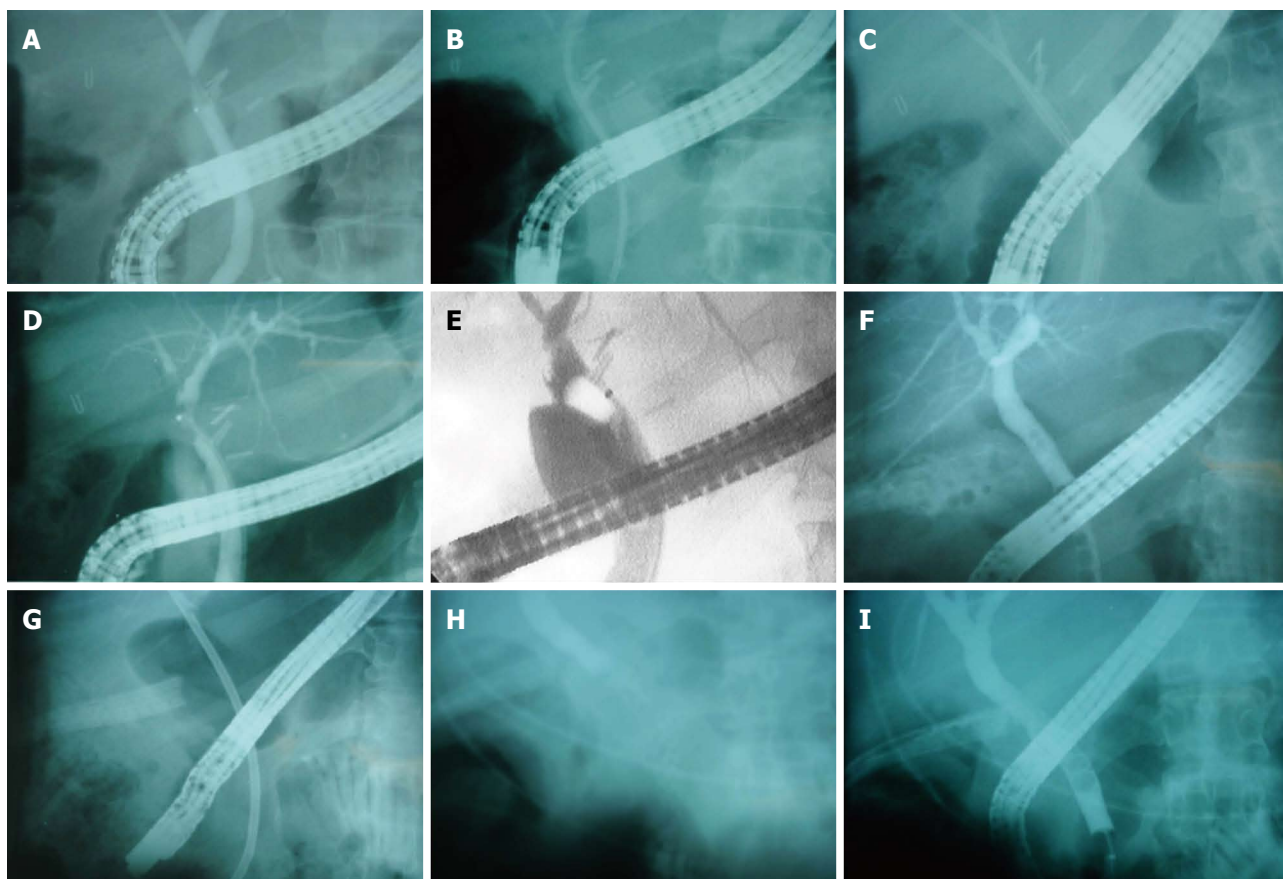


Figure 2 Stent placement for benign biliary strictures and bile leaks. A: A Left intrahepatic duct stricture after cholecystectomy and repair; B: Placement of biliary plastic stent for intrahepatic duct stricture; C: Placement of 2 plastic stents for persistent intrahepatic duct stricture; D: Persistent intrahepatic stricture after placement of 2 plastic biliary stents every 3 mo for 2 years. This stricture did not resolve therefore plastic stents were extracted and a Viabil fully covered metal stent was later placed; E: Intrahepatic stricture resolution following Viabil stent removal after 5 mo; F: Bile leak in a patient with a cystic stump and gangrenous gallbladder; G: Placement of plastic biliary stent in patient with bile leak; H: Placement of viabil stent since bile leak did not resolve with plastic stents; I: Resolution of bile leak following Viabil stent removal after 1 mo.

secondary to bile leak in the cystic duct and required percutaneous drain. She was lost to follow-up after eight and a half months and returned with abdominal pain. An ERCP revealed an occluded stent and intrahepatic ductal dilation. The stent was removed and a follow-up ERCP revealed a sealed bile leak.

Twelve patients had failed prior plastic stent placement and were referred to Harbor UCLA for refractory strictures (seven having had ≥ 2 stents). These subjects had fully covered metal stents placed for recurrent strictures. Because several of our subjects had stents placed at outside hospitals we are unable to determine the length of stenting, diameter or type of stent placed for all of these twelve patients. We did not encounter technical difficulties of FCSEMS placement in patients who had failed prior plastic stent therapy. There was no significant difference in total stenting time for patients that had failed prior plastic stenting and new onset strictures or bile leaks.

Upon stent removal, three patients were found to have biliary sludge and/or luminal debris requiring multiple balloon sweeps and irrigation. The incidence of sludge/luminal debris was noted to be proportional to

the duration of stenting. One patient was found to have a hepatic abscess of the right liver lobe on computed tomography scan after stent placement for a bile leak proximal to the cystic duct. The patient was transferred to the ICU for sepsis. It is unclear whether the abscess developed as a result of ERCP or secondary to an underlying infection. One patient had developed cholangitis due to an occluded stent. This patient was treated successfully with placement of another stent within the original stent, multiple balloon sweeps to remove sludge, and a course of antibiotics. This compares favorably to rates of cholangitis observed with plastic stent placement for BBS of 18%^[5]. The patient with stenting of a BBS localized to the right hepatic duct had an additional anastomosis done by surgery between the other hepatic duct and the duodenum. It is important to mention that unilateral placement of FCSEMS beyond the hepatic hilum harbors the risk of occluding the contralateral hepatic duct and side branches of the right or left hepatic ducts (depending on Bismuth stage of stricture). All complications in our study were treated conservatively.

Overall, our study showed that temporary placement of FCSEMS successfully treated BBS and bile leaks with

excellent long-term patency rates and relatively few complications. FCSEMS may provide an effective method in management of BBS and bile leaks while allowing easy endoscopic removability. FCSEMS can be easily removed after insertion and remain in place for several months although there is insufficient data as to what the optimal duration of placement is. The high cost of FCSEMS may be offset by a reduction in ERCP sessions and recurrent stenting for recurrent strictures^[14,15].

COMMENTS

Background

Management of bile leaks and benign biliary strictures (BBS) involves placement of plastic and uncovered metal stents which have been associated with limited long term stent patency secondary to stent lumen occlusion and epithelial hyperplasia, respectively.

Research frontiers

Recent advances in development of endoprosthesis have led to the development of fully covered self-expanding metal stents (FCSEMS) which are coated circumferentially with a material that prevents stent occlusion due to bacterial colonization, tissue hyperplasia, and tumor in growth thereby increasing the duration of stent patency in BBS and bile leaks.

Innovations and breakthroughs

In this retrospective review of patients with BBS and Bile leaks treated with FCSEMS, stricture and bile leak resolution was achieved in 16 of 17 patients after a median follow-up time of 575 d after stent extraction.

Applications

This study demonstrated that temporary placement of FCSEMS successfully treated BBS and bile leaks with excellent long-term patency rates and relatively few complications.

Peer review

The manuscript entitled "An evaluation of fully covered self-expanding metal stents in benign biliary strictures and complex bile leaks" provided valuable data about the safety and efficacy of FCSEMS for endoscopic treatment of benign biliary strictures and bile leaks.

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Successful treatment of cervical esophageal leakage by endoscopic-vacuum assisted closure therapy

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Abstract

AIM: To evaluate the efficacy and safety of endoscopic-vacuum assisted closure (E-VAC) therapy in the treatment of cervical esophageal leakage.

METHODS: Between May and November 2012, three male patients who developed post-operative cervical esophageal leakage were treated with E-VAC therapy. One patient had undergone surgical excision of a pharyngo-cervical liposarcoma with partial esophageal resection, and the other two patients had received surgical treatment for symptomatic Zenker's diverticulum. Following endoscopic verification of the leakage, a trimmed polyurethane sponge was fixed to the distal end of a nasogastric silicone tube and endoscopically positioned into the wound cavity, and with decreasing cavity size the sponge was positioned intraluminally to cover the leak. Continuous suction was applied, and the vacuum drainage system was changed twice a week.

RESULTS: The initial E-VAC placement was technically successful for all three patients, and complete closure of the esophageal leak was achieved without any procedure-related complications. In all three patients, the insufficiencies were located either above or slightly below the upper esophageal sphincter. The median duration of the E-VAC drainage was 29 d (range: 19-49 d), with a median of seven sponge exchanges (range: 5-12 sponge exchanges). In addition, the E-VAC therapy reduced inflammatory markers to within normal range for all three patients. Two of the patients were immediately fitted with a percutaneous enteral gastric feeding tube with jejunal extension, and the third patient received parenteral feeding. All three patients showed normal swallow function and no evidence of stricture after completion of the E-VAC therapy.

CONCLUSION: E-VAC therapy for cervical esophageal leakage was well tolerated by patients. This safe and effective procedure may significantly reduce morbidity and mortality following cervical esophageal leakage.

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Key words: Endoscopic-vacuum assisted closure therapy; Vacuum therapy; Negative pressure wound therapy; Cervical esophageal leakage; Anastomotic leakage

Core tip: Traditional methods to treat cervical esophageal leakage close to the upper esophageal sphincter are associated with high morbidity and mortality. The newly developed method of endoscopic-vacuum assisted closure (E-VAC) therapy using polyurethane sponges has been demonstrated as efficacious for treating gastrointestinal tract leakages. We applied E-VAC therapy to three patients with post-operative cervical leakage and achieved complete closure in all, without any procedure-related complications. The E-VAC therapy was well tolerated by patients with cervical esophageal leakage, and its application in this patient population may contribute to a significant reduction in morbidity

and mortality.

Lenzen H, Negm AA, Erichsen TJ, Manns MP, Wedemeyer J, Lankisch TO. Successful treatment of cervical esophageal leakage by endoscopic-vacuum assisted closure therapy. *World J Gastrointest Endosc* 2013; 5(7): 340-345 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i7/340.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i7.340>

INTRODUCTION

Anastomotic leakage is a potentially life-threatening complication that may follow esophageal surgery. The leakage may range in severity from a minor anastomotic defect to a fulminant leak with systemic sepsis and multiple organ failure^[1-3]. Cervical anastomoses have been associated with leakage rates as high as 40% and a mortality rate of 5%^[4-6]. The treatment of cervical anastomotic leakage above the upper esophageal sphincter is particularly challenging, and only limited treatment options are available. Traditionally, the repair of cervical leakage has involved surgical intervention^[7]; however, re-operation is associated with high morbidity and mortality rates^[8]. Placement of self-expandable metal stents in such situations is difficult or even impossible and is associated with a high rate of procedure-related complications, such as globus sensation and/or respiratory insufficiency. Therefore, the procedure is often not performed^[9-11].

Over the last decade, several endoscopic treatment options for repair of esophageal anastomotic leakages have emerged, including fibrin glue injection, endoscopic transluminal drainage and self-expanding metal stents^[12-14]. Endoscopic treatment using self-expandable metal or plastic stents has become the treatment of choice for anastomotic esophageal leakage, and its reported success rates are above 80%^[12,15-18]. Most recently, endoscopic-vacuum assisted closure (E-VAC) has been suggested as an effective treatment modality for esophageal anastomotic leakage in the upper gastrointestinal tract^[19]. E-VAC therapy involves placing polyurethane sponges into the wound cavity that was induced by the leak, followed by application of an external vacuum through a transnasal tube to drain the infected fluid and induce the formation of granulation tissue. Recent studies of E-VAC therapy for the treatment of leaks following esophageal anastomoses have demonstrated that the procedure is capable of achieving successful wound closure with no associated mortality^[20-23]. However, these studies have mainly examined intrathoracic anastomotic leakages. Here, we report the successful application of E-VAC therapy to treat cervical anastomotic leakages in three patients.

MATERIALS AND METHODS

Patients and procedure description

Between May and November 2012, three male patients

with post-operative cervical esophageal leakage were treated with E-VAC therapy at the Endoscopy Unit of the Hannover Medical School (Hannover, Germany). E-VAC placement was performed as described previously^[22] as the modified form of the VAC technique, which is an established treatment modality for chronic and infected cutaneous wounds^[24,25]. Briefly, a trimmed polyurethane sponge, pore size 400-600 μm (KCI, Wiesbaden, Germany) was fixed to the distal end of a nasogastric silicone tube (Freka 15 Ch; Fresenius Kabi, Bad Homburg, Germany) and introduced into the cavity under endoscopic vision. With decreasing cavity size, the sponge was placed endoluminally to cover the entire esophageal defect. A continuous negative pressure of 125 mmHg was applied using a vacuum pump (KCI). The vacuum drainage system was endoscopically changed two times per week. All endoscopic interventions were performed either under general anesthesia or conscious sedation with propofol and midazolam. All three patients gave informed consent for publication of their case, and retrospective analysis was performed in accordance with the Declaration of Helsinki.

Descriptive statistics were used to evaluate the patients' demographic and clinical characteristics. The data are presented as individual values, median, and ranges.

RESULTS

Characteristics of patients

We used E-VAC therapy to treat three male patients with post-operative cervical esophageal leakage. The patients were 69-, 71- and 80-year-old (Table 1). Patient 1 had undergone surgical excision of a pharyngo-cervical liposarcoma with partial esophageal resection followed by an insufficiency 3 cm below the upper esophageal sphincter (17 cm from the incisors). Patients 2 and 3 had suffered from cervical esophageal perforation following surgical treatment of a symptomatic Zenker's diverticulum. Patient 2 had open surgery with a diverticulectomy and myotomy (Figure 1). Patient 3 suffered from recurrent Zenker's diverticulum and was treated with transoral endoluminal mucomyotomy. The insufficiency in these two cases was located above the upper esophageal sphincter, at 17 cm from the incisors in patient 2 and at 19 cm from the incisors in patient 3.

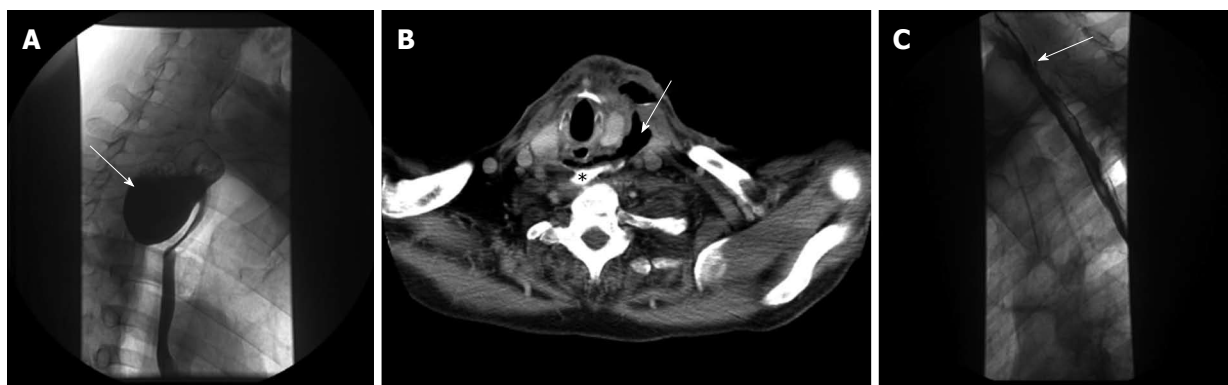
Results of E-VAC therapy

All three patients had endoscopically diagnosed esophageal leakage and their initial E-VAC placement was technically successful. In all three cases, the sponge was initially placed into the extraluminal cavity (intracavitary), which was changed to intraluminal placement with decreasing cavity size. Two patients immediately received a percutaneous enteral gastric feeding tube with jejunal extension (PEG-J tube) and the third patient received parenteral feeding (Table 2). The median duration of E-VAC therapy was 29 d (range: 19-49 d) with a median of seven sponge exchanges (range: 5-12 sponge exchanges) (Table

Table 1 Characteristics of three patients who underwent endoscopic-vacuum assisted closure treatment

Patient	Sex	Age, yr	Diagnosis	Surgical procedure	Cause of leakage	Distance from the dental arch, cm	Time interval from diagnosis to start of E-VAC therapy, d	Time interval from surgery to start of E-VAC therapy, d
1	Male	80	Liposarcoma	Thoracic esophageal resection	Anastomotic insufficiency	17	11	25
2	Male	71	Zenker's diverticulum	Diverticulectomy and myotomy	Anastomotic insufficiency	17	0	13
3	Male	69	Zenker's diverticulum	Mucomyotomy	Iatrogenic perforation	19	0	2

E-VAC: Endoscopic-vacuum assisted closure.

**Figure 1** Radiographic findings of the second patient with Zenker's diverticulum. A: Barium swallow showing the Zenker's diverticulum (arrow) out-pouching from the posterior wall of the esophagus. Computed tomography scan showing the cervical esophageal leakage with periesophageal mediastinal abscess and extraluminal air (arrow); B: Contrast esophagus (asterisk) with extravasation; C: Gastrografin swallow after endoscopic-vacuum assisted closure treatment showing a small residual saccular protrusion (arrow), but no leakage and no stenosis, clip *in situ*.**Table 2** Endoscopic-vacuum assisted closure treatment characteristics

Patient	Treatment type	Sponge exchanges, n	E-VAC treatment duration, d	Hospitalization duration, d	Endoscopic follow-up ² duration, d	Feeding method
1 ¹	Intracavitary/ intraluminal	1 × 9 1 × 3	1 × 34 1 × 15	108	None	PEG-J tube
2	Intracavitary/ intraluminal	5	19	42	47	Intravenously
3	Intracavitary/ intraluminal	7	29	46	206	PEG-J tube

¹Patient did not achieve complete healing after the first treatment cycle and underwent a second treatment; ²Days after sponge removal. E-VAC: Endoscopic-vacuum assisted closure; PEG-J tube: Percutaneous endoscopic gastrostomy with jejunal extension.

2). Median hospitalization time was 46 d (range: 42-108 d). In all three patients, complete closure of the leakage was achieved without any procedure-related complications and without the need for surgical re-intervention (Figure 2). Sponge therapy was well tolerated and there was no evidence of residual leakage either clinically or after Gastrografin swallow in patients 2 and 3. Inflammation was assessed by measuring white blood cell (WBC) counts and C-reactive protein (CRP) levels. In two patients, the WBC count was initially elevated but decreased to within the normal range following E-VAC therapy. All three patients had markedly elevated CRP levels (range: 152-296 mg/L) at the beginning of the treatment, which were reduced to almost normal (range: 3-34 mg/L) by the time of discharge (Table 3). Patients were clinically

followed-up after hospital discharge and endoscopy was performed in two patients at post-discharge days 47 and 206. All three patients had normal swallow function and no evidence of stenosis after completion of the E-VAC therapy.

DISCUSSION

Esophageal anastomotic leakage is associated with high morbidity and mortality rates, particularly when surgical repair is required^[1,4,8]. Consequently, efforts have been made to devise less invasive treatment modalities. A number of endoscopic techniques have emerged in recent years, including E-VAC therapy. Here, we report the successful use of E-VAC therapy for the treatment of post-

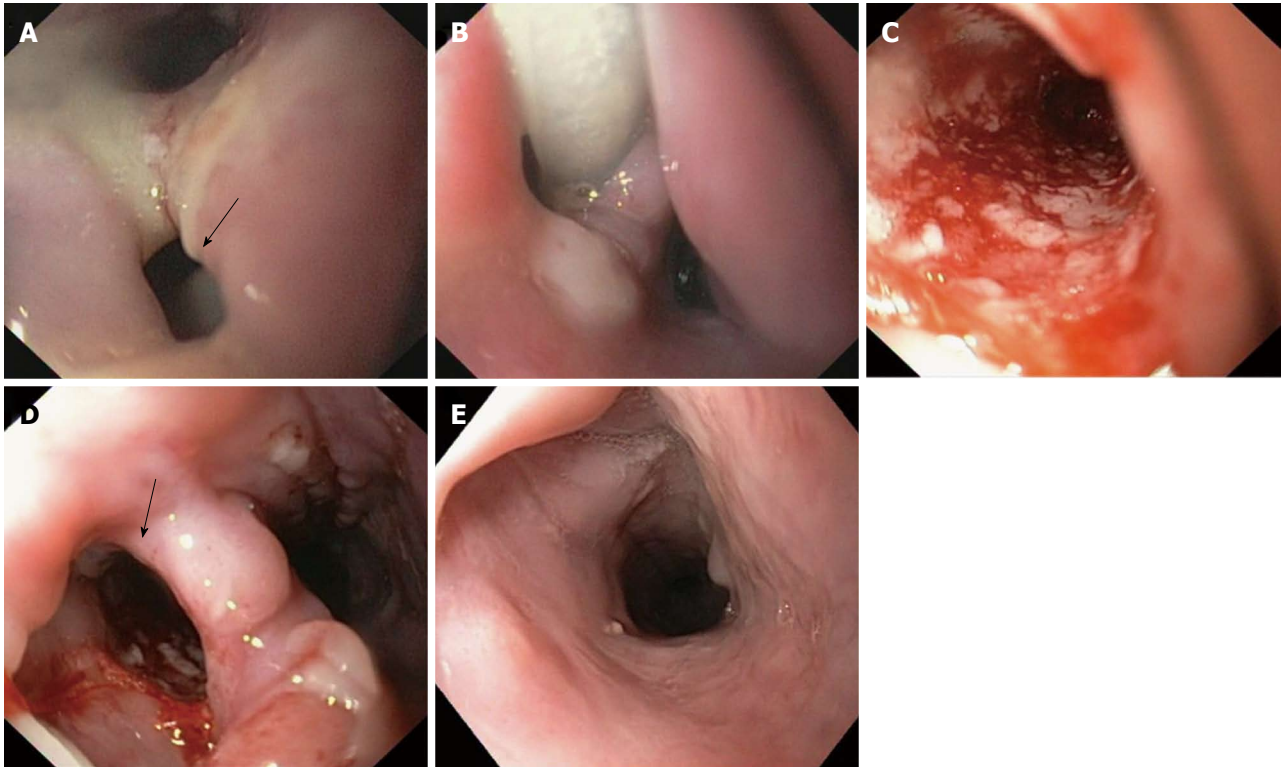


Figure 2 Endoscopic images of cervical esophageal leakage after surgical diverticulectomy and cricopharyngeal myotomy and subsequent treatment with endoscopic-vacuum assisted closure. A: The defect was large enough to be intubated with a standard endoscope (arrow); B: Sponge positioned in the extraluminal wound cavity and connected to a drainage tube; C: Clean wound ground and formation of fresh granulation tissue with good vascularisation at 3 d after the endoscopic-vacuum assisted closure (E-VAC) therapy; D: Appearance of esophageal defect (arrow) at 11 d after the E-VAC therapy; E: Complete healing of the leakage at 47 d after completion of the E-VAC treatment.

Table 3 Inflammation markers monitored during the endoscopic-vacuum assisted closure treatment

Patient	WBC		CRP	
	1 st sponge placement	Sponge removal	1 st sponge placement	Sponge removal
1	11.6	4.3	152	34
2	8.2	8.8	244	34
3	14.3	9.9	296	3

WBC: White blood cell count, normal range: 4.4-11.3 Tsd/ μ L; CRP: C-reactive protein, normal range: < 8 mg/L.

operative cervical esophageal leakage.

Previous studies of E-VAC treatment were mainly concerned with the management of thoracoabdominal esophageal leakages; although, cervical esophagogastric anastomoses have a higher incidence of leaks compared to thoracic anastomoses^[5]. Cervical leakages treated with E-VAC therapy have been rarely described^[20,26]. Here, we examined two cases of Zenker's diverticulum perforation with insufficiencies above the upper esophageal sphincter and one case of surgical excision of a pharyngo-cervical liposarcoma with partial esophageal resection followed by an insufficiency just below the upper esophageal sphincter. Due to high cervical localization of the perforation, stent placement was not considered. In all three patients, complete closure of the leakage was achieved

without any procedure-related complications. None of the patients required further surgical intervention, and all three patients displayed regular swallow function after completion of the E-VAC therapy. Follow-up endoscopy in patients 2 and 3 demonstrated complete healing of the esophagus.

These case series indicate that E-VAC therapy has clinical utility in the repair of cervical esophageal leakage. These data justify conducting further studies to examine the potential of E-VAC therapy for treating other iatrogenic cervical esophageal perforations, such as perforations after transesophageal echocardiography, foreign body impaction, or endoscopic and surgical procedures. Compared to the previous studies of E-VAC therapy for treating thoracic esophageal leakage^[20,26], our case studies of E-VAC therapy for treating cervical esophageal leakage required longer treatment times and a higher number of sponge changes. Therefore, we recommend early PEG placement for enteral feeding. However, despite the longer treatment times, the E-VAC therapy was well tolerated by all of our patients.

Our case studies suggest that use of E-VAC therapy allows for rapid removal of infected tissue. Prior to E-VAC therapy, all three patients displayed high levels of inflammatory markers that were indicative of systemic inflammatory complications from the esophageal leakage. Notably, a considerable reduction in the levels of these inflammatory markers was observed following treatment,

which suggests that the E-VAC therapy resulted in rapid drainage of the infected wound cavity and control of inflammation.

In summary, we report that E-VAC therapy is a safe and efficacious treatment option for cervical esophageal leakage. E-VAC therapy appears to provide adequate wound drainage, promotion of tissue granulation within the wound cavity, and closure of the cervical esophageal defect. Despite the high localization of the vacuum placement, sponge therapy was well tolerated by our patients. Application of this therapy may contribute a significant improvement in morbidity and mortality. A multidisciplinary approach, involving the coordinated efforts of abdominal and/or ear-nose-throat surgeons, may further enhance E-VAC therapy as a treatment modality for cervical esophageal leakage.

COMMENTS

Background

Traditionally, the repair of cervical esophageal leakage has involved surgical intervention, as placement of self-expandable metal stents in this situation is difficult or even impossible. Most recently, endoscopic-vacuum assisted closure (E-VAC) has been suggested as an effective treatment modality for esophageal leakage. Therefore, the authors investigated the efficacy of E-VAC therapy for cervical leakage above or slightly below the upper esophageal sphincter.

Research frontiers

Cervical esophageal leakage is associated with high morbidity and mortality rates, particularly when surgical repair is required. Therefore, this study evaluated the effectiveness and safety of a non-invasive endoscopic treatment using E-VAC therapy for treating cervical esophageal leakage.

Innovations and breakthroughs

This study demonstrates that E-VAC therapy is an efficacious and safe treatment option for treating cervical esophageal leakage. Despite the high localization of the vacuum placement, the sponge therapy is well tolerated.

Applications

E-VAC therapy can be used as an alternative treatment option for cervical esophageal leakages above or slightly below the upper esophageal sphincter. These findings indicate the benefit of future studies addressing whether E-VAC therapy may also be useful for treatment of other iatrogenic cervical esophageal perforations, such as perforations after transesophageal echocardiography, foreign body impaction, or endoscopic and surgical procedures.

Terminology

The VAC technique is an established treatment modality for chronic and infected cutaneous wounds. Recently, the endoscopic placement of a vacuum-assisted closure system (endoscopic-vacuum assisted closure, E-VAC) in the gastrointestinal tract has been shown to be an effective treatment option for anastomotic leaks. The trimmed polyurethane foam with an open-cell structure (sponge) is fixed to the distal end of a silicone duodenal tube and endoscopically introduced into the necrotic cavity of the upper or the lower gastrointestinal tract. A continuous negative pressure of 125 mmHg is applied using a vacuum pump and the sponge is replaced two to three times per week.

Peer review

The authors conclude that E-VAC therapy is a safe and effective treatment option for cervical esophageal leakage.

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Ultrathin endoscope flexibility can predict discomfort associated with unsedated transnasal esophagogastroduodenoscopy

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scope was equipped with a thin-type mouthpiece and tongue depressor. Conscious sedation was not used for any patient. EGD-associated discomfort was assessed using a visual analog scale (VAS; no discomfort 0-maximum discomfort 10).

RESULTS: Rates of preference for transnasal insertion were significantly higher in male (male/female 299/204 vs 118/117) and younger patients (56.8 ± 11.2 years vs 61.3 ± 13.0 years), although no significant difference was found in VAS scores between transoral and transnasal insertion (3.9 ± 2.3 vs 4.1 ± 2.5). Multivariate analysis revealed that gender, age, operator, and endoscope were independent significant predictors of VAS for transnasal insertion, although gender, age, and endoscope were those for transoral insertion. Further analysis revealed only the endoscopic flexibility index (EFI) as an independent significant predictor of VAS for transnasal insertion. Both EFI and tip diameter were independent significant predictors of VAS for transoral insertion.

CONCLUSION: Flexibility of ultrathin endoscopes can be a predictor of EGD-associated discomfort, especially in transnasal insertion.

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Abstract

AIM: To evaluate the effects of choice of insertion route and ultrathin endoscope types.

METHODS: This prospective study (January-June 2012) included 882 consecutive patients who underwent annual health checkups. Transnasal esophagogastroduodenoscopy (EGD) was performed in 503 patients and transoral EGD in 235 patients using six types of ultrathin endoscopes. Patients were given a choice of insertion route, either transoral or transnasal, prior to EGD examination. For transoral insertion, the endo-

Key words: Esophagogastroduodenoscopy; Ultrathin endoscope; Visual analog scale; Discomfort; Surveillance

Core tip: To evaluate the effects of choice of insertion route and ultrathin endoscope types for unsedated surveillance esophagogastroduodenoscopy (EGD), this prospective study was conducted including 882 consecutive patients who underwent annual health checkup using six types of ultrathin endoscopes in a single in-

stitute. EGD-associated discomfort was assessed using a visual analog scale (VAS) by patients themselves. Statistical analysis of VAS revealed the following two points; Transnasal insertion of ultrathin endoscopy for unsedated EGD can be preferable for younger males rather than elder females. Flexibility of ultrathin endoscopes can be a reliable predictor of reduction in transnasal EGD-associated discomfort rather than thinness of tip.

Ono S, Niimi K, Fujishiro M, Nakao T, Suzuki K, Ohike Y, Kodashima S, Yamamichi N, Yamazaki T, Koike K. Ultrathin endoscope flexibility can predict discomfort associated with unsedated transnasal esophagogastroduodenoscopy. *World J Gastrointest Endosc* 2013; 5(7): 346-351 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i7/346.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i7.346>

INTRODUCTION

With improvements in resolution and image enhancement, gastrointestinal endoscopic technology has advanced considerably, detecting an increasing number of superficial neoplasms during surveillance esophagogastroduodenoscopy (EGD)^[1-5]. New endoscopic treatments for superficial neoplasms, including endoscopic submucosal dissection, have been reported to be effective and less invasive compared with traditional open surgical exploration and treatment^[6-10]. Against the backdrop of such concerns, importance of detecting them in early stage has been emphasized more than ever to achieve curative resection endoscopically.

Although identification of patients at high risk for superficial esophageal squamous cell carcinoma (SESCC) and early gastric cancer (EGC) has been reported as useful, diagnoses must still be confirmed by histopathological assessment of biopsy specimens obtained via endoscopy^[11-13]. However, EGD-associated discomfort is a major problem for many patients, who are reluctant to undergo subsequent EGD procedures. Although sedation is possible for reduction of EGD-associated discomfort, cost and various adverse events associated with use of sedative agents must be considered among the risks and benefits of this option^[14-17].

Use of an ultrathin endoscope may also reduce unsedated EGD-associated discomfort. Transnasal insertion of ultrathin endoscopes is reported to be a promising alternative in terms of patient satisfaction and cardiopulmonary function^[18-21]. Although various types of ultrathin endoscopes are available at present, predictors of discomfort associated with EGD performed using ultrathin endoscopes have not been determined.

This prospective study was conducted to identify predictors of discomfort associated with unsedated EGD performed using ultrathin endoscopes.

MATERIALS AND METHODS

This study was conducted at the Center for Epidemiology and Preventive Medicine of the University of Tokyo after receiving ethics committee approval. From January to June 2012, 882 consecutive patients who underwent annual health checkups were included in this study. Subjects were given a choice of insertion route, either transoral or transnasal, prior to EGD examination. The subjects were prepared for transnasal insertion using the modified spray method, which involves spraying 0.05% naphazoline nitrate into each nostril, followed by injection of a viscous gel of 2% lidocaine hydrochloride^[22]. Conscious sedation was not used for any patient.

Six ultrathin endoscopes (A: GIF-XP260N, B: GIF-XP260NS, C: EG-530NW, D: EG-580NW, E: EG16-K10, and F: prototype EG17-K10) from three manufacturers (Olympus Corp., Tokyo, Japan; Fujifilm Holdings Corp., Tokyo, Japan; and Hoya Corp., Tokyo, Japan) were utilized in this study. Prototype EG17-K10 was equipped as part of a collaborative effort by the University of Tokyo Hospital and Hoya Corporation. Profiles of these endoscopes are shown in Table 1. All endoscopes were utilized for this study after being used for more than one hundred EGDs.

The flexibility of each endoscope was evaluated as follows. We fixed the middle portion of the endoscope to a flat surface, and allowed the tip of the endoscope to bend freely under the influence of gravity. After adjusting the length of endoscope from 150 to 400 mm allowed free movement under the influence of gravity, we mapped the position of the tip of the endoscope on a two dimensional grid. Continuous two-dimensional horizontal and vertical distances were plotted, as shown in Figure 1. The mean horizontal distances at the fixed points of 200, 250, 300, 350 and 400 mm were utilized as an endoscopic flexibility index (EFI) to provide a surrogate value of flexibility for each endoscope. Measurements of EFI for each endoscope were performed at room temperature.

The combination of endoscopes changed depending on the day of the week. Consequently, the patients were randomly allocated to six endoscope groups.

All examinations were performed by two operators who had been certified by the Japanese Gastroenterological Endoscopy Society. For transoral insertion, the endoscope was equipped with a thin-type mouthpiece and tongue depressor (Endo-leader; Top Corp.; Tokyo, Japan)^[23]. In cases where transnasal insertion failed due to narrowness of nasal cavity or intolerable discomfort, transoral insertion was performed continuously after confirmation with the patient. After completion of the examination, EGD-associated discomfort was evaluated using a visual analogue scale (VAS) by patients themselves in another room from 0 to 10, which were minimum and maximum of discomfort respectively.

Parameters analyzed in this study were examination

Table 1 Profiles of six endoscopes and outcomes for transnasal insertion

	A	B	C	D	E	F
EFI (mm)	224	192.4	175.2	174.8	146	166.6
Tip diameter (mm)	5	5.4	5.9	5.9	5.2	5.4
Transnasal insertion						
Insertion success rate	58/59	110/112	119/123	112/118	47/47	57/57
Nasal bleeding rate	0/58	2/110	2/119	2/112	1/47	0/57
VAS	4.2 ± 2.7	4.0 ± 2.1	4.0 ± 2.4	4.0 ± 2.3	3.2 ± 2.2	3.8 ± 2.3
Examination time (s)	351.0 ± 58.8	345.8 ± 62.2	324.9 ± 61.1	340.0 ± 48.1	376.7 ± 61.7	349.1 ± 57.3

VAS: Visual analog scale; EFI: Endoscopic flexibility index.

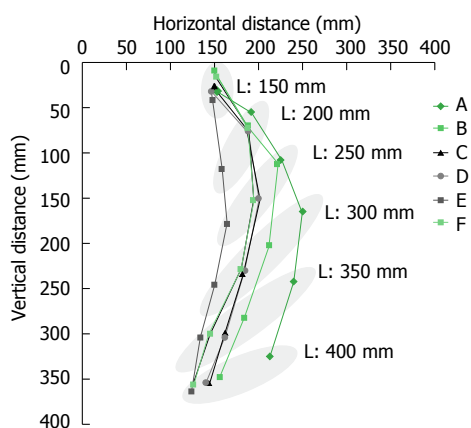


Figure 1 A two-dimensional plot of the transition from the tip of the endoscope. L: The length of endoscope allowed free movement under the influence of gravity.

time and VAS score. Moreover, the insertion success rate and nasal bleeding rate were evaluated for each endoscope for transnasal insertion. Patients with a past history of surgical resection in the upper gastrointestinal tract and those in whom biopsy or another procedure had been performed were excluded from the analyses to avoid effects of these factors on examination time or VAS scores.

Statistical analysis

Statistical analyses were performed using Student's *t*-test, χ^2 test, and Fisher's exact test. For multivariate analysis, the least-squares method was employed using dummy variables for nominal variables. All analyses were performed using JMP software (SAS Institute Inc., Cary, NC, United States). *P* < 0.05 was considered significant.

RESULTS

Among the 882 patients, 91 patients were excluded because of invalid responses or missing data. Thirty-nine patients were excluded because of past history of surgery in the upper gastrointestinal tract (*n* = 19) and biopsy during the examination (*n* = 20). One asymptomatic patient in whom anisakiasis was coincidentally discovered and who underwent endoscopy for removal of this parasite was also excluded from the analysis. In total, data of 751 patients were analyzed, as shown in Figure 2. Among

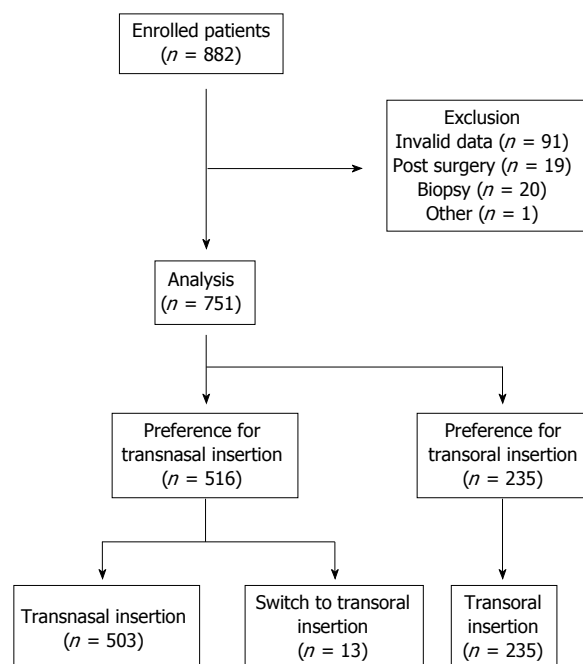


Figure 2 Flowchart of patient involvement in this study.

them, 516 patients (68.7%) preferred transnasal insertion and 235 patients (31.3%) preferred transoral insertion. Thirteen patients who preferred transnasal insertion were switched to transoral insertion after failure of transnasal insertion. EGD was performed more than once in 665 patients (88.5%).

Characteristics of patients and outcomes are shown in Table 2. Rates of preference for transnasal insertion were significantly higher in male patients (male/female 299/204 *vs* 118/117 for transnasal *vs* transoral insertion, respectively; *P* < 0.05) and younger patients (56.8 ± 11.2 years *vs* 61.3 ± 13.0 years; *P* < 0.05). Examination time for transnasal insertion was significantly longer than that for transoral insertion, although no significant difference was found between VAS scores for transnasal and transoral insertion (3.9 ± 2.3 *vs* 4.1 ± 2.5 ; NS).

For multivariate analysis of VAS scores, six parameters were employed: gender, age, experience of previous EGD, operator, type of endoscope, and examination time. Results of multivariate analysis of VAS scores for transnasal and transoral insertion are shown in Tables 3 and 4, respectively. For transnasal insertion, gender (posi-

Table 2 Characteristics of patients

	Transnasal insertion (<i>n</i> = 503)	Transoral insertion (<i>n</i> = 235)	<i>P</i> value
Gender M/F	299/204	118/117	< 0.05
Age (yr)	56.8 ± 11.2 (25-84)	61.3 ± 13.0 (27-88)	< 0.05
1st examination Y/N	54/449	19/216	0.29
Operator A/B	326/177	143/92	0.32
Endoscope			0.36
A	58	31	
B	110	52	
C	119	58	
D	112	61	
E	47	17	
F	57	16	
Examination time (s)	343.4 ± 59.4 (210-630)	324.5 ± 59.8 (196-600)	< 0.05
VAS	3.9 ± 2.3 (0-10)	4.1 ± 2.5 (0-10)	0.90

VAS: Visual analog scale; M: Male; F: Female.

Table 3 Multivariate analysis for visual analog scale in transnasal insertion

	Parameter estimate ± SE	<i>P</i> value
Gender (F)	0.780 ± 0.100	< 0.05
Age	-0.0193 ± 0.00886	< 0.05
1 st examination (N)	0.252 ± 0.160	0.12
Operator (A)	-0.341 ± 0.110	< 0.05
Scope (E)	-0.719 ± 0.281	< 0.05
Examination time	0.00270 ± 0.00180	0.134

tive correlation with female gender), age, operator, and endoscope (negative correlation with endoscope E) were independent significant predictors of VAS scores. On the other hand, gender (positive correlation with female gender), age, and endoscope (positive correlation with endoscope C) were independent significant predictors of VAS scores for transoral insertion.

Multivariate analysis was also performed using EFI and tip diameter as alternative features of the endoscopes. Although both EFI and tip diameter were independent significant predictors of VAS scores for transoral insertion, only EFI was an independent significant predictor of VAS scores for transnasal insertion as shown in Table 5.

DISCUSSION

The appropriate usage of ultrathin endoscopes in the transoral and transnasal insertion techniques remains controversial^[24]. In addition, although various ultrathin endoscopes are presently available, predictors of EGD-associated discomfort are unclear. This study demonstrated that both tip diameter and flexibility of ultrathin endoscopes can be predictors in reducing EGD-associated discomfort, especially for transnasal insertion.

Greater flexibility of the endoscope may lead to poorer handleability, resulting in prolonged examination time, which may in turn increase the discomfort accompanying EGD. However, although the most flexible endoscope (endoscope E) in this study required the longest

Table 4 Results of multivariate analysis of visual analog scale scores for transoral insertion

	Parameter estimate ± SE	<i>P</i> value
Gender (F)	0.575 ± 0.156	< 0.05
Age	-0.0343 ± 0.0125	< 0.05
1 st examination (N)	-0.00289 ± 0.294	0.99
Operator (A)	-0.297 ± 0.177	0.10
Scope (C)	0.634 ± 0.313	< 0.05
Examination time	-0.00159 ± 0.00291	0.59

Table 5 Parameters of endoscopic flexibility index and tip diameter by multivariate analysis for visual analog scale

	Transnasal insertion	Transoral insertion
EFI	0.0125 ± 0.00563 (<i>P</i> < 0.05)	0.0212 ± 0.00966 (<i>P</i> < 0.05)
Tip diameter	0.450 ± 0.338 (<i>P</i> = 0.18)	1.33 ± 0.561 (<i>P</i> < 0.05)

EFI: Endoscopic flexibility index.

examination time among the six endoscopes, VAS scores were lowest for EGD using this endoscope for transnasal insertion. This result indicates that prolonging the examination for a certain amount of time may be acceptable in terms of the level of tolerable discomfort.

In a high proportion of regular patients in this study, EGD had been periodically performed in the past. Almost all patients selected the insertion route based on their experience with discomfort in previous examinations. Consequently, although no significant difference in VAS scores was observed between transoral and transnasal insertion, patient characteristics and preferences showed their propensity for discomfort with either one technique or the other. Table 2 shows the trend toward preference for transnasal insertion among males and younger patients. We speculate that younger patients preferred transnasal insertion to suppress a stronger gagging reflex that is reported by Enomoto *et al.*^[25]. By contrast, smaller female patients may have preferred transoral insertion because of their narrower nasal cavities, which are more prone to discomfort caused by transnasal insertion. However, VAS scores are reported to be affected by gender^[26]. Additionally, there might be a gender deference in diminishing of gagging reflex or nasal pain by aging. We need further accumulation of data for appropriate insertion route in each gender or age-groups.

One limitation of this study is its unequal allocation of patients to each endoscope because of the system utilized in our institute. Moreover, the objectivity and reproducibility of VAS and EFI are questionable. EFI is affected by the weight of the endoscope, whose mass/length is not homogenous. However, this parameter can be a surrogate marker that can be evaluated simply and non-destructively.

In summary, this study demonstrated that flexibility of the ultrathin endoscope can be a reliable predictor of reduction in transnasal EGD-associated discomfort. Although further analysis of details concerning appropriate location and degree of flexibility is required, patient com-

pliance can be improved for follow-up and surveillance EGD by utilizing less uncomfortable tools.

COMMENTS

Background

As gastrointestinal endoscopic technology has advanced considerably with improvements in resolution and image enhancement, importance of surveillance esophagogastroduodenoscopy (EGD) to detect superficial neoplasms in early stage has been emphasized more than ever to achieve curative resection.

Research frontiers

Although EGD using an ultrathin endoscope has been accepted as a minimally invasive modality, the effects of choice of insertion route and ultrathin endoscope types have not been evaluated.

Innovations and breakthroughs

The authors' study using six types of ultrathin endoscopes demonstrated that flexibility of the ultrathin endoscope can be a reliable predictor of reduction in transnasal EGD-associated discomfort.

Applications

To decrease unsedated EGD-associated discomfort, transnasal insertion of ultrathin endoscopy should be chosen for younger males. A flexible ultrathin endoscope can reduce transnasal EGD-associated discomfort for the other people.

Terminology

Endoscopic flexibility index is a surrogate marker that can be evaluated simply and non-destructively.

Peer review

This is the first report of comparison of the difference between several models of ultrathin endoscope. The conclusion that the discomfort is associated with the flexibility of the endoscope is a novel and unique.

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Longest duration of retention of video capsule: A case report and literature review

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Key words: Video capsule endoscopy; Obscure gastrointestinal bleeding; Capsule retention; Crohn's disease; Enteropathy

Core tip: We present the longest case of asymptomatic video capsule retention in the literature. With our case we would like to highlight that asymptomatic video capsule retention is not an indication for surgical retrieval. Capsule can retain for long time without harm. Surgical retrieval should be reserved for those patients in whom the expectant management, medical management and endoscopic therapy fails or in patients who are symptomatic with intestinal obstruction or perforation.

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Abstract

Video capsule endoscopy (VCE) is a safe innovative tool for investigating obscure gastrointestinal bleeding, Crohn's disease and other small bowel pathologies. The capsule is usually excreted with faeces within 24-48 h. Retention of capsule rarely occurs, and it usually depends on the indication of VCE. The longest reported case of capsule retention in the literature is 2.5 years. Surgical approach is considered effective to retrieve the retained capsule. We present a case of asymptomatic retention of capsule for four and half years in a 49-year-old man who underwent VCE to explore the cause of obscure gastrointestinal bleeding. It was successfully retrieved endoscopically. We will also briefly review the literature regarding the causes, different presentations and management of capsule retention.

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INTRODUCTION

Video capsule endoscopy (VCE) since its approval from Food and Drug Administration in August 2001 has become the innovative tool for investigating small bowel pathology mainly to determine the cause of obscure gastrointestinal bleeding, Crohn's disease, polyposis syndromes and evaluation of patients with complicated celiac disease, *etc*^[1]. VCE is noninvasive and is considered a safe procedure because the capsule is usually excreted with the feces within 24-48 h^[2]. However, if capsule retention occurs, it would help determine the underlying cause of gastrointestinal pathology. But there is always a concern of capsule retention which could potentially lead to acute intestinal obstruction and perforation requiring surgery who otherwise would have been treated medically^[3,4]. Furthermore, it is rare for video capsule

to stay in the GI tract for long duration without any symptoms. We report a case of the longest duration of retention of video capsule which was retrieved successfully with an endoscope.

CASE REPORT

A 49-year-old man with history of ulcerative colitis-status post subtotal colectomy done 13 years ago was referred to gastroenterology clinic by his family physician for evaluation of occasional gastrointestinal bleeding with drop in his hemoglobin to 8.4 g/dL from baseline of 10-11 g/dL. Since the time of subtotal colectomy, his underlying colitis remained stable. His past medical history included Ankylosing Spondylitis for which he was following rheumatology. He was managed only with physical therapy not requiring medication.

His daily medications included iron, folic acid and B12 supplements. He denied use of any Non-steroidal anti-inflammatory drugs (NSAIDs). There was no history of smoking and alcohol abuse in the past. His family history was significant for ulcerative colitis in father; however, no history of bowel cancer was reported. The patient did not admit to have abdominal pain, nausea, vomiting. There was no history of change in bowel movements. Initially he was losing weight following surgery but for last two years his weight has been stable.

He then underwent upper endogastroduodenoscopy (EGD), flexible sigmoidoscopy later followed by colonoscopy which did not reveal the cause of the gastrointestinal bleed. He was planned for VCE. First he underwent small bowel follow through (SBFT) which demonstrated all normal appearing small bowel loops with patent ileorectal anastomosis. Subsequently, he underwent VCE uneventfully. He did not report spontaneous passage of the capsule in one week which was confirmed by abdominal X-ray revealing retained capsule in right lower quadrant of abdomen as shown in Figure 1A. The result of VCE did not reveal any pathology causing obscure gastrointestinal bleeding and retained capsule. He did not have features of bowel obstruction both clinically and radiographically. He followed up periodically for 2 mo with serial imaging studies which showed capsule in different parts of the loops of bowel (Figure 1B).

Then he lost to follow up with our gastroenterology department as he moved out from the area. Subsequently, he returned for follow up for his ulcerative colitis after 4 years. Even at this time he did not report to have any symptoms of intestinal obstruction such as nausea, vomiting, abdominal pain, diarrhoea, *etc.* His abdominal X-ray at this time again demonstrated persistent retained capsule overlying the right upper quadrant of abdomen without any evidence of intestinal obstruction (Figure 1C). He was discussed with several options of management including surgery to retrieve the retained capsule. But he preferred non-surgical approach as he explained that he was not having symptoms due to the retained capsule.

Computed tomography (CT) abdomen reported the capsule in the bowel lumen at anastomotic site in the right upper quadrant (Figure 2). He then underwent colonoscopy with successful retrieval of the intact 4 year 5 mo 21 d-old retained capsule by a Roth net basket (Figure 3) from patent surgical anastomosis at the site of prior diverting loop ileostomy located at 120 cm proximal to the anal verge. During the follow up after two months, the patient did not report to have any consequences from the capsule retrieval procedure.

DISCUSSION

VCE is a simple, safe, non-invasive, reliable procedure which is well accepted and tolerated by the patient, without requiring any sedation, surgery or radiation exposure^[5]. Though rare, capsule retention is the major risk following VCE. The International Conference on Capsule Endoscopy (ICCE) 2005 defines capsule retention as having a capsule endoscope remain in the digestive tract for minimum 2 wk. Capsule retention is further defined as the capsule remaining in the bowel lumen unless it is recovered medically, endoscopically or surgically^[6].

Retention rate of video capsule is variable depending mostly on the clinical indication for VCE^[7-10]. It ranges from 0% in healthy subjects, to 1.5% in patients with obscure gastrointestinal bleeding, to 5% in patients with suspected Crohn's disease and 21% in patients with intestinal obstruction^[7,8]. In a recently published systematic review by Liao *et al*^[9], there were 184 capsule retentions in both prospective and retrospective studies of total 22840 procedures giving a pooled retention rate of 1.4%. The retention rate in obscure gastrointestinal bleeding, Crohn's disease, neoplastic lesions are 1.2%, 2.6% and 2.1% respectively^[9]. The other causes of retention are NSAID induced enteropathy, post-surgical stenosis, adhesions, tuberculosis, ischemia and radiation enteritis^[9,11]. Furthermore, rare causes include Meckel's diverticulum, peptic ulcer, cryptogenic multifocal stenosing enteritis with frequencies of less than 2% of total capsule retention^[7]. Based on these studies, the probability of capsule retention is higher in Crohn's disease, NSAIDs induced enteropathy and history of abdominal surgeries. Our patient also had the history of abdominal surgery such as subtotal colectomy which increased the risk of capsule retention. Thus obtaining the good medical history is essential to prevent the capsule retention. There are no other accepted methods including the imaging studies prior to VCE are useful to prevent occurrence of capsule retention^[6,12].

Retention of capsule is mostly asymptomatic or sometimes it causes partial bowel obstruction^[4,10,13,14]. Retention usually helps identify the etiology and site of obstruction by indicating the presence of underlying pathology. There are some studies in which VCE was done in the patients who already had symptoms of partial bowel obstruction. Even in those studies, the patients did not develop symptoms of acute intestinal obstruction rather

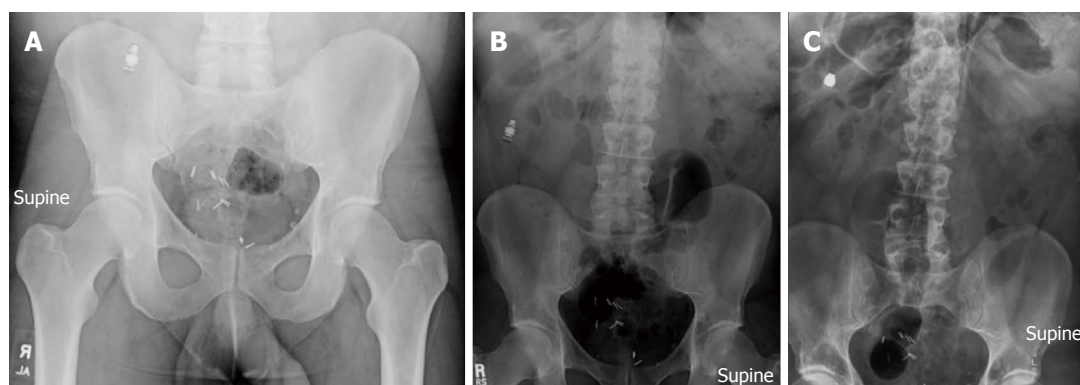


Figure 1 Abdominal X rays done at several time intervals following video capsule endoscopy showing retention of video capsule. Several surgical clips are also present at pelvis. A: Follow up in 1 wk showing capsule in right lower quadrant of abdomen; B: Follow up in two months showing capsule in right mid abdomen laterally; C: Follow up after 4 years showing capsule in right upper quadrant of abdomen.

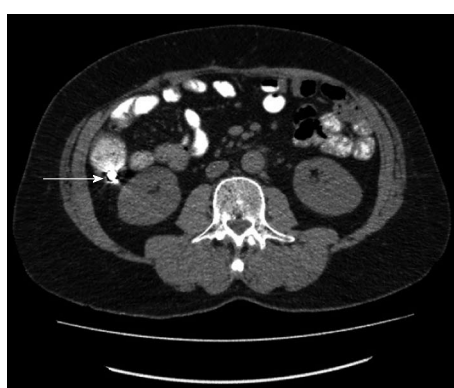


Figure 2 Computer tomography abdomen done for further evaluation of retained capsule which is present in bowel lumen (arrow).

the retention of capsule helped the clinician to determine the etiology^[4]. The retrospective study of 1000 capsule endoscopies by Li *et al*^[10] demonstrated 1.4% retention rate which all were asymptomatic. Similarly another study revealed development of partial small bowel obstruction in 15% of patients who had capsule retention; the remaining 85% were asymptomatic^[13]. In the study from Cheifetz *et al*^[4] with 19 cases and Yang *et al*^[14] with 31 cases of capsule study in patients of underlying suspected small bowel obstruction, none of the patients with retained capsule developed acute intestinal obstruction requiring surgery.

The studies have suggested that asymptomatic capsule retention can undergo expectant, medical and endoscopic management or even surgical intervention^[14-17]. Meanwhile, the longest duration of retention is 2.5 years reported by ICCE without reporting the sequelae associated with long term retention of capsule^[6]. But the patient should not undergo magnetic resonance imaging^[17]. Authors have advocated that surgical intervention not only allows removal of the capsule but also can remove the offending pathology causing capsule retention^[9,14-16]. In a systematic review of 184 capsule retentions from Liao *et al*^[9], retained capsules were excreted spontaneously or by pharmaceutical manipulation in 15%, endoscopically in 12% and the majority 58.7% were removed surgically. Baichi *et al*^[16]

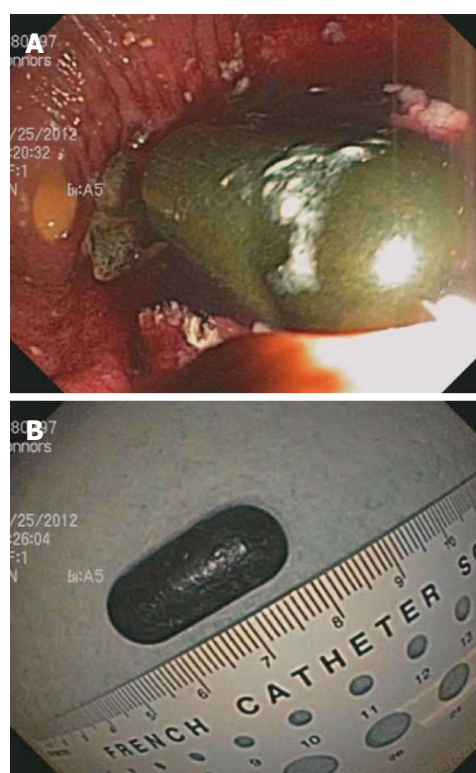


Figure 3 Capsule seen in colonoscopy (A) and video capsule was retrieved intact after 4 year 5 mo and 21 d with endoscopically (B).

studies five permanent capsule retention out of which two cases had successful endoscopic retrieval and remaining three cases required surgical intervention. Another study presented three cases of capsule retention out of which two patients needed surgery for retrieval and other patient passed capsule spontaneously in six months with medical treatment^[14]. Therefore, these studies have demonstrated that majority of patients eventually require surgical retrieval but non-surgical management could be the best option to begin with in a patient without symptoms of acute intestinal obstruction. This is also shown in another large study in which out of 32 retained capsules, 21 (65.6%) patients received medical treatment resulting in spontaneous passage

of the capsule in 11 (34.4%). Rest 10 (31.3%) patients ultimately underwent surgical intervention to retrieve the capsule^[15]. Medical management usually consists of use of anti-inflammatory agents and colonoscopy preparation fluids or enemas^[10,18]. There are few case reports of capsule retention causing intestinal obstruction in patients with underlying Crohn's disease and history of abdominal surgeries who were successfully treated with disimpaction with intravenous steroids and diatrizoate upper GI series and enemas^[17,18].

Nevertheless, there are only few cases of complication reported in the literature due to retained capsule. In a recent analysis of 2300 capsule examinations, six patients had acute obstructive symptoms and also reported one death related to complications after acute surgical capsule retrieval^[3]. There is also a case report of retained capsule causing intestinal perforation after two months following VCE in an elderly man who underwent VCE for evaluation of anemia^[19]. There is another case of capsule impaction and subsequent fracture of the capsule in the small bowel six months following VCE^[20]. Thus, though rare, we need to keep in mind that there is a possibility of acute complication of capsule retention.

With our case we would like to make physicians aware of the possibility of asymptomatic capsule retention even after four to five years following VCE. We also highlight that retained capsule can be retrieved non surgically even if it is retained for long period of time in the patient who is asymptomatic.

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Oldest biliary endoprosthesis *in situ*

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Author contributions: Familiari L and Consolo P performed the ERCP; Pallio S, Scalisi G, Cintolo M, Tortora A and Giacobbe G managed the patient during and after hospitalisation; Crinò SF performed the US; Crinò SF and Scalisi G wrote the paper and revised the English in the paper.

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Key words: Common bile duct stones; Cholangitis; Biliary endoprosthesis; Endoscopic retrograde cholangiopancreatography; Endoscopic sphincterotomy

Core tip: Endoscopic extraction of biliary tract stones is safe and effective. When the procedure is not successful the placement of a plastic biliary endoprosthesis can be a solution. To date no consensus has been reached regarding how long the biliary prosthesis should remain *in situ*. This case report represents the oldest *in situ* plastic biliary endoprosthesis ever reported in the literature. Despite the fact that endoprostheses will inevitably occlude after 3 to 5 mo *in situ*, they may still prevent impaction of stones in the distal part of the common bile duct and ensure free flow of bile even if the endoprostheses are obstructed, calcified and have a bilious coat.

Abstract

The advantages of endoscopic retrograde cholangiopancreatography over open surgery have made it the predominant method of treating patients with choledocholithiasis. After sphincterotomy, however, 10%-15% of common bile duct stones cannot be removed with a basket or balloon. The methods for managing "irretrievable stones" include surgery, mechanical lithotripsy, intraductal or extracorporeal shock wave lithotripsy and biliary stenting. The case presented was a referred 82-year-old Caucasian woman with a 7-year-old plastic biliary endoprosthesis *in situ*. To the best of our knowledge the examined endoprosthesis is the oldest endoprosthesis *in situ* reported in the literature. Endoscopic biliary endoprosthesis placement remains a simple and safe procedure for patients with stones that are difficult to manage by conventional endoscopic methods and for patients who are unfit for surgery or who are high surgical risks. To date no consensus has been reached regarding how long a biliary prosthesis should remain *in situ*. Long-term biliary stenting may have a role in selected elderly patients if stones extraction has failed because the procedure may prevent stones impaction and cholangitis.

Consolo P, Scalisi G, Crinò SF, Tortora A, Giacobbe G, Cintolo M, Familiari L, Pallio S. Oldest biliary endoprosthesis *in situ*. *World J Gastrointest Endosc* 2013; 5(7): 356-358 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i7/356.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i7.356>

INTRODUCTION

Nearly a third of patients with common bile duct (CBD) stones are at risk of developing recurrent cholangitis or pancreatitis^[1]. These complications are associated with significant mortality in elderly or infirm patients. Therefore a prompt intervention to remove the stones (or at least establish an uninterrupted flow of bile) is required. With a success rate of over 90% endoscopic sphincterotomy and stones extraction comprise the treatment of choice for patients of all ages affected by choledocholithiasis. Large stones that cannot be extracted with the conventional endoscopic means present a greater challenge,

and a variety of surgical and non-surgical techniques are now available to remove these stones. Endoscopic insertion of biliary endoprosthesis has been proposed as an alternative for such high-risk patients and primarily in the case of failed stones extraction. Biliary stenting aims to prevent stone impaction by perpetuation of bile flow and helps to avoid subsequent life-threatening complications such as cholangitis and even cholangiosepsis^[2].

CASE REPORT

An 82-year-old Caucasian woman complaining of symptoms characterised by itch and recurrent episodes of fever (maximum body temperature 38.5 °C) for approximately 6 mo and treated using quinolone and cholestyramine respectively was referred to our unit. The patient underwent cholecystectomy for gallstones in 2000 and in 2005, at a non referral centre, the patient underwent endoscopic-retrograde-cholangiopancreatography (ERCP), which revealed dilatation and multiple stones of the CBD. After the sphincterotomy, because of the failure of stones extraction, a biliary endoprosthesis was implanted to avoid cholangitis. ERCP was not repeated and the endoprosthesis remained *in situ* until this admission. During hospitalisation at our unit, the patient underwent abdominal ultrasonography that revealed hyperechoic streaks along the CBD and a computed tomography abdominal scan that revealed moderate dilatation of the CBD and intrahepatic bile ducts with aerobilia. The routine blood parameters were all normal except for gamma glutamyl transferase (GGT) (101 U/L; normal value: 10-54 U/L). It was decided that another ERCP would be performed. The old double pigtail endoprosthesis was removed, the sphincterotomy was extended and the stones were extracted using a Dormia basket. The original prosthesis was obstructed, calcified and had a bilious coat (Figure 1). The post-operative course was complicated by the occurrence of fever (maximum body temperature 38.5 °C), which cleared up after treatment with quinolone.

DISCUSSION

Choledocholithiasis is one of the most common gastrointestinal diseases encountered in clinical therapeutic endoscopy practice. Endoscopic sphincterotomy and stone extraction are widely performed as the primary treatment methods for patients with CBD stones, with an 80% to 90% success rate and a complication rate of less than 10%^[3]. Approximately 10% to 15% of CBD stones are difficult to remove using conventional endoscopic sphincterotomy and balloon/basket extraction techniques, including mechanical lithotripsy. Multiple or large CBD stones (> 20 mm in diameter), the presence of periampullary diverticula, narrowing or stricture of the distal CBD, limited sphincterotomy caused by small papillae and no visible intramural course of the CBD in the duodenal wall all influence the probability of successful stone extraction^[4]. In such cases, temporary biliary stenting is a safe and effective bridge therapy. This stenting

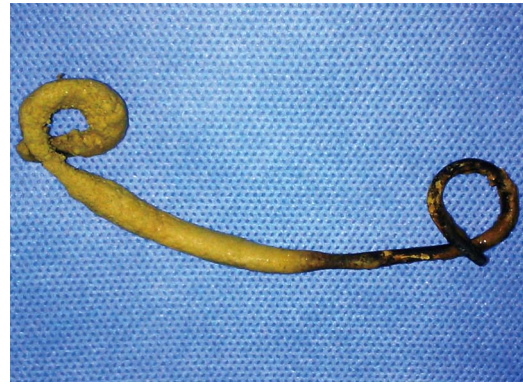


Figure 1 The oldest biliary endoprosthesis.

has several advantages, primarily the prevention of the incarceration of the stone at the ampulla of Vater and maintenance of biliary drainage. In addition, stenting can reduce the possibility of unnecessary surgery in patients exhibiting technical difficulties in stone removal^[5-7]. Furthermore, friction between the stones and the prosthesis induces fragmentation, decreasing stone size, and thus facilitating removal^[8]. To date, no consensus has been reached regarding how long the biliary prosthesis should remain *in situ*. Despite the fact that the endoprosthesis will inevitably occlude after 3 to 5 mo *in situ*, it is believed to work by splinting the stones or preventing impaction in the distal common bile duct or both, thus ensuring free flow of bile. The most serious drawback of a long-term indwelling biliary endoprosthesis is the risk of recurrent cholangitis, which is reported in 3.5% to 40% of patients. The median time to onset of cholangitis appears to be approximately 16 wk and occurs mainly in patients with an *in situ* gallbladder or in cases of prosthesis insertion without sphincterotomy^[9-12]. Several previous studies have suggested that permanent biliary stenting may be a definitive therapy for endoscopically unextractable common duct stones in selected elderly patients who are poor surgical candidates. When biliary symptoms do recur, they can usually be treated conservatively with antibiotics, a prosthesis change, or both^[2,13].

To the best of our knowledge, our case report represents the oldest *in situ* plastic biliary endoprosthesis ever reported in the literature. Other studies have reported stent survival up to 6 years^[12,14]. These reports confirm that biliary endoprostheses may prevent impaction of stones in the distal part of the common bile duct and maintain biliary flow despite being obstructed, calcified and having a bilious coat. The stent may function as a wick around to drain the bile, rather than as a conduit for bile. The present case demonstrates that in high-risk patients, a regular endoprosthesis exchange might be delayed according to the patient's individual needs without fearing inevitable complications. However, further case-controlled studies are needed.

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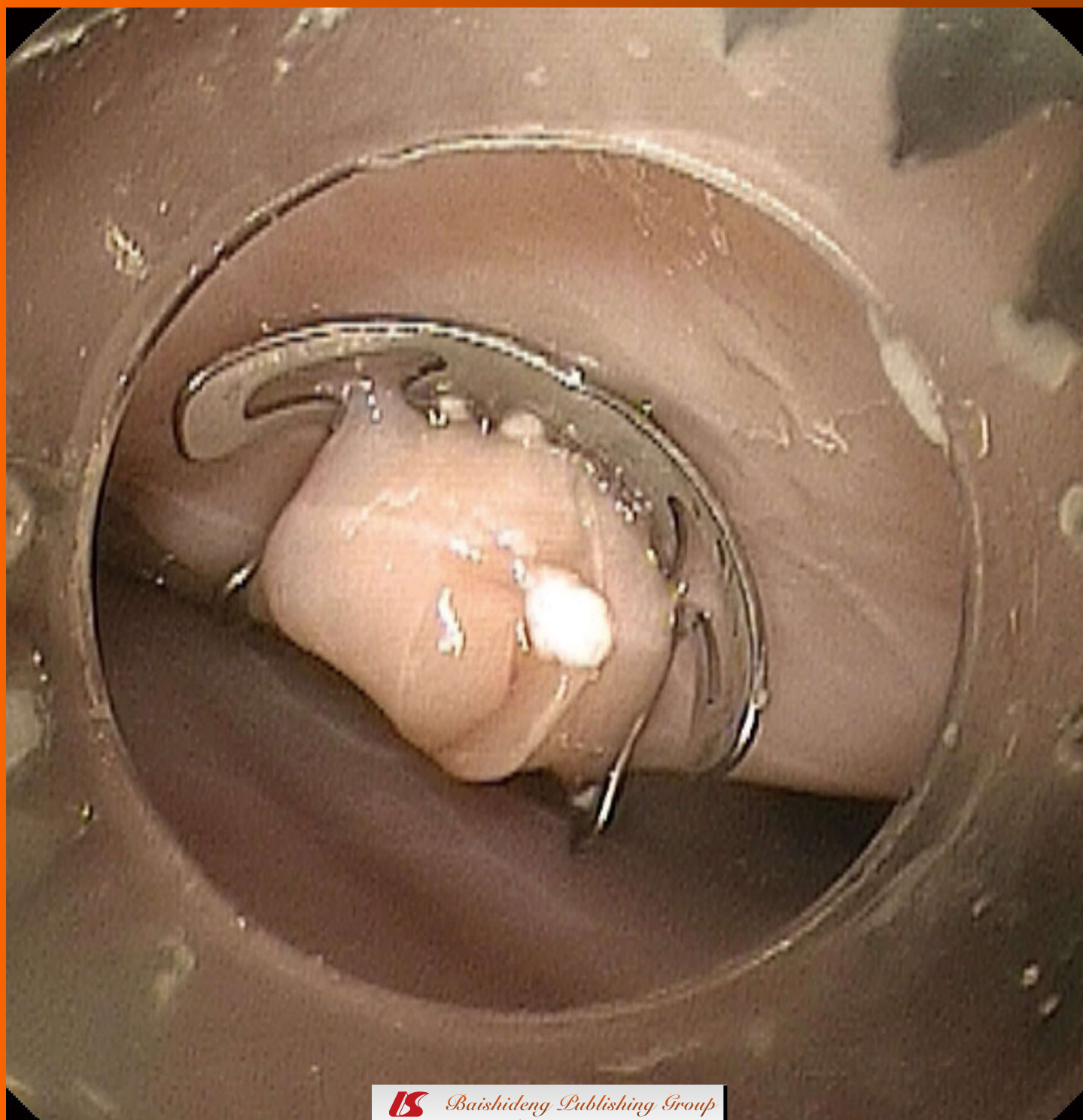
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Air embolism complicating gastrointestinal endoscopy: A systematic review

Suman Donepudi, Disaya Chavalitdhamrong, Liping Pu, Peter V Draganov

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Therefore, we wanted to review the risk factors, the clinical presentation, and the therapy of an air embolism from the perspective of the practicing endoscopist.

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Key words: Air embolism; Endoscopy; Endoscopic retrograde cholangiopancreatography; Complications; Therapy

Core tip: Air embolism at the time of endoscopy can cause cardiovascular, pulmonary, and neurological symptoms. Symptom onset during the position change from prone to supine is characteristic and should trigger immediate suspicion for air embolism. Potentially lifesaving therapeutic measures should be promptly initiated, including placing the patient in Trendelenburg and left lateral decubitus position, high-flow oxygen, volume expansion and urgent hyperbaric oxygenation therapy.

Abstract

Gastrointestinal endoscopy has become an important modality for the diagnosis and treatment of various gastrointestinal disorders. One of its major advantages is that it is minimally invasive and has an excellent safety record. Nevertheless, some complications do occur, and endoscopists are well aware and prepared to deal with the commonly recognized ones including bleeding, perforation, infection, and adverse effects from the sedative medications. Air embolism is a very rare endoscopic complication but possesses the potential to be severe and fatal. It can present with cardiopulmonary instability and neurologic symptoms. The diagnosis may be difficult because of its clinical presentation, which can overlap with sedation-related cardiopulmonary problems or neurologic symptoms possibly attributed to an ischemic or hemorrhagic central nervous system event. Increased awareness is essential for prompt recognition of the air embolism, which can allow potentially life-saving therapy to be provided.

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INTRODUCTION

Air embolism is a consequence of direct communication between a source of air and the vasculature and a pressure gradient favoring the passage of air into the circulation. The effect of an air embolus depends upon both the rate and the volume of air introduced into the circulation. A venous air embolism occurs when air enters the systemic venous circulation. An arterial air embolism results from introduction of air into the arterial system and can produce ischemia of any organ. An air embolism

is an uncommon but potentially catastrophic event. Many cases are subclinical with no adverse outcome. However, severe cases are characterized by hemodynamic collapse and/or acute vascular insufficiency of specific organs, such as the brain or the spinal cord. Symptoms may be nonspecific, and therefore, a high index of clinical suspicion for a possible air embolism is required to prompt investigations and initiate appropriate therapy.

RESEARCH

We conducted a systematic review by searching the PubMed database on reported air embolisms complicating all endoscopic procedures. Medical subject headings “endoscopy, complications, air embolism, cerebrovascular accident, cardiovascular abnormalities, esophago-gastroduodenoscopy (EGD), enteroscopy, colonoscopy, sigmoidoscopy, endoscopic ultrasound (EUS), and endoscopic retrograde cholangiopancreatography (ERCP)” were used in the title, the abstract, or the index term fields. Manual searches were then conducted using the reference lists from identified articles.

RISK FACTORS FOR AIR EMBOLISM

Air embolism is most commonly associated with an ERCP, but it can result from any endoscopic procedure including an EGD, an enteroscopy, an EUS, a colonoscopy, and a sigmoidoscopy.

Risk factors for an air embolism that have been reported are previous interventions or surgeries of the bile duct system, transhepatic portosystemic shunt^[1-3], blunt or penetrating trauma to the liver^[4], inflammation of the digestive system, post-surgical gastrointestinal fistula^[5-7], and particular interventional techniques.

The inflammatory conditions associated with an increased risk for an air embolism include inflammation of the bile duct or surrounding veins (pylephlebitis), hepatic abscesses, inflammatory bowel diseases, necrotizing enterocolitis, and mesenteric ischemia^[2,7,8]. In addition, gastrointestinal tumors and biliary atresia have been described as risk factors^[9,10].

Interventional techniques include cholangioscopy, biliary sphincterotomy, metal stent placement, liver biopsy, insufflation of air with high pressure, excessive amount and/or increased rate of air infusion, procedural site located higher than the level of the heart, and the use of nitrous oxide (N₂O)^[3,11-18].

MECHANISMS AND CLINICAL SIGNS AND SYMPTOMS

A number of potential mechanisms for air entry into the venous system have been described. These include intramural dissection of insufflated air into the portal vein, transection of duodenal vein radicles, biliary-venous fistulas/shunts, portocaval collaterals, air flow directly into the hepatic veins or inferior vena cava, retrograde

flow into cerebral veins *via* superior vena cava^[7], inability of the pulmonary circulation to filter out gas emboli^[19,20], or entry into the vertebral venous plexus^[21]. Rapid entry or large volumes of air entering the systemic venous circulation causes a substantial strain on the right ventricle, especially if this results in a significant rise in pulmonary artery pressures. This increase in pulmonary artery pressure can lead to right ventricular outflow obstruction and further compromise pulmonary venous return to the left heart. Consequently, the diminished pulmonary venous return will lead to decreased left ventricular preload with resultant decreased cardiac output, and eventually, systemic cardiovascular collapse.

Importantly, a venous air embolism can be limited to the portal venous system or can evolve into a systemic air embolism through intracardiac shunts, intrapulmonary right to left shunts, retrograde flow into cerebral veins *via* the superior vena cava, or air passage into the left atrium *via* the pulmonary veins^[18,22]. The most common cause of an intracardiac shunt is a patent foramen ovale^[11,23]. Atrial septal defect, arterio-venous shunts, and intrapulmonary shunts are also reported mechanisms^[24-26].

The systemic air embolism can cause cardiovascular, pulmonary, and neurological symptoms^[15]. Cardiovascular signs, symptoms, and findings include arrhythmia, hypotension, myocardial ischemia, right heart failure, cardiovascular collapse, and cardiac arrest. Pulmonary signs, symptoms, and findings include acute dyspnea, tachypnea, breathlessness, rales, wheezing, decrease in end tidal carbon dioxide concentration, hypoxia, cyanosis, and respiratory failure. Neurological signs, symptoms, and findings include eye deviation, dilated pupil(s), failure to regain consciousness after anesthesia, hypertonicity, altered mental status, loss of consciousness, hemiparesis, cerebral hypoperfusion, cerebral edema, and coma.

In the case of an ERCP-related air embolism, typically the symptoms appear or get significantly worse when the patient is repositioned from prone to supine position at the end of the procedure. This patient deterioration with position change should immediately raise a red flag and trigger suspicion for an air embolism as the underlying cause of the patient symptoms.

REPORTED CASES OF AIR EMBOLISM

We were able to identify 41 cases of air embolism in the published literature following various endoscopic procedures.

Air embolism cases following EGD and intraoperative small bowel endoscopy

The first case of air embolism following an EGD was reported by Lowdon *et al.*^[18] in 1988. A 5-wk old infant with biliary atresia status post Kasai procedure (hepatoporo-tojejunostomy) died during endoscopy, and the autopsy revealed air in both the right atrium and right ventricle and in the large hepatic vein in the area of the porta hepatis. The patient was also found to have a patent for-

men ovale and air in the coronary arteries. The authors proposed that air under pressure dissected across the diseased hepatic tissue into the large hepatic vein lying just below the denuded liver surface. This combined with her patent foramen ovale resulted in the systemic embolism.

Christl *et al*^[3] described the first incident of a cerebral air embolism following endoscopy in a patient with a duodenal ulcer and a duodenocaval fistula. It was believed that the air emboli exceeding the absorptive rate of the pulmonary capillary bed might be the cause in this patient, especially with the total amount of air entering the inferior vena cava.

A case report by Katzgraber *et al*^[14] identified an embolism risk when air insufflation occurs in the presence of damaged vessels. The patient, whom had a history of a perforated gastric ulcer surgically treated 13 years prior, underwent an upper endoscopy for the evaluation of epigastric pain. High-volume air insufflation was noted during the procedure. As the study was continued, the patient suddenly went into cardiac arrest and resuscitation was unsuccessful. On forensics, the right gastric vein was found to be eroded most likely due to his history of multiple ulcerations. The presence of this lesion in combination with the amount of insufflation required allowed air to enter the venous supply, and eventually, enter the heart causing death.

McAree *et al*^[27] reported a cerebral air embolism in a patient being evaluated for metastatic adenocarcinoma of an unknown origin. Abdominal computed tomography (CT) scan showed ascites and a thickened cecal wall; cytology study of the ascites determined the presence of an adenocarcinoma. Soon after, the patient began vomiting blood and an EGD showed erosive esophagitis. As the procedure was ending, the patient became unresponsive and displayed neurological symptoms. An emergency cerebral CT confirmed air in the brain, specifically the right frontotemporal area. The esophagitis mucosal breakdown is to be considered as the leading cause of the embolism.

Meier *et al*^[28] reported a patient with an air embolism during an EGD. The patient had a history of a pancreaticoduodenectomy for pancreatic adenocarcinoma and a percutaneous transhepatic cholangiography (PTC) for recent ascending cholangitis. An EGD was done due to the patient developing melena. As the scope was maneuvered towards the hepaticojejunostomy site, the patient's condition became unstable; unfortunately, the patient was unable to be successfully resuscitated and passed away. The investigators believed the PTC catheter may have created a fistula between the vasculature and the biliary tract. This abnormality allowed the air to enter the venous supply, specifically the hepatic veins and inferior vena cava, upon air insufflation during endoscopy.

Pandurangadu *et al*^[24] reported about an incident of a cerebral embolism in 2010. The patient received an outpatient EGD, which required an esophageal biopsy and ablation of duodenal arteriovenous malformations. Shortly after the EGD procedure, he presented to the emergency room with neurological symptoms of sudden

onset lethargy and left-sided weakness. CT scan of the brain showed multiple gas emboli in two areas, the right frontal lobe and frontoparietal region. A transesophageal echocardiogram (TEE) was also done, which ruled out a patent foramen ovale. Therefore, the study proposed the most likely cause of the embolism was the duodenal arteriovenous malformations.

Additionally in 2010, a case reported by Park *et al*^[23] described a paradoxical air embolism during an intraoperative small bowel endoscopy. An adolescent female, with a history of a Kasai operation for biliary atresia, presented with gastrointestinal bleeding. The plan was for an exploratory laparotomy and intraoperative endoscopy for further evaluation. It must also be noted she had a previous exploratory laparotomy three months prior for hematochezia, which was unremarkable with the exception of some bluish edema on the small bowel wall. All preoperative protocols were performed, including an abdominal CT scan; the scan revealed a highly, irregular liver architecture showing massive fibrosis. As the endoscopy procedure ensued, excessive air insufflation was needed to facilitate visualization. An ulcerative lesion was found near the site of the previous Kasai procedure. The patient thereafter became unstable systemically, and immediate stabilization methods were started. TEE confirmed air bubbles entered the heart and the systemic vasculature. In this case, there were multiple risk factors present. The high amount of air insufflation administered and the ulcerative lesion are two of the immediate possibilities. However, two other risk factors can be added. Hopkins *et al*^[29] found that 47% of patients with chronic liver disease possess an intrapulmonary right to left shunt. The other possibility is the patient's history of biliary atresia. A previous study showed that 18 of 88 biliary atresia patients, a total of 9.1%, between the ages of 8 mo and 16 years old possessed an intrapulmonary shunt; this shunt can cause fatal complications in previously operated biliary atresia patients^[9].

Reported air embolism cases following colonoscopy and sigmoidoscopy

Chorost *et al*^[21] reported on a case of a routine screening colonoscopy. Three days after the procedure, the patient presented with severe, lower back pain. After a CT scan of the abdomen, it became evident there was air anterior to the lumbar vertebrae. Batson^[30], in 1940, suggested that an increase in intraabdominal pressure could allow venous effluent from the pelvis to enter into unimpeded valveless venous channels, such as in this example, the vertebrae. Therefore in this case, it was proposed the combination of the high intraabdominal pressure along with the low intraluminal pressure system of the vertebral venous system provided an optimum pressure gradient for air to seep, causing an air embolism.

Mittnacht *et al*^[31] reported the only sigmoidoscopy case known to be complicated by an air embolism. The patient had a history of long-standing Crohn's disease and 2 years status post left partial colectomy with de-

Table 1 Reported cases on air embolism complicated endoscopic retrograde cholangiopancreatography

Case	Ref.	Age/sex	Risk factor(s)	Diagnosis	Outcome
1	Bisceglia <i>et al</i> ^[7]	78/male	Surgical gastroduodenal resection	Pulmonary air embolism	Dead
2	Rabe <i>et al</i> ^[12]	87/male	Metal stent placement	Cerebral air embolism	Survived
3	Rabe <i>et al</i> ^[12]	54/male	Billroth II operation, Metal stent placement	Cardiac air embolism	Dead
4	Jow <i>et al</i> ^[38]	65/male	Biliary duct stones/inflammation	Cardiac air embolism	Dead
5	Maccarone <i>et al</i> ^[1]	45/male	Percutaneous transhepatic biliary drainage	Cerebral air embolism	Survived
6	Siddiqui <i>et al</i> ^[37]	43/female	Biliary sphincterotomy, liver biopsy	Venous air embolism	Dead
7	Nayagam <i>et al</i> ^[39]	57/male	-	Cerebral air embolism	Dead
8	Kennedy <i>et al</i> ^[8]	63/female	Biliary sphincterotomy	Venous air embolism	Dead
9	Stabile <i>et al</i> ^[6]	65/male	Biliary sphincterotomy, PTC	Cerebral air embolism	Dead
10	Mohammedi <i>et al</i> ^[4]	27/male	Biliary sphincterotomy, blunt hepatic trauma	Cardiac air embolism	Survived
11	Romberg ^[40]	53/male	Biliary duct stones	Cardiac air embolism	Survived
12	Rangappa <i>et al</i> ^[41]	50/female	Biliary duct stones	Cerebral air embolism	Dead
13	Bechi <i>et al</i> ^[33]	79/female	Biliary sphincterotomy	Cerebral air embolism	Survived
14	Goins <i>et al</i> ^[16]	72/female	Cholangiocarcinoma	Cerebral air embolism	Survived
15	Cha <i>et al</i> ^[42]	50/female	Biliary duct stones, liver abscesses, choledochoduodenostomy	Cardiac air embolism	Dead
16	Di Pisa <i>et al</i> ^[13]	8/male	Splenoenteric portal shunt	Venous air embolism	Survived
17	Giuly <i>et al</i> ^[43]	60/female	Biliary sphincterotomy, choledochal varices	Venous air embolism	Survived
18	van Boxel <i>et al</i> ^[44]	82/male	-	Cerebral air embolism	Survived
19	Tan <i>et al</i> ^[45]	82/female	Metal stent placement	Cerebral air embolism	Dead
20	Nern <i>et al</i> ^[46]	58/female	Cholangiocarcinoma	Cerebral air embolism	Dead
21	Simmons ^[47]	Not available	Biliary sphincterotomy	Venous air embolism	Survived
22	Merine <i>et al</i> ^[48]	39/female	Biliary sphincterotomy	Venous air embolism	Survived
23	Barthet <i>et al</i> ^[49]	31/male	Biliary sphincterotomy	Venous air embolism	Survived
24	Efthymiou <i>et al</i> ^[11]	62/female	Cholangioscopy	Cerebral air embolism	Survived
25	Our case ^[50]	66/male	Metal stent placement	Cerebral air embolism	Dead
26	Our case ^[50]	51/female	Status post Whipple's operation	Spinal air embolism	Survived

PTC: Percutaneous transhepatic cholangiography.

scending colostomy, which was complicated by poor wound healing and fistula formations. The patient required the sigmoidoscopy before a revision of her previous abdominal bowel surgery. During the procedure, the patient went into cardiac arrest as a result of an air embolism. The history of Crohn's disease, which led to inflamed and deteriorated mucosa, was proposed to allow air entry. Also proposed, there was possible injury to hemorrhoidal veins during the biopsy of the sigmoid. An additional risk was the patient being in Trendelenburg position, allowing for the surgery site to be above the heart.

Reported air embolism cases following EUS

Pfaffenbach *et al*^[32] reported about a patient with severe upper abdominal pain requiring an EUS for evaluation of a pancreatic head lesion. EUS-guided fine needle aspiration was performed. Hepatic portal venous gas was found on a follow up abdominal ultrasonography.

Reported air embolism cases following ERCP

Most described cases of endoscopy-related air embolism have been related to an ERCP. We recently reported two air embolism cases following an ERCP, one with an intracranial air embolism and one with a spinal air embolism. To date, a total of 26 cases of systemic air embolism complicating ERCP have been reported (Table 1). Described risk factors for an air embolism following an ERCP are previous interventions or surgeries of the bile duct system, transhepatic portosystemic shunts, per-

cutaneous transhepatic biliary drains, blunt or penetrating trauma to the liver, sphincterotomy, metal stent placement, the inflammation of the bile duct or surrounding veins, hepatic abscesses or tumors, liver biopsy, and insufflation of air with high pressure. Cholangioscopy with air insufflation directly into the bile duct appears to be a particularly strong risk factor for an air embolism. Reported clinical presentations are cardiovascular, pulmonary, and neurological symptoms. Again, we want to emphasize the onset of symptoms or symptom escalation with change of patient position from prone to supine should immediately trigger suspicion for an air embolism.

DIAGNOSIS

The diagnosis of an air embolism is often difficult and is complicated by the fact that air may be rapidly absorbed from the circulation while diagnostic tests are being arranged. Exclusion of other life-threatening processes is generally required.

Transthoracic and transesophageal echocardiography have been used to document the presence of air and may show evidence of acute right ventricular dilation and pulmonary artery hypertension consistent with air embolism. An echocardiography also aids in the diagnosis of cardiac anomalies, assessment of volume status, and cardiac contractility; this allows exclusion of other causes of hypotension, dyspnea, and aiding in further patient management. End-tidal CO₂ monitoring may show a fall in end-tidal CO₂; however, this finding is nonspecific and also

occurs with pulmonary embolism, massive blood loss, circulatory arrest, and disconnection from the anesthesia circuit. The pulmonary artery catheter may show a rise in pulmonary artery pressure in venous air embolism, but this is a nonspecific finding. Ventilation-perfusion scan abnormalities may be seen in the setting of a massive air embolism, but this is also a nonspecific finding and the perfusion defects resolve rapidly. The chest CT can detect air with higher sensitivity for massive air emboli. A pulmonary angiography could also be useful but may be normal often times in patients who have suffered an air embolism because of rapid resorption of air.

MANAGEMENT

The most crucial step in patient management is to maintain a high index of suspicion for an air embolism. An air embolism should be included in the differential diagnosis of procedural or periprocedural cardiopulmonary instability and neurologic symptoms, particularly in patients with recognized risk factors. Since the clinical presentation of an air embolism can significantly overlap with sedation-related problems and ischemic or hemorrhagic cerebrovascular events, some simple maneuvers to decrease the impact of a potential air embolism should be promptly initiated while the definitive diagnosis is established. These maneuvers include: (1) immediately stop the procedure if at all possible; (2) administer high flow 100% oxygen, which can reduce air bubbles expansion; (3) initiate high volume normal saline infusion; (4) place the patient in Trendelenburg (feet higher than the head) and left lateral decubitus position in order to minimize air migration to the brain and to force-out air from the right ventricular outflow tract^[33], thereby increasing venous return^[23]; and (5) if N₂O is being used, it must be discontinued because of its ability to rapidly diffuse into the trapped air bubbles, causing an additive effect on the embolism^[23].

After these initial stabilizing measures are implemented, which should take no more than a few minutes, a decision has to be made regarding the type of evaluation needed to secure the diagnosis. This is a crucial branching point in the management of these patients. Since cerebrovascular accident is most commonly suspected in patients with neurologic symptoms, arrangements for an urgent head CT scan are typically made. If the underlying problem is an air embolism, the patient being sent for a CT scan can have some serious, adverse consequences, because it will delay the diagnosis and the application of specific targeted therapy. Therefore if an air embolism is suspected, a bedside echocardiogram should be promptly performed to quickly secure the diagnosis with visualization of air within the right heart. This can have immediate therapeutic implications. An air aspiration *via* a central venous catheter can be done, and arrangements for urgent hyperbaric oxygenation therapy can be carried out. Hyperbaric oxygenation therapy may reduce air bubble size, accelerate nitrogen reabsorption, and increase the

oxygen content of arterial blood; this potentially reduces the ischemia. In the event of circulatory collapse, cardiopulmonary resuscitation (CPR) should be initiated in order to maintain the cardiac output. CPR may also serve to break large air bubbles into smaller ones and force air out of the right ventricle into the pulmonary vessels.

PROPHYLACTIC MEASURES TO DECREASE THE RISK OF AIR EMBOLISM

Using CO₂ for insufflation instead of air can eliminate the risk of an air embolism, because CO₂ can be easily absorbed^[34]. The use of CO₂ for insufflation during gastrointestinal endoscopy has been shown superiority than using room air by multiple randomized controlled trials and a meta-analysis^[35,36]. It was associated with a decreased postprocedural pain, flatus, and bowel distension. CO₂ insufflation also appears to be safe in patients without severe underlying pulmonary disease. This finding supports the use of CO₂ in most cases if available. In our unit, we perform all endoscopies with CO₂; if CO₂ is not available for routine use, we believe it must be used in all cholangioscopy cases or when other risk factors are present.

Another option for patients at risk is to use a precordial Doppler probe monitor during the procedure; it can quickly detect air within the heart and pulmonary vasculature before clinical symptoms may appear^[37].

CONCLUSION

In summary, endoscopists should be aware of the signs and symptoms of an air embolism. In patients with risk factors, prophylactic measures can be applied. A high index of suspicion for an air embolism should be maintained, because prompt recognition can allow timely administration of specific, potential life-saving therapy.

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Fetal radiation exposure: Is monitoring really needed?

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Core tip: The effects of endoscopic retrograde cholangiopancreatography (ERCP) on pregnant women, addressed in the recent article by Smith *et al*, is an interesting topic. Despite the large sample of patients investigated by the authors, strong experimental evidence on this topic is still lacking. ERCP should be performed only with a therapeutic purpose and by experienced ERCP endoscopists, preferably during the second trimester of pregnancy.

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Abstract

The effect of fetal radiation during endoscopic retrograde cholangiopancreatography (ERCP) on pregnant women is a very interesting topic. Smith *et al* recently estimated the fetal radiation exposure in pregnant women undergoing ERCPs using thermoluminescent dosimeters (TLDs). The authors concluded that TLDs are unnecessary during ERCP with modified techniques. We believe that an extreme caution is needed in clinical practice before drawing such conclusions when they are not strongly supported by enough experimental evidence. Therefore, we recommend that fetal radiation exposure be monitored in clinical practice by using dosimeters, bearing in mind that all relevant techniques to control and minimize the exposure must be applied.

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Key words: Endoscopic retrograde cholangiopancreatography; Pregnancy; Fetal radiation exposure; Thermoluminescent dosimeters; Post-endoscopic retrograde cholangio-pancreatography pancreatitis

COMMENTARY ON HOT TOPICS

The effects of endoscopic retrograde cholangiopancreatography (ERCP) on pregnant women, addressed in the recent article by Smith *et al*^[1], is an interesting topic. It is estimated that 3%-12% of pregnancies are complicated by gallstone disease. In pregnant women weight increase and hormonal changes are responsible for an increase in the prevalence of cholelithiasis or gallbladder sludge. Uncomplicated cholelithiasis should preferably be treated before planning the pregnancy or during the postpartum phase. Fortunately, a pregnancy does not increase the frequency or the severity of complicated gallstone disease. However, when pancreatobiliary disease comes in an acute form, such as acute pancreatitis or cholangitis, there are increased rates of the morbidity and mortality for both the mother and the fetus^[2-4]. Since 1990, ERCP has been used in biliary stone disease during pregnancy, although this technique could increase the risk of maternal complications (such as bleeding, perforation, pancreatitis), as in non-pregnant women. Moreover, fetal teratogenicity or tumorigenesis is an additional risk factor for pregnant patients. For these reasons, ERCP is

nowadays only used for therapeutic purposes.

The irradiation risk for the fetus depends on both deterministic and stochastic effects. Deterministic effects are dose-correlated, can affect the growth and development of the fetus, and are most probable between the second and fifteenth week of gestation. According to the consensus statements from the relevant major national organizations, in particular the American Congress of Obstetricians and Gynecologists, the risk of malignancy, miscarriage, or major malformations is negligible in fetuses exposed to 50 mGy or less^[5]. The risk of developing cancer following irradiation, although characterized by a small probability, is a stochastic effect and does not have any threshold level. In fact, the probability of stochastic effects shows a monotonic increase as a function of the absorbed dose and follows a “no-threshold” model. According to this model, the carcinogenesis risk has a linear dependence with the radiation doses, and even the smallest dose can potentially increase the risk of cancer occurrence^[6].

Numerous studies have addressed the estimation of the radiation exposure levels for the fetus. Cappell^[7] performed a comprehensive analysis of 46 previous studies including 296 pregnant women. He observed that the rate of complications after therapeutic ERCP is similar for both pregnant and not-pregnant patients. Cappell identified the most common maternal complications to be pancreatitis, with a rate of 6.4% (only one case was severe and no cases required surgical intervention), and post-sphincterotomy bleeding with an incidence of 1%. Among the 254 cases examined in the Cappell’s review the most common fetal complications were: (1) prematurely born infants with a low birth weight (4.3%); (2) late spontaneous abortion (1.2%); (3) infant death right after the birth (0.8%); and (4) voluntary abortion (0.4%).

It is important to mention that the teratogenic effects of radiation on the fetus have a stochastic nature and are essentially unknown. The reason for this may be related to the lack of follow-up after birth in most of the studies on ERCP in pregnancy, potentially underestimating eventual complications. To the best of our knowledge, only Gupta *et al.*^[8] performed a long term follow up, which revealed that after a median time of 6 years all the babies were healthy.

The aim of the article by Smith *et al.*^[1] was to estimate the fetal radiation exposure in pregnant women undergoing ERCPs using thermoluminescent dosimeters (TLDs). This is the largest prospective study of ERCP during pregnancy ever published: 35 patients were subjected to ERCP performed by expert endoscopists. In order to minimize the amount of maternal and fetal exposure, the authors suggest performing a modified ERCP technique where colangiography is used only to detect the presence and position of stones after blind common bile duct cannulation and sphincterotomy. Complications occurred in 6 patients (17%): 2 post-sphincterotomy bleeding (5.7%), 2 post-ERCP pancreatitis (5.7%), 1 fatal acute respiratory distress syndrome (2.8%), 1 cholecysti-

tis (2.8%). Four of these patients were carrying a term-fetus, while only two were pre-term, and no data were available regarding the outcome of the uncomplicated pregnancies. In this paper, the authors reported that the fetal irradiation, supposedly due to ERCP, was less than 0.2 mGy in 88.6% of the patient population, concluding that TLDs are actually unnecessary during ERCP with modified techniques since the radiation exposure of the fetus was well below the threshold established by the International Commission of Radiological Protections (10 mGy)^[9].

However, this very strong statement it seems not to be strongly supported by sufficient experimental evidence. We strongly disagree with the authors as we believe that extreme caution should always be advocated before drawing such conclusions in clinical practice. We will now critically address all the unclear points and inconsistencies present in the paper. Firstly, we wish to repeat the main message of the paper as reported by the authors themselves: “for a routine ERCP with modified techniques, estimating the fetal radiation exposure from the fluoroscopy time and measuring it with the use of TLDs is unnecessary”. This is in apparent contradiction with the statement which appears in the following paragraph of their manuscript: “The threshold may be exceeded in complicated long-lasting ERCPs and in these complicated long-lasting ERCPs, dosimeters may be used to estimate the fetal radiation exposure”. In these situations a clear decision cannot be taken, since there are no objective clinical and imaging parameters that can be evaluated prior to ERCP, which are able to predict the duration of the procedure and its difficulty. Furthermore, continued monitoring offers a quality benchmark or an opportunity to keep doses “as low as reasonably attainable”.

An additional weak point of the paper is the lack of a proper discussion of age and physical issues. The authors affirmed that the 10% of the dose recorded by TLDs on the upper back could be considered to be the fetal dose. However, different gestation ages and different physical and demographic features of the mother could dramatically influence these parameters, considerably modifying their value.

We suggest using a more empirical approach to the problem. In order to verify the real need for radiation dose monitoring, a mathematic model correlating the estimated fetal exposure with physical observables associated with the treatment of the patient should be developed and tested. These parameters could include fluoroscopy exposure time, the procedure time, the gestation age, maternal features, and could vary in number according to the complexity of the model. In this framework, we suggest that entrance skin exposure of the mother could be used as the input variable in an appropriate algorithm able to derive the absolute value of the fetal exposure. This approach would have the advantage of being selective and specific to each patient.

Despite the findings from Smith *et al.*^[1] and any pos-

sible analytical model, many studies have shown that repeated exposures to low levels of ionizing radiation can cause cancer. In fact, stochastic effects of radiation do not exhibit any threshold dose. For this reason, ESGE Guidelines^[10] recommend that the kerma-area product should be monitored, and its cumulative value should be recorded for every ERCP.

In conclusion, we have discussed disease occurrence, radiation risks and fetal exposure during ERCP on pregnant women. In particular we closely evaluated the results obtained by Smith *et al*^[11] who estimated the fetal radiation exposure in pregnant women undergoing ERCPs using TLDs, and claimed that TLDs are unnecessary when ERCP is performed with modified techniques. Despite the large sample of patients investigated by these authors, strong experimental evidence is still lacking on this topic. Therefore, until other prospective studies show that TLD monitoring is not necessary, fetal radiation exposure should be always monitored in clinical practice by dosimeters, bearing in mind that all relevant techniques to control and minimize exposure should be applied. Moreover, ERCP should be performed only with a therapeutic purpose and by experienced ERCP endoscopists, preferably during the second trimester of pregnancy.

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Training in endoscopic submucosal dissection

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Abstract

Endoscopic submucosal dissection (ESD) represents an important advancement in the therapy of early neoplastic gastrointestinal lesions by providing higher *en-bloc* curative resection rate with lower recurrence compared to endoscopic mucosal resection (EMR) and by sparing the involved organ and protecting patient's quality of life. Despite these advantages ESD is associated with long procedure times and a higher rate of complications, making ESD a challenging procedure which requires advanced endoscopic skills. Thus, there has been a recognized need for structured training system for ESD to enhance trainee experience and, to reduce the risks of complications and inadequate treatment. ESD has a very flat learning curve. However, we do not have uniformly accepted benchmarks for competency. Nevertheless, it appears that, in Japan, more than 30 supervised gastric ESD procedures are required to achieve technical proficiency and minimize complications. A number of training algorithms have been pro-

posed in Japan with the aim to standardize ESD training. These algorithms cannot be directly applied in the West due to substantial differences including the availability of highly qualified mentors, the type of pathology seen, choice of devices, and trainee's background. We propose a training algorithm for Western physicians which integrates both hands-on training courses, animal model work as well as visits to expert centers. No specific preceptor training programs have been yet developed but there is a consensus that these programs are important for permeation of ESD worldwide.

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Key words: Endoscopic submucosal dissection; Training; Learning curve; Early gastrointestinal cancer; Endoscopic mucosal resection

Core tip: Endoscopic submucosal dissection (ESD) is a complex procedure associated with high complication rate. In Japan, training in ESD follows the traditional mentor/apprentice approach but significant variability in training approaches exists. We review the learning curves for ESD and describe the training algorithm proposed in Japan aiming to standardize training, and its applicability in the West. We highlight the challenges for ESD dissemination in the West, describing both the consensus and the diverging opinions between Asian and Western training models. Finally, we emphasize the need for structured training system to enhance trainee experience and, most importantly, to reduce the risks of complications and inadequate treatment.

Coman RM, Gotoda T, Draganov PV. Training in endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; 5(8): 369-378 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i8/369.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i8.369>

INTRODUCTION

Endoscopic submucosal dissection (ESD) was developed in Japan in the late 1990s as an advanced, minimally invasive technique for endoscopic removal of early gastric cancers^[1-5]. *En-bloc* resection with standard endoscopic mucosal resection (EMR) techniques is limited to lesions less than 2 cm in diameter, while ESD yields a higher complete resection regardless of size. EMR remains the typical approach in Western countries to treat dysplastic lesions and early cancers^[6-9] while in Asia, ESD has become the preferred therapeutic modality of superficial tumors in both the upper and lower gastrointestinal tract^[3]. It is even considered that it brought about a renaissance of therapeutic endoscopy^[10] as it is able to offer organ-sparing cure in patient with early gastrointestinal (GI) cancers^[11].

ESD has been a significant advancement in therapeutic endoscopy with its major advantages being the ability to achieve a higher *en-bloc* resection rate, accurate histological evaluation and lower cancer recurrence rates compared to EMR^[3,12-15]. In addition, ESD enables *en-bloc* removal of previously unresectable lesions, such as large mucosal tumors, tumors with scars and submucosal fibrosis, or recurrent tumors after EMR^[16,17]. Finally, as opposed to surgery, ESD preserves the structural integrity of the GI tract therefore protecting patient's quality of life.

Despite its obvious advantages, ESD is one of the most complex endoscopic techniques, with several technical difficulties to overcome and potentially high complication rates, especially in the beginning of the learning curve^[18-20]. The most frequent complications are bleeding and perforation. Bleeding during the procedure is very common but only rarely can be significant to the extent which requires the procedure to be stopped^[21]. Compared to conventional EMR, the rate of perforation with ESD is higher, at about 1%-4% and it might require emergent surgical treatment but most of the time, perforations can be successfully managed conservatively^[9,21,22].

In Japan, where there is a high incidence of the gastric cancer, a mass screening program with photofluorography, double-contrast radiography, chromoendoscopy, and endoscopy has been conducted since 1960^[23-28]. Thus, a large proportion of Japanese gastric cancers are detected at an early stage, with a better overall survival rate^[29,30]. ESD is routinely performed for resection of these early cancers in most centers in Japan including local branch hospitals. On the other hand, in the West ESD is still largely not available and is done only in a handful of centers by few advanced therapeutic endoscopy enthusiasts. Although ESD is largely not available in Europe and the United States, over the last 2-3 years there has been significant interest in ESD live demonstrations and hands-on seminars. There is a number of reasons for this slow dissemination of ESD in the West, including the complexity of the procedure, long procedure time, device availability, increased utilization of endoscopic resources,

higher complication rates and, in the United States, lack of dedicated reimbursement code. However, the main obstacle for the wide availability of ESD in the West has been and remains the very flat learning curve and lack of training resources^[31]. As ESD, with its advantages and challenges, has permeated deeper in the gastroenterology community, it became obvious that more endoscopists will be interested in acquiring this technique. It has been anticipated that the widespread adaptation of ESD for the treatment of pre- and early GI cancers will require major shifts in training and practice culture^[32]. Therefore, we wanted to review the current state of training in ESD and emphasize the need for a structured training system in order to enhance trainee experience and, most importantly, to reduce the risks of procedural complications and inadequate treatment.

ESD LEARNING CURVE

It has been showed that when prior knowledge of advanced resection techniques is limited and no supervision by an expert in ESD is available, there is a learning curve in which not only the *en-bloc* resection rate and procedure duration improve with increasing experience but, more importantly, the perforation rate decreases too^[33].

Learning curve for gastric ESD

Several reports have analyzed the learning curve for ESD in the stomach. Gotoda *et al*^[34] found that experience of at least 30 cases is required for a beginner to gain early proficiency in this technique^[34]. Choi *et al*^[33] investigated the learning curve for ESD and reported an increase in the *en-bloc* resection rate from 45% to 85% after experience of 40 cases. They concluded that trainees need to perform 20-40 procedures to be able to use the technique effectively, although their method consisted of mucosal incision and snaring rather than standard ESD. From their data, which included 383 ESD procedures for gastric epithelial neoplasms performed over a 5-year period, Kakushima *et al*^[11] estimated that a trainee could begin to treat lesions in the lower part of the stomach independently after performing about 30 supervised ESD procedures. In a more recent study, two of the three operators could not achieve a sufficient self-completion rate for submucosal dissection after 30 cases, which suggests that more extensive experience is required before the trainees can be considered proficient^[35]. However, in this study, the trainees performed the ESD under the supervision of an experienced endoscopist and their training did not include hands-on training on *ex-vivo* animal models or living animals, which might have improved the learning curve. A study conducted by the same group in 2012 showed that the trainees required approximately 40 and 80 cases for successful removal of guideline-indication lesions and expanded-indication lesions by ESD. The procedural outcomes of ESD performed by preceptees who had experience in over 80 cases were similar to those by expert endoscopists. Thus,

these findings suggest that the amount of training for achieving proficiency in ESD can be the performance of as many as 80 procedures^[36]. Tsuji *et al*^[37] concluded that the training system at their institution (which included training in animal models) enabled trainees to perform gastric ESD without decline in clinical outcomes, although 30 procedures were not enough for them to perform all gastric ESD independently without expert supervision, as expert assistance was still needed in a remaining 20% of ESDs. The keys to improving the learning curve were considered to be: good hemostasis technique and a sufficient level of submucosal dissection skill. Oda *et al*^[38] used procedure time as an indicator of ESD proficiency and determined that 30 cases were necessary to acquire the basic technical skills for successfully performing ESD in the lower third of the stomach. In their estimation, performing at least 40 ESD would be the minimum learning curve point before starting to perform ESD in the middle and upper thirds of the stomach.

Learning curve for extra-gastric ESD

Recent studies showed that high cure rates are achievable using ESD for appropriate lesions in the esophagus and colorectum with no increase in complication rates, when the procedure is done by experienced endoscopist^[39-42]. In a meta-analysis including 14 studies, Puli *et al*^[43] concluded that ESD is the best minimally invasive endoscopic technique, and an important alternative to surgery, in the treatment of large (> 2 cm) sessile and flat polyps because it allows full pathological evaluation and cure in most patients. In a match-control study comparing ESD with EMR for treatment of early-stage colorectal tumors, Kobayashi *et al*^[9] showed that colonic ESD achieved a high *en-bloc* resection rate and a low recurrence rate in short term. Most of the learning curve studies and training strategies have been developed for gastric ESD. However, the increased use of ESD in the colon and esophagus created a demand to further study and ESD skill acquisition in extra-gastric sites^[9,44-51]. In Japan, endoscopists typically first experience ESD in the stomach because of the high incidence of gastric neoplasms and the relative safety of ESD in this location^[36]. These conditions allow for opportunities to acquire sufficient experience in performing ESD. However, esophageal and colonic ESD presents the significant hurdle of technical difficulty and risk of severe complications even among Japanese endoscopists, who generally have greater experience in ESD than endoscopists in other countries.

Some experts consider that ESD in extra-gastric locations should not be attempted unless the endoscopist has experience in performing gastric ESD. Dinis-Ribeiro *et al*^[52] suggested that only after performing 20-40 ESDs in the distal stomach, should lesions located in proximal sites in the stomach, esophagus, and colon be tried. Hotta *et al*^[53] reported on the learning curve for colonic ESD, and they concluded that performance of approximately 40 procedures was sufficient to acquire the skill to avoid

causing perforations during the ESD procedure, and approximately 80 procedures must be carried out to acquire adequate skill to successfully remove large colorectal tumors. Sakamoto *et al*^[54] reported that trainees can perform colorectal ESD safely and independently after preparatory training and experience with more than 30 cases. In these two latter studies, the operators had performed 20 upper GI ESD before starting colorectal ESD.

A small number of analyses conducted in an earlier Japanese multicenter study indicated a higher complication rate during colorectal ESDs and that standardization of the colorectal ESD procedure would be difficult^[55]. Despite greater risks of postoperative complications, particularly, more and more endoscopists are making an effort to study this new technique in terms of its capability of larger neoplasms resection, higher *en-bloc* resection rate and lower local recurrence rate of neoplasms in comparison with other endoscopic treatments. Ohata *et al*^[56] proposed a 7-step training system for learning colorectal ESD, which is very similar to the training algorithms used for gastric ESD, but with the emphasis on technical differences imposed by performing the procedure in a narrower space with thinner wall. One of the mandatory enrolment criteria was performance of at least 30 gastric ESDs. The results suggested that trainees with relatively little prior experience with gastric ESD (*i.e.*, 30 procedures) could reach a stable level of technical competency in colorectal ESD after an average of 30 cases of the latter procedure. The study found that, regardless of the gastric ESD experience, the mean procedure time of each trainee became less than 80 min after performing more than 30 cases. Trainees with experience in many (*i.e.*, 200) gastric ESDs could perform colorectal ESD skillfully from the initial period of training onward^[56].

What have we learned about ESD learning curves

Despite significant efforts to evaluate the learning curve of acquiring ESD skills no definitive conclusions can be reached due to the differences among studies as far as the type of lesions included, type of ESD devices used, degree of supervision, type of training system, trainee exposure to animal models, definition of outcomes and in the case of colonic ESD the degree of prior experience with gastric ESD. Therefore, in Japan, although ESD training varies among institutions, skills are still acquired in the traditional time honored apprenticeship model of training in endoscopy “see one, do one, teach one”. There has been a recognized need for structured training system for ESD in order to enhance trainee experience and, most importantly, to reduce the risks of procedural complications and inadequate treatment^[11].

ESD TRAINING SYSTEMS

At present there is no universally accepted algorithm for training in ESD. Nevertheless, it appears that there is a consensus on some key points. Given the complexities

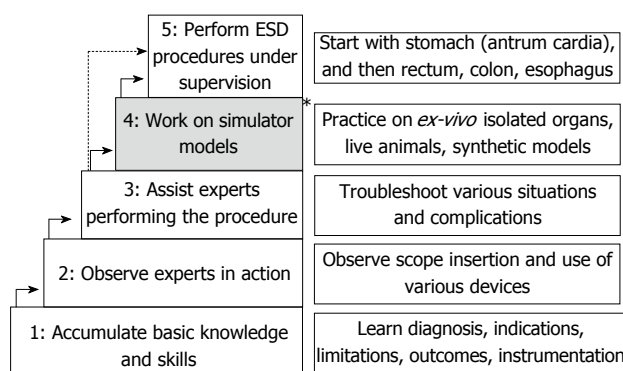


Figure 1 Japanese model for a structured endoscopic submucosal dissection training. The * indicates the 4th step (practice on *ex-vivo* and live animal models) which is not employed in all Japanese training algorithm. ESD: Endoscopic submucosal dissection.

of this technique, the training program must contain a solid cognitive-based preparation, and hands-on patient-based training. Also, the minimal requirements and final attainments for trainees at each level must be established prior to starting the training^[37].

As expected, most well-implemented training programs/algorithms are in Japan. These algorithms typically include two major stages of training: pre-procedural, theoretic preparation and hands-on training^[32,35-38]. The first stage has two phases: phase 1-accumulation of basic knowledge and phase 2-observe experts in action. The second stage includes phase 3-assist experts performing the procedure, phase 4-working on simulator models, such as *ex-vivo* and *in-vivo* animal model, or synthetic models of organ of interest, and phase 5-perform ESD procedures under supervision (Figure 1).

Recently, several training algorithms have been proposed. One of the earliest proposed training algorithms by Yamamoto *et al.*^[35] in 2009 puts emphasis on the initial pre-procedural phase of the training. Thus, the endoscopists who intend to learn ESD must attend pre- and post-treatment conferences, and take part in actual ESD procedures as an assistant for at least 1 year before beginning doing the procedure themselves. In addition to gastroenterologists, surgeons and pathologists are included in these conferences, and thus the trainee learns how to diagnose the extent and depth of the tumor, establish the optimum treatment strategy, and manage the patients appropriately according to the histopathological findings in resected specimens. By assisting experienced endoscopists, trainees acquire the skills needed to troubleshoot various situations. Moreover, obtaining expertise in hemostasis before starting ESD is highly recommended since most of the difficulties surrounding the procedure were related to uncontrollable hemorrhage^[35]. The same group expanded the requirements of the pre-procedural training to master detailed preoperative examination by magnifying endoscopy with narrowband imaging, preoperative marking using ink and endo-clips, hemostasis of second-look endoscopy after ESD^[36]. Similar approach

is proposed by Kaltenbach *et al.*^[32], where the trainees are assisted in developing crucial diagnostic skills to select appropriate lesions and specific management strategy for ESD cases. The next step is for trainees to observe expert endoscopists in action as they perform various ESD procedures^[38].

ESD is a technically demanding procedure requiring a high level of endoscopic skill. Consequently, in the second stage of the training, the trainees start by assisting experts in performing ESD procedure. Next, the trainees are exposed to animal models to enhance their technical skills. Hands-on experience with ESD in isolated pig stomach or live pigs facilitates familiarity with the tools and techniques of the procedure. Trainees can appreciate the differences in technique depending on lesion size and location. After gaining familiarity with the tools and technique, trainees typically start performing ESD in patients by removing small gastric lesions in the antrum or body under the close supervision of an experienced endoscopist, who both offers advice and can complete the procedure if necessary^[32,38]. Yamamoto *et al.*^[35] propose a system where the trainees do not use animal models but start as assistants in live patient cases and then continue with performing ESD on patients under expert supervision. For this reason, they recommend that in this “supervision-only” training algorithm, one should start with small lesions in the lower third of the stomach. These lesions are relatively easy and less time-consuming to remove, so the trainees have the opportunity to learn the entire ESD procedure. After this, it is easier to move on to larger lesions, because the procedure for large lesions consists of repeating certain basic steps^[35].

In summary, in Japan, a consensus exists on the following issues: (1) need of solid cognitive background regarding lesion evaluation, indications, contraindications and technical aspects of ESD; (2) need for observation of ESD as done by experts; (3) need to assist experts and operate the ESD devices; (4) need for hands-on training in humans under direct expert supervision; and (5) starting hands-on training with easier lesions and progressing to more difficult ones. Importantly, in Japan there is a number of areas where diverging opinions exist. These include: (1) need for simulation-based training; (2) need to use live animal models; (3) need to acquire a predetermined number of ESD cases in the stomach before moving to esophagus and colorectum; and (4) specific milestones for competency that the trainee has to meet before starting to practice ESD independently.

ESD TRAINING IN THE WEST

Unfortunately, the extensive Japanese experience in ESD training cannot be directly applied in the West due to a number of substantial differences. At present, in the West, there is only a handful of highly qualified experts in ESD. Therefore, doing ESD under direct expert supervision is not feasible in most cases. Importantly, the type of pathology seen in the West is different than the

one in Japan. Specifically, there are very few cases of early gastric cancer and therefore no opportunity for the trainee to start their training in locations that are considered easier, such as the gastric antrum^[35,57,58]. In addition, the choice of devices, endoscopes and ancillary equipment for ESD available in the West is different compared with the one available in Japan^[59]. Likewise, the technical expertise and backgrounds of endoscopists embarking on ESD in the West differs significantly than their Eastern counterparts. At present, in Japan, the typical trainee learning ESD is a GI fellow. On the other hand, in the West, physicians embarking on ESD typically are more mature and otherwise well experienced therapeutic endoscopists. Furthermore, in Japan, physicians learning and performing ESD tend to focus their practice exclusively on ESD as opposed to the endoscopists in the West who tend to incorporate ESD into a developed advanced therapeutic endoscopy practice that typically includes endoscopic retrograde cholangiopancreatography (ERCP) and/or endoscopic ultrasound (EUS). In addition, even if ESD is considered more economical and less invasive, in the West laparoscopic surgery and transanal resection for colorectal lesions are more established techniques^[59]. It has been well recognized that the specific circumstances in the West call for tailored approach in ESD training.

In the West, opportunities to pursue ESD training using the Japanese training algorithm have been limited by the low rates of early gastric cancer and thus the inability to enter the ESD learning curve at the relatively safest location^[19,32]. To master the techniques of ESD, particularly in areas with a low incidence of early GI cancers, it was recommended to formulate a standardized protocol for training following the Japanese training model. The role of adequate training is, of course, to influence the spread of this technique, to set standards for training and certification, to promote quality management, and to limit complications inherent to early learning^[31]. Several studies published good results after successful ESD procedures performed in humans in several Western countries^[52,60-62].

In 2008, a panel of experts gathered in Rotterdam ("Experts meet experts," Rotterdam, The Netherlands, 11-12 February 2008) to discuss indications, training, and the wider use of ESD. The minimum training requirements were also defined: knowledge in indications and instruments, exposure to experts (currently mostly in Japan), hands-on experience in a model of isolated pig stomach and in live pigs, and management of complications. The experts did not reach a consensus on a minimum case load, or whether the technique should be restricted to expert centers. Dr. Jelle Haringsma proposed a structured training algorithm with the following steps: (1) acquire basic knowledge, defined as knowledge about the types of disease treated with this approach, instrumentation, operation of the electrosurgical unit, and familiarity with indications, limitations, risks, and outcomes of ESD; (2) see experts at work, namely in Japan;

(3) assist in procedures; (4) training on animal models-isolated pig stomach and live pigs. In animal models, a minimum of 30 resections reaching a resection speed of 30 min for a lesion with maximum diameter of 5 cm, and management of complications, were suggested as aims of training; (5) perform procedures on patients; and (6) continue training. Emphasis is also put on a training continuum with books, DVDs, journals, conferences, live demonstrations (master classes and courses), and visits to expert centers.

As outlined earlier, in Japan, one area of diverging opinions is the value of practice in explanted or live animal models. Kakushima *et al.*^[11] noticed that there does not seem to be any differences in the perforation rates when performing ESD between trainees and experts when the former are supervised by the latter. As a result, training on animal models is not routinely accepted practice in Japan. While training in animal models may not be needed in Japanese institutions where supervision by experts is easily available, these models can be a valuable resource when training in the West. Models could allow endoscopists to ascend the learning curve in a relatively short time, especially when training in low volume centers or/and without direct expert supervision^[32,37,63,64]. Two prospective studies were aimed in determining the results, efficacy, and safety of ESD performed in pigs by an endoscopist at the beginning of the learning curve prior to its application in humans. The strategy proposed was to start training in ESD on animal models in the absence of experts to supervise the procedures and ensure the patients' safety. The studies showed that training in pigs could be started without such previous learning, and may augment the acquisition of skills in low-volume centers. However, ESD involves maneuvers that traditionally have not been used during flexible endoscopy, which would be difficult to master by oneself^[64,65].

The harvested porcine organs are ready-to-use and inexpensive means of becoming proficient in these techniques. Multiple large resections in the esophagus and stomach may be practiced before using a live porcine model. However, one of the main perceived disadvantages is that the *ex-vivo* animal models do not help in acquiring the skills of hemostasis and approaching a deep enough level of the submucosal layer, because bleeding does not occur^[32].

The live pig model simulates a more realistic endoscopy setting and provides the opportunity to respond to and treat potential complications including bleeding and perforation^[19]. However, some of the differences between pig and human stomach, such as infrequent bleeding and lack of fibrosis in the pig stomach might make the procedure less challenging than in humans. Another potential disadvantage is that live animal models are expensive and not all institutions or hospitals are equipped for their usage.

Animal models could be used not only for training in gastric ESD but also for esophageal and colonic ESD^[66-69]. Tanaka *et al.*^[67] developed an original training

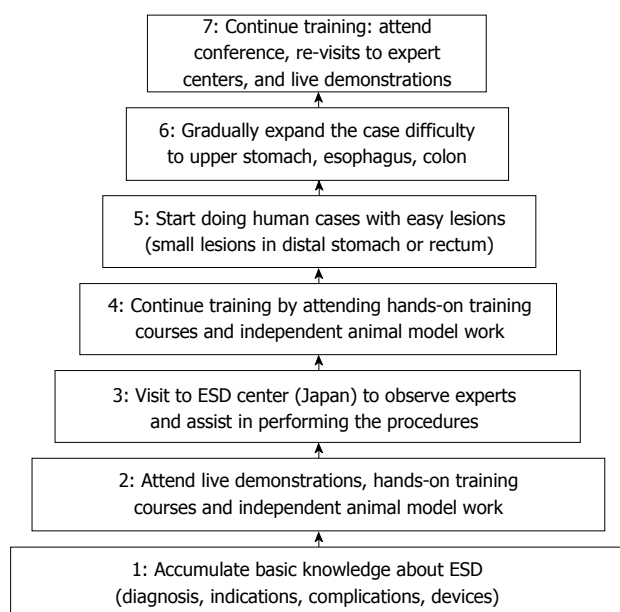


Figure 2 Proposed training algorithm for Western physicians, which integrates hands-on training courses, animal model work and visit to expert centers. ESD: Endoscopic submucosal dissection.

model for esophageal ESD using isolated pig esophagus and assessed this *ex-vivo* model in endoscopists with experience in gastric ESD. The operation time and number of muscularis propria layer injuries decreased gradually as endoscopists gained training experience, while the mean number of muscularis propria layer injuries significantly decreased for all of the endoscopists in the latter period compared with the former period.

While it has been demonstrated that certain skills can be acquired during self-guided animal model training, learning from experts appears crucial to achieve the ability to perform ESD safely in humans^[64]. Therefore observing experts and performing ESD under expert supervision in addition to practicing on animal model appears a necessary step while training in the West^[31,70-72]. Since, at this time most highly experienced endoscopists performing ESD are in Japan, a visit to a specialized center in Japan most likely will remain, for some time, an essential component of ESD training in the West. Other possible strategies would be to organize training courses (with animal and/or human training) under the supervision of experts, or to attempt ESD procedures supervised by means of a videoconference. However, the impact of these methods on ESD performance has yet to be determined^[64]. Such, Western and Asian centers should collaborate closely in terms of training, exchange of data, and initiation of international multicenter trials^[60].

We propose a training algorithm for Western physicians which integrates both hands-on training courses, animal model work as well as visit to expert centers (Figure 2). The initial step of the training can be accomplished through independent effort, using printed and video materials to learn about the procedure, indication and diagnosis. We believe that at this stage a dedicated effort to acquire detailed knowledge of the principles of electrosurgery is an essential

step. Modern electrosurgical generators provide menus of predetermined settings for most routine procedures (*e.g.*, polypectomy, sphincterotomy, *etc.*). On the other hand, no such preset menus exist for ESD. Settings can vary dramatically based on stage of the procedure, type of instrument and lesion location. In addition, multiple other variables can significantly contribute to the final tissue effect. These include the surface area of the device electrode in contact with the tissue, the speed of movement of the electrode, the pressure applied with the electrode, the presence of coagulated tissue debris sticking to the electrode and the target tissue itself (fibrotic versus high water content). Importantly, the most significant factor remains the endoscopist's ESD technique. Therefore, a thorough understanding of the various modulated currents and their relation to ESD technique is essential to allow individualized choice of electrosurgical unit settings. Then, the endoscopists should attend live presentations and enroll in hands-on training courses to learn about the use of various devices and to practice on animal or synthetic models. After accumulation of this theoretical and practical fund of knowledge, we recommend a visit to an expert center. Most of these centers are currently located in Japan. However, with more endoscopists learning this technique, we anticipate that new training centers will open throughout the world. We are aware that not all endoscopists can spend long periods of time outside their practice, but we encourage at least 3 to 4 wk visit to a high volume ESD center in Japan. During this time, the trainees will assist experts in performing procedures, thus reaching the necessary diagnostic and therapeutic skill level. Upon return, the trainees should practice their newly acquired skills continuing training on simulator models. The next step is to start performing ESD on human patients. We advocate to start with lesions located in the distal stomach or rectum, as these are easier to remove and have a lower complication rate. During the initial human cases, expert supervision by means of videoconference is encouraged if direct supervision is not possible. Review of the endoscopy images prior to the ESD by an expert can provide the valuable opportunity to outline a specific procedure strategy which is an essential part of successful ESD. Then, gradually, the endoscopists can expand to cases of increasing difficulty such as treating larger lesions, or lesions located in the cardia, fundus, colon or esophagus. Finally, as in any other field, we recommend continuous training, with attending/presenting at conferences, re-visiting expert centers, reviewing literature and participating in courses and live demonstrations.

TRAINING PROGRAMS FOR TRAINERS

This is a relatively new but important concept, as the training program for trainers is highly demanded for permeation of ESD worldwide and it is also necessary for trainers to be evaluated and rewarded. Endoscopists in Asian as well as Western countries are waiting for Japanese endoscopists to assist them more or less,

in different ways according to the background of each country^[73]. To assess the prerequisites for preceptorship, Goda *et al.*^[74] used a questionnaire survey to Japanese experts in representative teaching hospitals regarding their training method of gastric and esophageal ESD. This study indicated many requirements for the preceptor: having quite a high level of diagnostic ability, and proficient ESD techniques in the colorectum as well as the stomach and esophagus. It is also necessary that they are a regular staff with a certified qualification.

In a previous report, most Japanese experts set the level of expertise at 50-100 cases of gastric ESD in order to become proficient in gastric ESD. In a more recent study, Yamamoto *et al.*^[36] agreed with previous finding, showing that the minimal amount of training for achieving preceptorship in ESD is performance of at least 80 of the procedures.

Thus, so far, it appears that, to reach preceptorship level, the endoscopists need both a certain level of expertise, defined in number of procedures performed and a certification of their skills by an authorized body such as Gastroenterological or Endoscopy Societies. However, no specific preceptor training programs have been yet developed but there is a consensus that these programs are important for spreading ESD worldwide^[73].

CONCLUSION

ESD represents an evolutionary step in therapeutic endoscopy. Using new skills, devices, and disposables, ESD achieves high rates of *en-bloc* curative resection rates for early GI cancers. However, the learning process for this advanced endoscopic procedure requires a lengthy training period and considerable experience to be proficient. A well-structured training program, safe, effective and easily reproducible is essential for the trainee, because the outcome of ESD is highly dependent on the experience of the endoscopist. It is also recommended that the training program should be tailored around needs based on culture and/or country since the incidence of disease and working environment may be different.

In Western countries, training in ESD is challenging given the lack of training in early gastric cancer lesions, assumed to be a relatively safer location to enter the learning curve. Currently, esophageal and colonic ESD are getting wider acceptance in the West where there is an effective screening process for Barrett's and colon cancer with a large number of these lesions been detected in an early stage. We are proposing a training algorithm that will employ local resources to start the training in ESD and consolidate the knowledge and skill by learning from experts in Japanese centers.

Despite of all obstacles, ESD applications are continuing to grow in the West. Close collaboration between Western and Asian countries will be helpful to improve ESD technique for various sites and to benefit patients who are suffering from early gastric, esophageal or colorectal cancer.

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Endoscopic approach to achalasia

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Abstract

Achalasia is a primary esophageal motor disorder. The etiology is still unknown and therefore all treatment options are strictly palliative with the intention to weaken the lower esophageal sphincter (LES). Current established endoscopic therapeutic options include pneumatic dilation (PD) or botulinum toxin injection. Both treatment approaches have an excellent symptomatic short term effect, and lead to a reduction of LES pressure. However, the long term success of botulinum toxin (BT) injection is poor with symptom recurrence in more than 50% of the patients after 12 mo and in nearly 100% of the patients after 24 mo, which commonly requires repeat injections. In contrast, after a single PD 40%-60% of the patients remain asymptomatic for ≥ 10 years. Repeated on demand PD might become necessary and long term remission can be achieved with this approach in up to 90% of these patients. The main positive predictors for a symptomatic response to PD are an age > 40 years, a LES-pressure reduction to < 15 mmHg and/or an improved radiological esophageal clearance post-PD. However PD has a significant risk for esophageal perforation, which occurs in about 2%-3% of cases. In randomized, controlled studies BT injection was inferior to PD and surgical cardiomyotomy, whereas the efficacy of PD, in patients > 40 years, was nearly

equivalent to surgery. A new promising technique might be peroral endoscopic myotomy, although long term results are needed and practicability as well as safety issues must be considered. Treatment with a temporary self expanding stent has been reported with favorable outcomes, but the data are all from one study group and must be confirmed by others before definite recommendations can be made. In addition to its use as a therapeutic tool, endoscopy also plays an important role in the diagnosis and surveillance of patients with achalasia.

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Key words: Achalasia; Pneumatic dilation; Botulinum toxin injection; Per oral endoscopic myotomy; Dysphagia; Laparoscopic cardiomyotomy

Core tip: Upper gastrointestinal-endoscopy is an important part in the diagnostic algorithm of achalasia. Although it does not have a high sensitivity in detection of early stage achalasia, it is essential to rule out pseudoachalasia. This updated review included the newest data on treatment and surveillance of achalasia patients with special emphasis on the new treatment option of per oral endoscopic myotomy, including all fulltext publications until January, 2013.

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INTRODUCTION

Idiopathic achalasia is a rare primary esophageal motor disorder of unknown etiology, with an estimated incidence of 1 case per 100000 of the general population^[1]. It represents a neurodegenerative disorder, in which neurons of the myenteric plexus become destroyed.

Although major strides have been made in understanding the pathogenesis, including a probable autoimmune mediated destruction of inhibitory neurons caused by an unknown insult in genetically predisposed patients, the definite pathophysiology is still unknown^[2].

Achalasia is characterized by a loss of function of the lower esophageal sphincter and the esophageal peristalsis. The classical features are incomplete relaxation of a frequently hypertensive lower esophageal sphincter (LES) and a lack of peristalsis in the tubular esophagus, which causes symptoms such as dysphagia, regurgitation, weight loss and chest pain.

The diagnosis of achalasia is suspected clinically on the basis of the symptoms mentioned above and confirmed by diagnostic tests, such as barium swallow, and esophageal manometry. However, an endoscopic examination is always necessary to distinguish primary achalasia from the secondary form, in cases of possible malignancy^[3].

Since the underlying defect cannot be reversed, the treatment of achalasia remains palliative. Therefore, the aim of all current therapies is the improvement of the esophageal food passage by reducing the distal esophageal obstruction. Such improvement will lead to symptomatic relief of dysphagia, regurgitation, as well as weight gain.

This goal can be achieved by pharmacologic therapy, by endoscopic treatment with pneumatic dilatation (PD) or botulinum toxin (BT) injection, or by surgery. Recently, new therapy options such as stent implantation or peroral endoscopic myotomy (POEM) have been reported^[4,5]. However, the efficacy of these treatment options varies and the recommendation for the best therapy is still controversial. Although pneumatic dilation and Heller myotomy seemed to be the most effective treatments for achalasia^[6], the choice of treatment modality depends on multiple factors, such as patients' characteristics, clinical presentation, local expertise and patients preference^[7].

In addition, surveillance strategies remain a matter of debate. Despite an increased risk for malignancy there are no existing guidelines for surveillance of cancer or other complications such as esophagitis, peptic strictures or megaesophagus^[8,9].

This review will provide an evidence-based approach for the use of endoscopic options for the diagnosis, treatment and surveillance of achalasia.

DIAGNOSTIC USE OF ENDOSCOPY

Endoscopy is one of the primary tools in the diagnosis of achalasia as the leading symptom of the disease is dysphagia. Esophago-gastroscopy, esophageal barium swallow and esophageal manometry are the standard diagnostic procedures in suspected achalasia. Although an endoscopic diagnosis can only be made in about 1/3 of all patients with achalasia, its sensitivity increases with progressive stages of disease^[10]. Typically the resistance at the gastroesophageal junction is increased, but still

relatively easy to pass with the endoscope. In advanced stages of achalasia the esophagus is dilated and contains retention of food or secretions^[11]. The esophageal mucosa usually appears normal, although sometimes inflammation or ulceration caused by retained food can be demonstrated. The endoscopic examination is especially important to rule out other possible causes for the symptoms. These include esophageal and gastric tumors as well as stenosis caused by scarring or inflammatory conditions or by aberrant vascular patterns (*e.g.*, dysphagia lusoria). Especially the esophagogastric junction, as well as the gastric cardia and the fundus, should be examined carefully for evidence of neoplasm, because gastric adenocarcinoma is the most common neoplasm associated with pseudoachalasia^[12].

Furthermore, esophago-gastroscopy might be important for the detection and treatment of complications that can be a result of the disease itself such as megaesophagus or carcinoma, or of successful treatment for example reflux esophagitis or peptic stricture^[13].

ENDOSCOPIC TREATMENT

The treatment options remain strictly palliative; therefore the primary goal of all therapies is the improvement of the esophageal food passage by reducing the distal esophageal obstruction. Such improvement will lead to symptomatic relief of dysphagia, regurgitation, as well as weight gain. Endoscopic treatments include mechanical rupture of the smooth muscle fibers of the LES and relaxation of the hypertensive lower esophageal sphincter by injection of botulinum toxin, an inhibitor of acetylcholine release from nerve endings^[14] as well as novel reported endoscopic therapies such as stent placement, and POEM respectively^[4,5].

ENDOSCOPIC INJECTION OF BT

Strictly speaking, botulinum toxin injection into the LES is a pharmacologic treatment, but it requires upper endoscopy for its application.

Botulinum toxin is a neurotoxin that leads to a blockade of the release of acetylcholine from vesicles of excitatory motor neurons. Therefore, it counteracts the loss of inhibitory input to the LES and helps to restore the LES to a lower resting pressure^[15].

Botulinum neurotoxins are divided into seven subgroups, identified by the letters A-G. In clinical practice subtype A is most frequently used^[16].

The application of BT is performed by prograde or retrograde injection into the LES using a standard sclerotherapy needle. The most common approach is the injection of 20-25 units BT-A diluted in 1 mL of saline, in each of the 4 lower esophageal sphincter quadrants approximately 1 cm above the Z-line into the bulging muscle (Figure 1)^[17]. Whether the use of endoscopic ultrasound or manometry to identify the LES can achieve better clinical results has not been definitively estab-

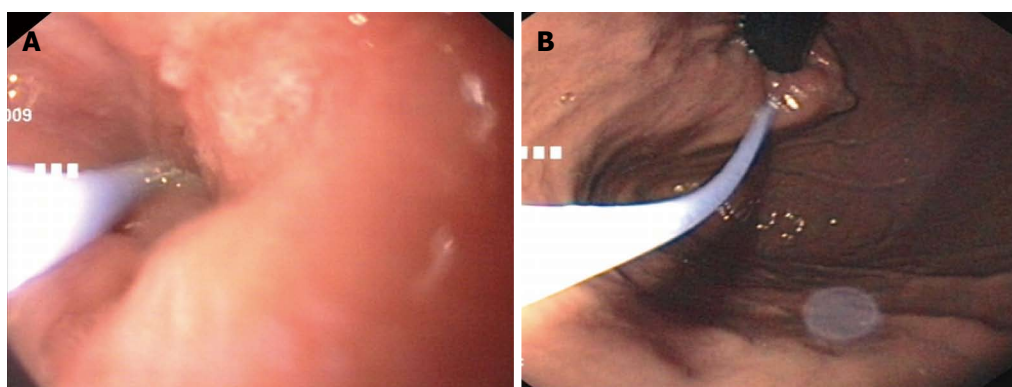


Figure 1 Endoscopic images of botulinum toxin injection. Injection with the standard sclerotherapy needle deep intramuscular in the region of the cardia. A: Prograde injection with an endoscopic view of the distal esophagus; B: Retrograde injection with a retroflexed view of the cardia.

Table 1 Efficacy of botulinum toxin injection in the treatment of achalasia

Ref.	n	BT-dose U	Initial symptomatic response	Injection rate	Long-term symptomatic response	Follow up (mo)
Wehrmann <i>et al</i> ^[19]	20	100	80%	2.5	70%	24
Annese <i>et al</i> ^[20]	36	100	90%	0	78%	6
Pasricha <i>et al</i> ^[28]	31	80	90%	1.6	68%	12
Fishman <i>et al</i> ^[31]	60	80	70%	1.3	36%	12
Annese <i>et al</i> ^[32]	38	100	82%	1	68%	24
Gordon <i>et al</i> ^[100]	16	80	75%	1.25	58%	7
Cuillière <i>et al</i> ^[101]	55	80	85%	1.2	60%	6
Vaezi <i>et al</i> ^[102]	22	100	64%	1.1	32%	12

BT: Botulinum toxin.

lished^[18,19]. Botulinum toxin diffuses into the surrounding tissue of up to 10 mm, therefore absolute precision might not be necessary^[18]. In two studies, instead of BT-A (Allergan Inc., Irvine, CA, United States), Dysport (Ipsen, Milan, Italy) was used at doses of 200-240 U and was equally effective^[20]. BT injection is a safe method no more demanding than a routine endoscopy with no major complications. The most common side effect is retrosternal pain in up to 25% of patients^[15]. It is an outpatient procedure and the patients can go home after they recover from sedation. The patients are allowed to drink in the recovery room and to eat soft foods later in the day. Symptomatic improvement occurs gradually and usually peaks 1-3 d later, although this may be delayed even further in the occasional patient^[21].

The first clinical studies were conducted in the 1990th, after preliminary studies in piglets^[22-24]. In these initial studies, patients were treated with endoscopic injection of botulinum toxin in comparison to placebo injection of saline with symptomatic improvement as well as a remarked reduction of the LES pressure after BT injection were demonstrated^[25]. However, the clinical effect of botulinum neurotoxins is reversible, because of the regeneration of the presynaptic membrane^[26]. Therefore, the efficacy of a single BT injection has been found to vary from 3 mo to 3 years. In numerous placebo-controlled trials, significant improvement of symptoms has been shown in approximately 75% (70%-90%) of the patients^[27] (Table 1). Although, after 12 and 24 mo symp-

toms recurred in more than 50% and in nearly 100% of the patients, respectively^[28-30]. Therefore, repeat injections are commonly required and nearly 75% of the initially responsive patients will respond to a second BT treatment. However, patients who failed to respond to initial BT injection respond to a second injection in less than 20%^[31]. Furthermore, it is known that increasing the dose to 200 U BT does not improve the success rate whereas two injections of 100 U of BT 30 d apart seemed to be the most effective therapeutic schedule^[32].

However, the long-term safety and efficacy are less certain^[20]. It is known that repeated BT injections may lead to decreased effects due to the development of inhibitory antibodies^[15] and there is some evidence that injection of BT into the LES is associated with increased difficulty of performing esophagomyotomy^[33].

The long-term success of BT injection into the LES in patients with achalasia was highest in elderly patients (> 55 years), in patients with vigorous achalasia and those with an LES pressure not exceeding the upper normal level by 50% or more prior to treatment^[34,35]. In fact, several investigators have speculated that the better long-term response to BT injections seen in the elderly might be explained by diminished nerve regeneration^[36].

In summary, the advantages of this method are that it is simple, effective and relatively inexpensive, with no major side effects and excellent short-term results. Unfortunately this result only lasts for 6-9 mo on average in most patients and only half of them benefit for more than 1

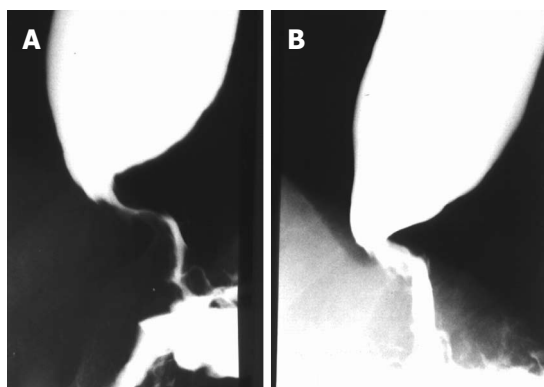


Figure 2 Radiologic image of the esophagus of an elderly patient. A: Before Botox injection; B: After Botox injection, with a decrease of the diameter in the area of the lower esophageal sphincter.

year^[37]. Because of its less invasive nature compared with other therapeutic alternatives Botox injection may be the preferred approach in the treatment of some patients with achalasia, such as elderly patients (Figure 2) or patients with multiple medical problems who are poor candidates for more invasive procedures as well as those unwilling to have either surgery or pneumatic dilatation^[38]. Furthermore, BT injection might be a useful therapy in patients with atypical achalasia, or complex achalasia in whom it is unclear whether more invasive procedures such as pneumatic dilation or surgical myotomy are the correct therapy^[39].

DILATION OF THE LES

Theoretically, there are two possible modalities used to dilate the LES in patients with achalasia: bougienage and pneumatic balloon dilation.

Although bougienage is a technique known to be highly effective in peptic or anastomotic strictures, it provides only temporary and incomplete symptom relief in patients with achalasia^[40,41]. Therefore, the more forceful stretching of the LES with pneumatic balloon dilation that weakens the LES by tearing its muscle fibers is the preferred approach.

PD

Pneumatic dilatation has been a well established and proven treatment for achalasia for decades and is currently considered the most effective nonsurgical treatment option for achalasia^[42].

Since the first description of treating achalasia with whale bone by Sir Thomas Willis in 1674, the aim of the procedure has principally remained the same. That is to rupture the hypertensive smooth muscle of the LES. In the past different kinds of balloons such as Witzel or Mosher balloons, with a remarkable variation in the methods of dilatation were used for the forceful dilation^[43,44]. The procedure has become more standardized with the development of the so called Rigiflex balloon System (Boston Scientific Corporation, MA, United States), a low

compliance polyethylene balloon available in 3 diameters (3.0, 3.5, and 4.0 cm) (Figure 3A). It is fixed on a flexible catheter that can be placed over an endoscopically placed guidewire with subsequent fluoroscopic monitoring of the balloon position across the LES. The rapid inflation of the balloon with air leads to stretching of the LES muscle fibers, resulting in at least partial rupture. In order to avoid radiation exposures, some centers monitor balloon position by direct endoscopic observation^[45]. A pressure of up to 10-12 psi (average 7 psi) is used to inflate the balloon for 1-2 min until the waist of the balloon, which lies in the region of the LES, is completely elapsed (Figure 3B). The dilation protocols and follow-up varies among different investigators in the United States and Europe^[13]. Some authors have used single dilation^[46], others performed serial graded dilations on consecutive days or a few weeks apart with balloon sizes ranging from 3 to 4 cm^[47-50] and a few European centers perform serial progressive dilations over several days, until the manometrically measured LES pressure is below 10-15 mmHg^[51].

However, in the past numerous comparative studies found no significant different symptomatic response rates for the use of different balloon systems, or different length of inflation or peak pressures respectively, although previous studies could show that the use of a Rigiflex dilator and multiple dilations during the initial treatment might improve efficacy^[13,43].

The technique of graded balloon dilation starting with 3.0-cm Rigiflex balloon as the initial dilator and progressing to 3.5-cm and 4.0-cm balloon in absence of response to previous balloon size seems to be the safest approach^[52]. Following dilation, radiologic esophagograms with water-soluble contrast agents are frequently performed to rule out serious complications; whereas others do not recommend a routine esophagogram in the absence of symptoms suggestive of a perforation, such as chest pain often with radiation to the back or to the shoulder, followed in one third of patients by vomiting and shortness of breath^[53].

Transmural perforation, mostly located just above the cardia along the left side of the esophagus where there is an anatomic area of weakness. The perforation rate reported in different studies ranges between 0%-5% with a mean range of 2%-3% (Table 2). In the review of Katzka *et al.*^[43] in which 29 studies of pneumatic dilation in achalasia were evaluated the overall perforation rate was 2% of which only 1% required surgery.

The mortality rate (5%-6%) after transmural perforation due to pneumatic dilation is usually caused by the development of mediastinitis or bleeding into the mediastinum^[54]. In general, conservative treatment with fluid resuscitation, gastric decompression, and antibiotics, best combined with an immediate endoscopic closure of the perforation, is a possible option^[43,52]. Complications following pneumatic dilation, if recognized and treated promptly, were not associated with adverse, long-term sequelae^[50]. Multiple dilations, the use of inflation pressures

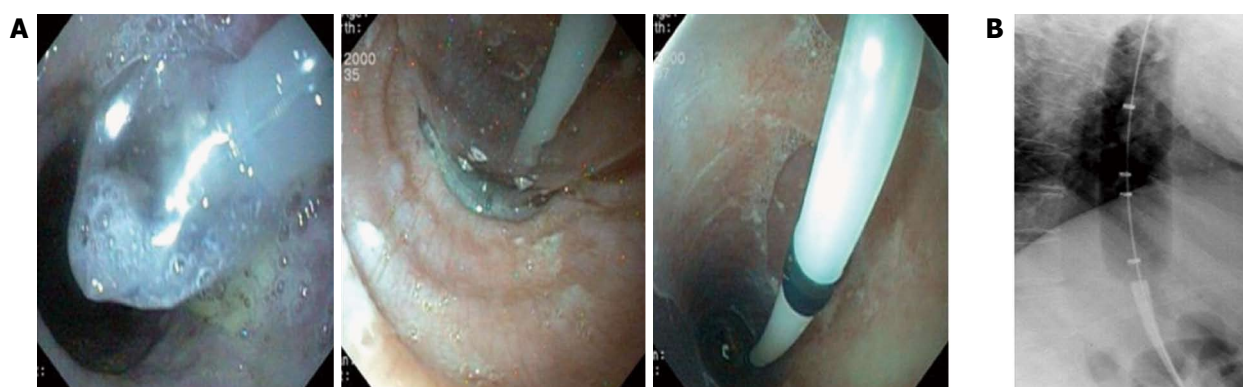


Figure 3 Pneumatic dilation with a rigiflex balloon. A: Endoscopic image; B: Radiologic images. The waist of the balloon lies in the region of the lower esophageal sphincter.

Table 2 Initial efficacy of pneumatic dilation in the treatment of achalasia

Ref.	Dilator-system	n	Symptomatic response	Perforation rate
Chuah <i>et al</i> ^[52]	Rigiflex	32	91%	3%
Eckardt <i>et al</i> ^[61]	Brown-McHardy	54	78%	2%
Wehrmann <i>et al</i> ^[62]	Rigiflex	40	88%	3%
Csendes <i>et al</i> ^[73]	Mosher	39	65%	5%
Stark <i>et al</i> ^[103]	Brown-McHardy	10	100%	0%
Parkman <i>et al</i> ^[104]	Brown-McHardy	123	88%	2%
Coccia <i>et al</i> ^[105]	Rider-Moeller	16	75%	0%
Bourgeois <i>et al</i> ^[106]	Rider-Moeller	53	80%	4%
Gelfand <i>et al</i> ^[107]	Rigiflex	24	83%	0%
Vaezi <i>et al</i> ^[108]	Rigiflex	20	75%	5%
Rai <i>et al</i> ^[109]	Rigiflex	56	89%	0%

> or = 11 psi or a large balloon (4 cm) at initial dilation as well as older age (> 65 years) seemed to be risk factors for esophageal perforation^[55]. Although suspected by early observations, a hiatus hernia, a diverticulum of the esophagus and vigorous achalasia do not increase this risk^[56]. Other minor complications include esophageal mucosal tears, bleeding, intramural hematomas, aspiration and diverticula at the cardia^[50,56]. Post procedural fever usually resolves spontaneously without the use of antibiotics, and in approximately 15% of patients severe but self-limited chest pain occurs^[50,55].

Furthermore, some patients will develop reflux when measured by 24-h esophageal pH monitoring. Although severe complications of gastro esophageal reflux disease such as peptic stricture, or Barrett esophagus are rare, 15%-45% of the patients will complain of heartburn responding to proton pump inhibitor treatment^[57,58].

The only absolute contraindication for pneumatic dilation is poor cardiopulmonary status or other comorbid illness preventing surgery, if a transmural perforation might occur^[17].

Outcome of PD

Initial success rates are high with up to 85% of patients reporting symptom improvement after one month. Table 2 summarizes the results of several studies according to

the short-term symptomatic success rate of PD.

A recently published review of 21 studies using Rigi-flex balloons demonstrated that the initial success rates depends on the balloon size, with larger balloons showing better outcomes. Success rates of 74%, 80% and 90% were achieved when using balloon sizes of 30, 35 and 40 mm, respectively^[45].

However, a decline in success rates over time was consistently found. For example, researchers achieved success rates of 74% at 6 mo, 68% at 12 mo and 58% after 36 or more months. If patients are observed for more than 10 years, only 40%-60% will remain asymptomatic after a single PD. Therefore, repeated on demand PD might be necessary and long term remission can be achieved with this approach in up to 90% of the patients^[47,50,58].

Nevertheless, it must be considered that the patients with frequent PD are exposed to potentially serious complications such as esophageal perforation, intramural hematoma or aspiration and the uncertain durability of symptom free intervals between dilations^[59,60]. Therefore, it is important to predict which patient is less likely to respond or will have an early recurrence of symptoms. In fact, patients older than 40 years generally have better outcomes following dilation than those who are younger^[61,62]. Further positive predictive factors are a LES-pressure of < 15 mmHg or a LES pressure reduction of more than 50% in comparison to the pre-dilation LES pressure^[63,64]. By contrast, a wide esophagus, the use of small balloon sizes, an incomplete obliteration of the balloon waist during the procedure, a failed response to one or two dilations, type I or III patterns of achalasia in high resolution manometry, poor esophageal clearance on a timed barium swallow and younger male patients have been shown to predict a poor treatment response^[63,65-67].

A recently published study reported a new predictor of treatment success by measuring the distensibility of the esophagogastric junction with an endoscopic functional luminal imaging probe (EndoFLIP[®]). Even when LES pressure was low, esophagogastric junction distensibility could be reduced, which was associated with

impaired emptying and recurrent symptoms^[68]. Although it must be considered that even if LES pressure is not an optimal predictor, it still remains a valuable measure in clinical practice.

In summary, PD is safer than commonly thought and very effective even in the long term, although multiple dilations will be needed over a lifetime in most patients. The technique of graded balloon dilation starting with 3.0 cm Rigidflex balloon as the initial dilator and progressing to 3.5 and 4.0 cm balloon in absence of response to previous balloon size seems to be the safest approach^[69]. Patients not responding to three serial dilations are less likely to respond to repeated dilations and should be offered surgery.

Comparative trials between various treatment modalities

The review of six randomized controlled trials comparing PD to BT injection in patients with primary achalasia demonstrated no significant difference in symptomatic remission and the mean esophageal pressure within 4 wk of the initial intervention. However, in the long term (> 6 mo) PD was more effective^[30]. The combination of both treatments does not improve the outcome^[35].

In summary, BT injection has similar efficacy as pneumatic dilatation in achieving an initial improvement in dysphagia. It can also be effective in some patients with tortuous megaesophagus and vigorous achalasia, but serial injections are required to sustain relief and its long term efficacy is inferior to PD^[70]. Furthermore, serial BT injection is more costly than PD dilation, if the life-expectancy is > 2 years^[71].

The role of PD in comparison to surgical myotomy is less clear. The difficulty in comparing both therapies is due to the lack of prospective randomized studies with a long follow up (> 5 years) in a large population and the lack of standardized technique of balloon dilation.

In the past years meta-analyses have favored surgery as the best treatment to achieve long-term success^[42,72]. However, these analyses mostly included retrospective studies of different sizes and quality and did not include approaches with on demand repeat dilations. In fact, a repeated dilation was the negative endpoint in some of the studies.

Until recently, only one randomized study existed. The study by Csendes *et al*^[73], in which conventional cardiomyotomy plus Dor fundoplication was compared with the pneumatic dilation using the so-called “Mosher Bag”, reported symptomatic response rates 5 years after treatment of 95%, and 65% in the surgical and PD group, respectively. However, the technique used for the pneumatic dilation was possibly suboptimal and a later published long-term follow-up of the same patient group showed that the results of the surgery were less favorable after more than 15 years of observation, with only 75% of patients being in sustained remission.

Last year, the results of a European multicenter study were published^[74]. In one study arm, patients were treated ($n = 94$) with PD, starting with a 30 mm Rigidflex

balloon, followed 1 to 3 wk later by dilation with the use of a 35-mm balloon. All patients thus underwent at least two dilations. If the Eckardt score 4 wk later was greater than 3, a third dilation was performed, with the use of a 40-mm balloon. The other group ($n = 104$) received a laparoscopic Heller cardiomyotomy with antireflux technique (LHM). Both treatments had comparable therapeutic success at 2 years, with 86% of the patients achieving symptomatic relief with PD and LHM, respectively. Furthermore, there was no significant difference in the LES pressure or esophageal emptying, as assessed by the height of barium-contrast column in both groups. Although age was not an overall predictor for therapeutic success for treatment, similar to previous investigations, an inferior symptomatic response of PD in patients with age < 40 years was observed.

The rate of complications as well as the frequency of induction of gastroesophageal reflux was similar in both groups. This data suggests that PD and LHM have equal efficacy, given that PD is performed with at least two dilations.

Not surprisingly, the only study comparing BT injections with laparoscopic cardiomyotomy showed an inferiority of BT. The 1-year remission rate was 53% in the BT group and 90% in the myotomy group and 2 years later only 34% of the patients treated with BT and 88% of the operated patients were in clinical remission^[75].

NEW ENDOSCOPIC THERAPEUTIC APPROACHES

POEM

POEM is a new endoscopic treatment for achalasia. Ortega *et al*^[76] first reported an endoscopic myotomy in the treatment of achalasia using a needle knife to cut the inner circular muscle fibers of the LES by cutting directly through the mucosa during endoscopy.

After this small study with excellent results the method fell into oblivion, until Pasricha *et al*^[77] reported a technique of endoscopic submucosal method on a pig model. Afterwards Inoue *et al*^[78] described a clinical application of the modified Pasricha technique as POEM. This approach involves endoscopic dissection of the esophageal submucosal space (under CO₂ insufflation) to gain access to LES muscle fibers. The semicircumferent dissection starts approximately 6-13 cm proximal to the esophagogastric junction and is extended 2 cm into the stomach. Circular muscle bundles are then dissected, leaving the longitudinal muscle layer intact. Inoue *et al*^[78] could show a significant improvement of dysphagia and reduction of LES pressure after this intervention, although the mean postinterventional LES pressure was still high at 20 mmHg. Most recently, several centers are using the POEM technique and reported excellent short term results and no “serious” complications, although pneumomediastinitis, C-reactive protein elevation are common and long term results are required^[78-80]. A short overview of the results to date is given by Table 3.

Table 3 Results of peroral endoscopic myotomy for the treatment of patients

Ref.	n	Mean age (yr)	Myotomy length (cm)	Follow-up (mo)	Symptomatic response (Eckardt score before/after POEM)	LES-tone (before/after POEM, mmHg)
Inoue <i>et al</i> ^[5]	17	41	8	5	10/1.3	52/20
von Renteln <i>et al</i> ^[80]	16	45	12	3	8.8/1.1	27/12
Swanström <i>et al</i> ^[110]	5	64	7	1	Not quantified	Not measured
Costamagna <i>et al</i> ^[111]	11	32	10	1	7.1/1.1	45/17
Chiu <i>et al</i> ^[112]	16	48	11	6	5.5/0	44/30

Only full text publications are considered. LES: Lower esophageal sphincter; POEM: Peroral endoscopic myotomy.

The procedure is promoted as less invasive than surgical myotomy, but it still requires general anesthesia and is not less time consuming than a laparoscopic approach. It is a sophisticated and demanding technique even for experienced endoscopists and so far has shown suboptimal results for lowering LES pressure compared in comparison to the published results with surgery. Furthermore revisional surgery might be more difficult because the space between the submucosal and muscular layers might become inflamed and scarred^[81].

In summary, it is a very interesting approach but long term results as well as a comparison of POEM with other treatment modalities in randomized controlled studies are required and its use should only be applied in the context of clinical trials.

Stenting

Another novel therapeutic approach is temporary esophageal stenting. Recently, a strategy of using retrievable stents has been successfully applied in the treatment of benign esophageal strictures^[82,83]. A few studies, from a single Chinese study group reported a symptomatic benefit with the use of self expanding metal stents in patients with achalasia. In this endoscopic approach a partially covered, self-expanding metal stent (SEMS) with a diameter of 20, 25 or 30 mm was applied in unsedated patients with achalasia. It was kept in place for 1 wk and then it was removed endoscopically. The best results after 10 years were shown in patients treated with a 30 mm stent. The clinical remission rate was 86%, 27%, 13%, 0%, in 30 mm SEMS, 25 mm SEMS, 20 mm SEMS and PD, respectively^[84,85]. In contrast, other study groups could not confirm these results and complications, such as stent migration, chest pain and reflux esophagitis have been reported, with a mortality and morbidity of 33% and 50% respectively^[86,87].

Ethanolamine oleate injection

Case reports from southern Europe^[88,89] and Iran^[90] reported a good response after endoscopic injection of the sclerosing agent ethanolamine oleate in the cardia. As a possible mechanism inflammatory destruction of the LES is discussed. Symptom relief as well as improved esophageal emptying has been demonstrated. However, the reported number of cases is very small and the longest follow up was 17 mo.

USE OF ENDOSCOPY FOR SURVEILLANCE

In patients with achalasia surveillance is important for several reasons. First, treatment success needs to be documented by objective parameters. Second, regular follow-up enables the clinician to detect symptomatic recurrences at an early stage and, third, endoscopic surveillance has the potential for early recognition of late complications, such as esophageal squamous cell cancer, megaesophagus or reflux esophagitis.

Objective evaluation of treatment success at least with a structured symptom orientated questionnaire and esophageal manometry, or better with additional timed barium esophagogram and endoscopy should be performed early (4-12 wk) after the initial intervention. Some centers even perform esophageal manometry intra-operatively or immediately after pneumatic dilation^[91,92]. A post-dilation LES resting pressure of < 10-15 mmHg is generally considered to be predictive of a good long-term response^[61,62]. However, falsely elevated LES pressure could be measured immediately after disruption of the LES due to associated edema. In the immediate post interventional period endoscopy is less important, but it is useful for further surveillance. Endoscopy might have a role in the detection or prevention of long-term complications. Up to 10% of all patients with long-standing achalasia (more than 10 years after first diagnosis) develop progressive enlargement of the esophagus, which can lead to a sigmoid-shaped esophagus and/or megaesophagus^[93] (Figure 4). This complication more frequently develops in patients who remain ineffectively treated for years. If these morphological changes are only recognized at an advanced stage, esophageal resection may be the only remaining therapeutic option^[13].

In addition, the risk of esophageal cancer in achalasia patients is estimated to be approximately 30-fold higher than in the general population^[8,9]. Especially in male achalasia patients, a substantially greater risk for both squamous cell carcinoma and adenocarcinoma of the esophagus has been shown, whereas the risk in female patients could not be evaluated due to the small numbers^[94].

The first prospective evaluation of esophageal cancer risk in a large cohort of achalasia patients with long-term follow-up demonstrated an increased rate of esophageal cancer. The mean age at cancer diagnosis was 71 years,

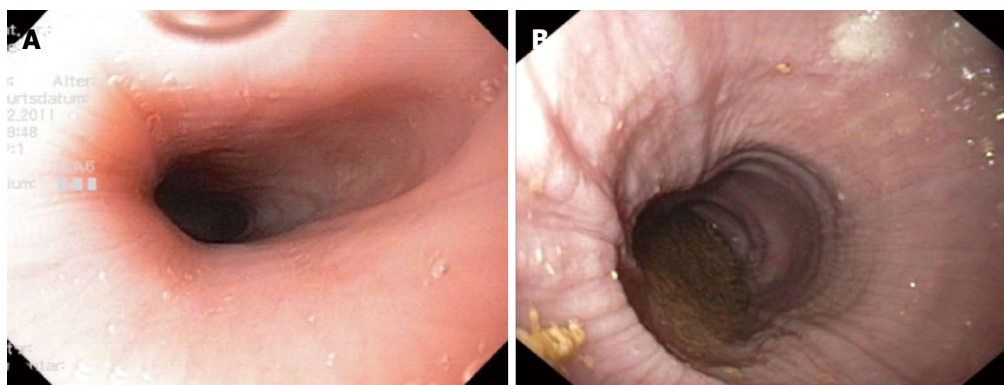


Figure 4 Endoscopic images of patients with achalasia. A: Early achalasia; B: Advanced achalasia with a megaesophagus, hyperplasia of the esophageal epithelium.

after a mean of 11 years (range 2-23 years) following initial diagnosis, and a mean of 24 years (range 10-43 years) after symptom onset. Although, most neoplastic lesions remained undetected until an advanced stage, despite structured endoscopic surveillance, the authors suggested such a surveillance strategy in patients with longstanding achalasia^[95].

Even if the latest American Society of Gastrointestinal Endoscopy guidelines correctly state that there are still “insufficient data to support routine endoscopic (cancer) surveillance for patients with achalasia”^[96], endoscopic surveillance might be beneficial in particular if one considers that cancer is not the only late complication of this disease. Therefore, most experts favor some form of endoscopic surveillance in patients with achalasia if the disease has been present for more than 10-15 years^[97,98]. It could be considered that chromoendoscopy or narrow band imaging might be superior for early detection of neoplastic lesions, but further studies are needed to compare these techniques with standard endoscopy.

Another long-term complication that requires careful attention is the development of clinically significant gastro-esophageal reflux disease (GERD), which occurs in up to 25% of patients with achalasia who are followed up for > 15 years^[99]. GERD-related findings range from reflux esophagitis and peptic strictures to Barrett’s esophagus, which in rare instances may progress to esophageal adenocarcinoma. In our practice follow-up visits are recommended biannually. The patients undergo structured interviews using a scoring system (Eckardt score) for the symptoms and upper gastrointestinal (GI)-endoscopy to detect reflux-esophagitis or the development of a megaesophagus. If achalasia has been present for more than 10 years the follow-up interval is shortened to annual intervals.

However, further studies are needed to determine whether such surveillance strategies will improve the overall outcome.

CONCLUSION

Upper GI-endoscopy is an important part in the diag-

nostic algorithm of achalasia. Although it does not have a high sensitivity in detection of early stage achalasia, it is essential to rule out pseudoachalasia.

Treatment remains palliative as the neuronal defect of the disease seems to be irreversible. Therefore, the primary goal of all therapies is the improvement of the esophageal passage by disruption of the LES and the prevention of long-term complications. The most effective endoscopic therapy is graded pneumatic dilation with Rigiflex balloons, whereas the endoscopic injection of Botulinum toxin injection is mostly reserved for old patients or those with major comorbid illnesses preventing surgery. A new promising technique might be POEM although long-term results and comparison of POEM to PD and LHM are needed.

Treatment with a temporary self expanding stent are reported by one group who reported a better long term effect than PD, but the results of PD were poor in this study and the data must be confirmed by others before this method can be recommended. In addition, multiple complications such as stent migration, bleeding and chest pain can occur with this technique.

Most experts favor some form of endoscopic surveillance in patients if achalasia has been present for more than 10-15 years. However, no guidelines exist and further studies are needed to determine whether and which surveillance strategies will improve overall outcome.

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Prevalence and clinical features of colonic diverticulosis in a Middle Eastern population

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Abstract

AIM: To determine the prevalence, location, associations and clinical features of colonic-diverticulosis and its role as a cause of lower-gastroenterology-bleeding.

METHODS: We retrospectively reviewed the medical records of 3649 consecutive patients who underwent a colonoscopy for all indications between 2007 and 2011 at King Khalid University Hospital, Riyadh, Saudi Arabia. The demographic data were collected retrospectively through the hospital's information system, electronic file system, endoscopic e-reports, and manual review of the files by two research assistants. The demographic information included the age, sex, comorbidities and indication for the colonoscopy. The association among colonic polyps, comorbidities and diverticular disease was also measured.

RESULTS: A total of 270 patients out of 3649 were diagnosed with colonic diverticulosis, with a prevalence of 7.4%. The mean age was 60.82 years \pm 0.833, (range 12-110). Females comprised 38.89% (95%CI: 33-44.7) of the study population. The major symptoms were rectal bleeding in 33.6%, abdominal pain in 19.3%, constipation in 12.8% and anemia in 6%. Diverticula were predominantly left-sided (sigmoid and descending colon) in 62%, right-sided in 13% and in multiple locations in 25%. There was an association between the presence of diverticulosis and adenomatous polyps (P -value < 0.001), hypertension (P -value < 0.0001) and diabetes mellitus (P -value < 0.0016). Diverticular disease was the second most common cause of lower gastrointestinal bleeding, in 33.6% (95%CI: 27.7-39.4), after internal hemorrhoids, in 44.6% (95%CI: 40.3-48.9). On multivariable logistic regression, hypertension (OR = 2.30; 95%CI: 1.29-4.10), rectal bleeding (OR = 2.57; 95%CI: 1.50-4.38), and per year increment in age (OR = 1.05; 95%CI: 1.03-1.07) were associated with diverticulosis but not with bleeding diverticular disease. Limitations: A small proportion of the patients included had colonoscopies performed as a screening test.

CONCLUSION: Colonic-diverticulosis was found to have a low prevalence, be predominantly left-sided and associated with adenomatous-polyps. Age, hypertension and rectal bleeding predict the presence of diverticular disease.

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Key words: Colonic diverticulosis; Diverticular disease; Saudi Arabia; Prevalence; Lower gastrointestinal bleeding; Epidemiology

Core tip: Colonic-diverticulosis is common in Western populations as well as an emerging disease in Eastern populations but prevalence data for Arab populations is scarce. We retrospectively reviewed the medical

records of 3649 consecutive patients who underwent a colonoscopy for all indications. The demographic information included the age, sex, comorbidities and indication for the colonoscopy. The association among colonic polyps, comorbidities and diverticular disease was also measured. Colonic-diverticulosis was found to have a low prevalence among the Saudi population, be predominantly left-sided and associated with adenomatous-polyps. Age, hypertension and rectal bleeding predict the presence of diverticular disease.

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INTRODUCTION

Diverticulosis of the colon is a common disease in Western societies^[1]. Although the true prevalence of diverticula is unknown, a large observational study of 9086 consecutive patients undergoing colonoscopy found a prevalence of 27%^[2], which increased with advancing age. Some studies suggested that the prevalence of diverticula may be as high as 60% in patients older than 80 years of age^[3] and has no sex predilection. Most patients with diverticulosis will have clinically quiescent disease; approximately 80% to 85% are believed to remain asymptomatic.

Recent evidence showed a rising prevalence of diverticulosis in Europe, the United States and Canada^[4-6]. Although Western populations have predominantly left-sided diverticulosis^[7], right-sided diverticulosis is common in Asia. Diverticulosis of the colon is rare in rural Asia and Africa, and its incidence increases with age^[8-15]. The prevalence in Southeast Asia ranges from 8% to 22%^[8,9], affecting the right side of the colon in most cases (70%-98%) and showing a peak incidence in patients 50 to 60 years of age^[10,11]. Studies from China and South Korea have noted a prevalence of 0.5% to 1.7% with a right-side predilection in 75% of the patients^[12]. However, an even lower prevalence of diverticulosis was reported in Sub-Saharan Africa, with a slightly younger age (45 to 60 years) with right colon involvement in 62% of the cases^[13-15]. Data from the Arab world examining the prevalence and clinical features of colonic diverticulosis are scant. In a retrospective evaluation of 274 consecutive barium enemas performed at a single institute in patients aged 20 to 85 years over a three-year period (1979 to 1981) in Jordan, colonic diverticula were found in 4%^[16]. A study from Iran examined the frequency of diverticulosis in 656 barium enemas and found it to be 2.4% in patients older than 50 years^[17]. A higher prevalence was reported in Israel, reaching up to 9.5% among Arabs, with a seven-fold increase over a 10-year period^[18]. Diverticular disease (DD) refers to symptomatic diverticula

that cause complications, including acute diverticulitis, perforations and lower gastroentero-intestinal bleeding. Bleeding from colonic diverticula is the most common cause of acute lower gastrointestinal (GI) bleeding^[19,20]. Acute lower intestinal bleeding has been reported to occur in up to 3%-5% of colonic diverticula^[21,22]. Most cases of diverticular bleeding resolve on their own, and diverticular bleeding stops spontaneously in 70%-80% of cases^[23]. Shennak *et al*^[24] reported that hemorrhoids were the most common cause of lower GI bleeding in 701 Jordanian patients, followed by polyps and colitis. No data are available from Saudi Arabia, and whether the incidence, prevalence or epidemiology of the disease is similar or differs from that in other populations is not clear. The aim of our study was to investigate the prevalence, location, distribution, clinical features and associations of colonic diverticulosis as well as the factors that contribute to bleeding in Saudi patients with DD.

MATERIALS AND METHODS

Ethics

This study was approved ethically by the Internal Review Board (IRB) (Study No. E-12-818) at King Khalid University Hospital, Riyadh, Saudi Arabia.

Data Collection

A retrospective cohort study was conducted using an endoscopic reporting database of individuals seen at a major tertiary care university hospital (King Khalid University Hospital) in Riyadh, Saudi Arabia. The demographic data of consecutive patients who underwent a complete colonoscopy for all indications between August 2007 and April 2011 were collected retrospectively through the hospital's HIS system, electronic file system, endoscopic e-reports, and a manual review of the files by two research assistants. The demographic features included age, sex, symptoms, indication for colonoscopy, medication history and comorbidities. Patients with a history of any of the following were excluded from this study: colon cancer, colonic resection, incomplete colonoscopy, active colitis, active diverticulitis and inflammatory bowel disease. Colonic diverticulosis was defined as the presence of one or more diverticula, which is a saccular out pouching of the colon. The location of the diverticula was classified as follows: left-sided refers to diverticulosis involving the descending colon and/or sigmoid colon with or without the transverse colon, right-sided refers to diverticulosis involving the caecum and/or ascending colon with or without the transverse colon and hepatic flexure, and multiple locations refers to both right and left colonic involvement. The ethics committee of King Khalid University Hospital approved the study.

Statistical analysis

Descriptive statistics were computed for continuous variables including means, SD and minimum and maximum values. Frequencies and inter-quintile ranges were used

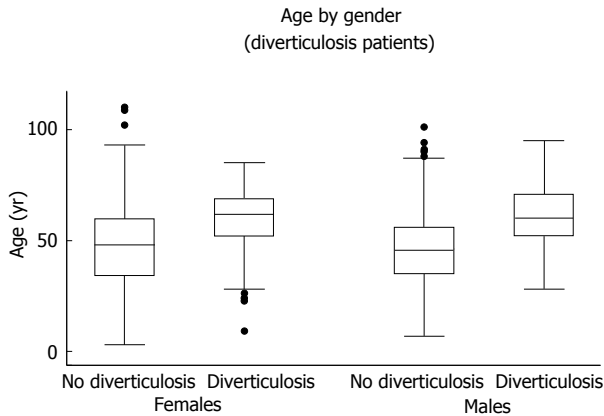


Figure 1 The age distribution of patients stratified by the presences or absence of diverticulosis as well as gender. Source: King Khalid University Hospital.

for categorical variables. The χ^2 test was used for categorical variables, and the *t*-test for continuous variables. Univariable and multivariable logistic regressions were used to examine the association between independent variables and the presence of diverticulosis. The OR and 95%CI were estimated. We used the software STATA 11.2 (StataCorp, TX, United States) in our analysis. A *P*-value of < 0.05 was considered statistically significant.

RESULTS

Out of 3649 patients undergoing colonoscopy, 270 patients (7.4%) were diagnosed with colonic diverticulosis. The mean age was $60.82 \text{ years} \pm 0.833$ (range 12-110), and the majority were Saudi nationals (92.9%). Females were $38.89\% \pm 2.97$ and males were $61.11\% \pm 1.51$ of the cohort, and there was no gender-specific predilection ($P < 0.218$) (Figure 1). The comorbidities and the indications for the colonoscopy for all patients are presented in Table 1. Diverticulosis was predominantly left-sided (sigmoid and descending colon) in 62%, followed by right-sided in 13% and multiple locations in 25%.

In the patients with diverticulosis, there was a higher history of hypertension (63.88% *vs* 25.92%, *P*-value < 0.01), diabetes (44.44% *vs* 24.32%, *P*-value < 0.01), dyslipidemia (22.22% *vs* 10.77%, *P*-value = 0.03) and a higher history of the use of aspirin (21.33% *vs* 9.23%, *P*-value = 0.01). Furthermore, those with diverticulosis were referred for a colonoscopy more frequently for rectal bleeding (33.60% *vs* 22.08%, *P*-value < 0.01) and were less likely to be referred for surveillance (10.40% *vs* 16.72%, *P*-value < 0.01), diarrhea (2.40% *vs* 9.28%, *P*-value < 0.01), or weight loss (2.00% *vs* 5.79%, *P*-value < 0.01) (Table 1).

The univariable analysis revealed that diverticulosis was associated with a history of hypertension (OR = 5.05; 95%CI: 3.06-8.34), diabetes (OR = 2.49; 95%CI: 1.53-4.05), dyslipidemia (OR = 2.37; 95% CI, 1.31-4.27), and aspirin use (OR = 2.67; 95%CI: 1.48-4.81) and that the diverticulosis patients were more likely to be

Table 1 Comorbidities of patients and indications for a colonoscopy for the complete cohort of patients

Variable	Percentage	95%CI
Comorbidities		
Hypertension	63.88%	52.52-75.25
Diabetes	44.44%	32.68-56.20
Dyslipidemia	22.22%	12.38-32.06
Aspirin	10.07%	8.35-11.82
Chronic kidney disease	5.55%	0.10-11.00
Coronary artery disease	4.16%	0.10-9.00
Indication for colonoscopy		
Bleeding per rectum	22.94%	21.50-24.38
Abdominal pain	19.30%	17.94-20.64
Surveillance	16.29%	15.03-17.55
Constipation	9.57%	8.57-10.58
Diarrhea	8.75%	7.79-9.72
Screening	7.57%	6.67-8.48
Weight loss	5.50%	4.72-6.28
Anemia	5.02%	4.27-5.76
Melena	3.13%	2.54-3.73
Anal pain	1.91%	1.45-2.38
Altered bowel habits	1.76%	1.31-2.21
Perianal fistula	1.19%	0.82-1.55
Positive for occult blood	0.52%	0.27-0.76

referred for a colonoscopy for rectal bleeding (OR = 1.79; 95%CI: 1.35-2.35) but less likely to be referred for surveillance (OR = 0.58; 95%CI: 0.38-0.87), diarrhea (OR = 0.24; 95%CI: 0.11-0.55), or weight loss (OR = 0.33; 95%CI: 0.14-0.82) (Table 2).

The multivariable analysis revealed that the only factors associated with the presence of diverticulosis were age (OR = 1.05; 95%CI: 1.03-1.07 per year), hypertension (OR = 2.30; 95%CI: 1.29-4.10), rectal bleeding (OR = 2.57; 95%CI: 1.50-4.38), and the finding of internal hemorrhoids (OR = 1.96; 95%CI: 1.06-3.65) (Table 3). However, none of these variables predicted bleeding in the patients with DD (Table 4).

There was an association between the presence of diverticulosis and adenomatous polyps (OR = 1.76; 95%CI: 1.33-2.33).

Regarding the etiology of the patients presenting with rectal bleeding based on the colonoscopy findings, internal hemorrhoids was the most common cause (44.7%), followed by DD (33.6%), colonic mass (31.5%), polyps (24.8%), and colitis (19.0%) (Table 5).

We found that bleeding as an indication for a colonoscopy was present in 58% of the patients with left-sided DD, 18% with right-sided DD, and 23% with DD in multiple locations.

DISCUSSION

Colonic diverticulosis is a prevalent gastrointestinal disorder in Western populations and less so in Eastern ones^[4,25,26]. Ascertaining the true prevalence of diverticulosis in the general population is difficult given that most affected individuals will remain asymptomatic. Our knowledge about the magnitude of the effect and prevalence in Arab populations is limited. The results

Table 2 Comorbidities of patients and indications for a colonoscopy stratified by the presence and absence of diverticulosis as well as the univariable analysis between the presence of diverticulosis and the corresponding variables

Variable	Diverticulosis	No diverticulosis	P-value	Univariable analysis	
				OR	95%CI
Comorbidities					
Hypertension	63.88%	25.92%	< 0.01	5.05	3.06-8.34
Diabetes	44.44%	24.32%	< 0.01	2.49	1.53-4.05
Dyslipidemia	22.22%	10.77%	0.03	2.37	1.31-4.27
Aspirin	21.33%	9.23%	0.01	2.67	1.48-4.81
Chronic kidney disease	5.56%	3.12%	0.38	2.91	0.82-10.29
Coronary artery disease	4.16%	1.43%	0.27	1.82	0.62-5.30
Indication for colonoscopy					
Bleeding per rectum	33.60%	22.08%	< 0.01	1.79	1.35-2.35
Abdominal pain	19.30%	15.20%	0.06	0.73	0.51-1.05
Constipation	12.80%	9.31%	0.11	1.43	0.96-2.11
Surveillance	10.40%	16.72%	< 0.01	0.58	0.38-0.87
Screening	6.40%	7.67%	0.43	0.82	0.49-1.39
Anemia	6.00%	4.94%	0.5	1.23	0.71-2.12
Melena	3.13%	4.40%	0.31	1.47	0.78-2.79
Diarrhea	2.40%	9.28%	< 0.01	0.24	0.11-0.55
Altered bowel habits	2.00%	1.74%	0.78	1.15	0.46-2.90
Weight loss	2.00%	5.79%	< 0.01	0.33	0.14-0.82
Anal pain	1.20%	1.97%	0.29	0.6	0.19-1.94
Positive for occult blood	1.20%	0.46%	0.29	2.62	0.75-9.19
Perianal fistula	0.40%	1.25%	0.06	0.32	0.04-2.32

Table 3 Variables associated with the presence of diverticulosis on multivariable analysis

Variable	Multivariable analysis	
	OR	95%CI
Age	1.05	1.03-1.07
Hypertension	2.30	1.29-4.10
Bleeding per rectum	2.57	1.50-4.38
Internal hemorrhoids	1.96	1.06-3.65

Table 4 Factors associated with of bleeding per rectum in those with diverticulosis on univariable analysis, none of the variables were associated with bleeding per rectum on multivariable analysis

Variable	OR	95%CI
Age	1.00	0.97-1.02
Hypertension	0.73	0.27-1.95
Diabetes	1.27	0.48-3.32
Dyslipidemia	1.00	0.32-3.15
Atrial fibrillation	0.44	0.05-3.50
Abdominal Pain	0.19	0.07-0.57
Constipation	0.75	0.33-1.70
Diarrhea	0.39	0.04-3.38
Internal hemorrhoids	2.61	1.48-4.61
Polyps	1.28	0.72-2.29

of this study showed that the prevalence of colonic diverticulosis is 7.4%, which is low compared with Western and Eastern populations and slightly higher compared with data from other countries in the Arab world^[16,17].

The mean age of the patients with diverticulosis was 60.82 years, and the majority (92.3%) were older than 50 years of age. The disease was more prevalent

Table 5 Findings on colonoscopy and possible etiologies for patients referred for bleeding per rectum

Etiology	Percentage	95%CI
Internal hemorrhoids	44.66%	40.36-48.96
Diverticulosis	33.60%	27.73-39.47
Mass	31.45%	26.03-36.87
Polyps	24.76%	21.37-28.15
Colitis	18.97%	14.44-23.49

with advancing age, which is in agreement with the international data^[27].

The distribution pattern of diverticulosis differs between Western and Eastern populations, with sigmoid diverticula predominating in the Western population and the right colon most commonly affected in Asians^[28-30]. Left-sided diverticulosis was found to be more common, which is most likely due to urbanization in the gulf region, with the increased consumption of red meat and a low fiber diet. The study was conducted in one of the largest tertiary care hospitals in Riyadh, the capital of the Kingdom of Saudi Arabia. The catchment area of the hospital covers the population inhabiting the northern part of Riyadh, which has an urban inhabitation. Right colonic diverticulosis is thought to be congenital, which differs from the development of sigmoid diverticula, which in turn is thought to be acquired as a result of the raised intraluminal pressure within the colon^[31] that is attributable to inadequate dietary fiber intake^[32,33].

Colonic neoplasia and colonic diverticulosis have common epidemiological trends and risk factors, such as age and a lack of dietary fiber^[34]. However, the association between these diseases remains elusive. In a pro-

spective study, Morini *et al*^[35] found an increased risk for sigmoid colon adenomas in Italian patients with DD. In a cross-sectional study in the United States, an increased risk for distal neoplasia was found in women with extensive distal diverticulosis^[36]. Such an association was also observed in our study (OR = 1.76; 95%CI: 1.33-2.33), with a predominantly left-sided location for diverticulosis in 62% and for adenomatous polyps in 65% of our cohort.

Studies have shown that NSAID use in patients with complicated DD is nearly double the rate of NSAID use in patients with normal, healthy colons^[37]. In addition, multiple studies have demonstrated a clear link between NSAID use and an increased risk of diverticular hemorrhaging. Hypertension was also found to be associated with the risk of DD complicated with a high bleeding risk, which is predominantly due to vascular endothelial injury and atheroma formation that lead to arteriosclerosis and increased pressure within exposed blood vessels, which elevate the risk for bleeding^[38,39]. Sakuta *et al*^[40] reported the first study that evaluated the prevalence rates of type 2 diabetes and hypertension among the subjects with asymptomatic colonic diverticula and found that type 2 diabetes (21.6% *vs* 14.0%, *P* = 0.047) and hypertension (30.9% *vs* 19.8%, *P* = 0.011) were more prevalent among the subjects with colonic diverticulum than in those without it. The mechanism of the association between diabetes and colonic diverticula is not yet clear. However, low dietary fiber intake is assumed to contribute to the development of colonic diverticula^[41-43]. Our data showed similar associations with hypertension, diabetes mellitus, dyslipidemia, the history of aspirin use and colonic diverticulosis, but the only factors that predicted the presence of colonic diverticulosis were age (OR = 1.05; 95%CI: 1.03-1.07 per year), hypertension (OR = 2.40; 95%CI: 1.31-4.39), rectal bleeding (OR = 2.57; 95%CI: 3.06-8.34), and the finding of internal hemorrhoids (OR = 1.96; 95%CI: 1.06-3.65). Surprisingly, these factors were not associated with complicated diverticulosis patients who presented with lower GI bleeding.

Before the era of the colonoscopy, DD was thought to be the most common cause of massive lower GI bleeding^[44], as it was often diagnosed by barium enemas in earlier studies. Recently after the introduction of colonoscopy, however, DD was shown to be the second-most common etiology of massive GI bleeding in the elderly after colonic angiodysplasia^[45]. Our data found that internal hemorrhoids were the most common etiology of rectal bleeding, with DD being second. This result is likely related to the retrospective study design.

Our study may have suffered bias towards symptomatic patients because it was an observational study instead of a population-based study. In addition, because of the limited number of patients with screening colonoscopy as an indication, a definitive conclusion could not be drawn, especially given the lack of previous studies from Saudi Arabia or Gulf countries for

comparison. However, this study is the first, to the best of our knowledge, evaluating the prevalence, clinical features, and associations of colonic diverticulosis in Saudi Arabia and may open the door for future research with a larger cohort to elucidate the true prevalence, behavior, risk factors and association of DD in our population.

COMMENTS

Background

Colonic diverticulosis is common in Western populations as well as an emerging disease in Eastern populations but data are scarce about the prevalence among the Arab population with no previous reported studies on the prevalence of diverticular disease.

Research frontiers

Diverticulosis of the colon is a common disease in the Western populations and associated with many gastrointestinal complications that might be life threatening as in case of lower gastrointestinal (GI) bleeding. The prevalence of colonic diverticulosis have been studied thoroughly in Western and Eastern populations, however it was never studied in Arab or among gulf populations. In this study, the authors aimed to look at the prevalence, clinical pictures, and locations of colonic diverticulosis as well as its role to the patients who presented with lower GI bleeding.

Innovations and breakthroughs

The study demonstrate that the colonic diverticulosis prevalence among Saudi population was low compared to the reported prevalence from the other ethnic population, however colonic diverticula were predominantly at the left side similar to Western populations. Other important issue was being associated with the presence of adenomatous polyps in left side of the colon. Its role in contributions of lower GI bleeding was also studied and found that diverticular disease was the second most common etiology for lower GI bleeding in these cohort.

Applications

Future population based studies to look at the true prevalence of colonic diverticulosis among patients for screening colonoscopy are highly recommended.

Peer review

The manuscript underlies the prevalence, clinical pictures, locations, and association of colonic diverticulosis among Saudi populations which never been studied before and it looks also at the factors that predict the presence of colonic diverticula which might help in patients selection to undergo colonoscopic studies. It is well written manuscript in an important GI topic.

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Conservative management of small bowel perforation in Ehlers-Danlos syndrome type IV

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Abstract

Ehlers-Danlos syndrome (EDS) is a group of inherited connective tissue disorders caused by collagen synthesis defects. EDS type IV, or vascular EDS, is caused by loss-of-function mutations in the type III pro-collagen gene (*COL3A1*). Common complications of EDS type IV include gastrointestinal bleeding and bowel perforations, posing diagnostic and therapeutic dilemmas for both surgeons and gastroenterologists. Here, we describe a complicated case of EDS type IV in a 35-year-old caucasian female who presented with overt gastrointestinal bleeding. The patient had a prior history of spontaneous colonic perforation, and an uncomplicated upper endoscopy was performed. A careful ileoscopy was terminated early due to tachycardia and severe abdominal pain, and a subsequent computed tomography scan confirmed the diagnosis of ileal perforation. The patient was managed conservatively, and demonstrated daily improvement. At the time of hospital discharge, no further episodes of gastrointestinal blood loss had occurred. This case highlights the benefit of conservative management for EDS patients with gastrointestinal hemorrhage. It is recommended that surgical treatment

should be reserved for patients who fail conservative treatment or in cases of hemodynamic instability. Finally, this case demonstrates the necessity for a higher threshold of operative or endoscopic interventions in EDS type IV patients.

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Key words: Type-IV Ehlers-Danlos syndrome; Gastrointestinal hemorrhage; Bowel perforation; Conservative management; Non-operative; *COL3A1*; Connective tissue disorder

Core tip: Gastrointestinal bleeding and bowel perforations are known complications of Ehlers-Danlos syndrome (EDS) type IV. Tissue fragility and hemorrhage tendency pose diagnostic as well as therapeutic dilemmas for both surgeons and gastroenterologists. We performed an upper gastrointestinal endoscopy and ileoscopy in a bleeding patient with history of EDS type IV. The upper endoscopy procedure was uneventful with minimal air used for luminal distension. A small bowel perforation was found. This case highlights the tissue fragility and serosal tears that can occur upon slight handling. Conservative management proved the best course of action.

Allaparthi S, Verma H, Burns DL, Joyce AM. Conservative management of small bowel perforation in Ehlers-Danlos syndrome type IV. *World J Gastrointest Endosc* 2013; 5(8): 398-401 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i8/398.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i8.398>

INTRODUCTION

Ehlers-Danlos syndrome (EDS) comprises of a heterogeneous family of inherited connective tissue disorders

known for its features of fragile, hyperextensible skin, hypermobile joints, and tissue fragility. EDS type IV, also known as vascular EDS, is an inherited connective tissue disorder caused by loss-of-function mutations of the pro- α -1 chains of type III pro-collagen (*COL3A1*). Vascular EDS causes severe fragility of connective tissues with increased risk of arterial and gastrointestinal (GI) rupture and complications during surgical and radiological interventions. Spontaneous vascular dissection, GI perforation, or organ rupture are the presenting signs in the majority of adults identified to have EDS type IV^[1-3]. Diagnostic criteria for EDS type IV includes reduced levels of type III collagen protein or identification of the *COL3A1* gene along with two of the following diagnostic criteria: (1) easy bruising; (2) thin skin with visible veins; (3) characteristic facial features (in some individuals); and (4) rupture of arteries, uterus, or intestines^[3]. These aberrations in collagen processing correlate with reduced strength of the vascular and hollow organ soft tissue, abnormalities of the large and small bowel architecture including abrupt changes in the caliber of the lamina muscularis, secondary diverticula formation, and strongly reduced expression of collagen 3^[4].

We report a complicated clinical course of a 35-year-old female with EDS type IV and multiple complications (including spontaneous colonic perforation with ileostomy, spontaneous pneumothorax, carotid artery dissection, and multiple orthopedic joint surgeries), who presented with overt GI bleeding.

CASE REPORT

A 35-year-old Caucasian female with history of EDS type-IV was transferred to our institution for evaluation of overt GI bleeding. She was diagnosed with classical vascular EDS type-IV at age 16 with easy bruising, thin skin with visible veins, characteristic facial features, and positive family history of EDS in her mother and grandmother. She had a stroke secondary to carotid artery dissection at age 17, ruptured ovarian cyst at 19, postpartum spontaneous sigmoid perforation at 23, spontaneous pneumothorax at 26, and multiple orthopedic surgeries for joint dislocations. The spontaneous colonic perforation at age 23 occurred during labor and required colon resection with resultant ileostomy. She presented to an outside institution with sharp abdominal pain, vomiting, and bright red blood present in the ileostomy pouch. The patient was unable to keep food down and had had several episodes of vomiting over the course of the previous 24 h. She was hemodynamically stable and in no acute distress, but laboratory results revealed hemoglobin of 12 g/dL, which subsequently dropped to 6.1 g/dL, blood urea nitrogen of 60 mg/dL and creatinine of 3.1 mg/dL. An initial abdominal computed tomography (CT) scan was positive for some abdominal distension but no signs of intestinal obstruction or perforation. The subsequent upper endoscopy was normal, and no bleeding site was identified. The patient was then transferred to

our institution's medical intensive care unit due to the unknown source of the GI bleeding and to manage the particular complexity of her case.

The gastroenterology team determined that the patient was actively bleeding into her ileostomy pouch. Considering the worsening renal parameters, all further imaging studies were suspended. After weighing the risks and benefits with the patient, in view of her history of EDS and spontaneous bowel perforations, an upper GI endoscopy and possible ileoscopy was planned. The upper endoscopy was performed safely with minimal luminal distension, and no evidence of active bleeding was found. At the time of the upper endoscopy, however, fresh blood emerged from the ileostomy; this issue was addressed by performing an additional ileoscopy using the utmost care and following the same principles as above. However, after the scope was advanced less than 10 cm, the patient developed tachycardia and severe abdominal pain, which prompted early termination of the procedure. Abdominal CT scan revealed free air and extravasation of oral contrast into the peritoneum, confirming the diagnosis of ileal perforation. CT angiography was negative for extravasation of parenteral contrast. Following surgical consultation about the patient's prior abdominal surgical interventions and complexity of the case, and discussion with the patient, a conservative management procedure was designed to address the ileal perforation. The patient was treated with nasogastric suction, antibiotics, and blood transfusions as needed, and total parental nutrition and bowel rest. The patient demonstrated daily improvement and spontaneous resolution of the bleeding. After four days, the patient was able to tolerate oral intake. On day 7 of hospitalization, the patient was discharged in stable condition. Ultimately, no etiology for GI hemorrhage was found.

DISCUSSION

Ehlers-Danlos syndrome is a heterogeneous group of hereditary disorders of connective tissue, whose prevalence is estimated between 1/10000 and 1/25000, with no ethnic predisposition^[5]. According to the Villefranche classification, there are 6 clinical types^[6], with type IV, or vascular EDS, accounting for about 5%-10% of cases^[7]. The symptoms of each EDS type differs based on the causative gene and inheritance pattern. As a result, the genetic heterogeneity of EDS is very strong. Moreover, each clinical entity of EDS needs to be considered as a different disease that results from different causative gene based on clinical symptoms and family history (Table 1).

Based on Villefranche diagnostic criteria (Table 2)^[6], the combination of any two of the major diagnostic criteria should have a high specificity for vascular EDS and further testing is strongly recommended to confirm the diagnosis. The presence of one or more minor criteria supports the diagnosis of vascular EDS but is not sufficient to establish the diagnosis^[5]. Vascular EDS is

Table 1 Classification of Ehlers-Danlos syndrome

New classification, Villefranche (1997)	Former classification Berlin (1988)	MIM number ¹	Inheritance	Biochemical defects
Classic	Type I	130000	AD	COL5A1
	Type II	130010		COL5A2
Hypermobility	Type III	130020	AD	Unknown
Vascular	Type IV	130050	AD	COL3A1
Kyphoscoliosis	Type VI	225400	AR	Lysyl hydroxylase
Arthrochalasia	VIIA, VII B	130060	AD	COL1A1, COL1A2
Dermatosporaxis	VII C	225410	AR	Type I collagen N-peptidase
Others	V	305200	XR	
	VIII	130800	AD	
	X	225310	AR	
	XI	147900	AD	

It's adapted from Beighton *et al*^[6], Wenstrup *et al*^[17] and Steinmann *et al*^[18]. ¹The MIM number is a numerical assignment for inherited diseases, genes and functional segments of DNA. AD: Autosomal dominant; AR: Autosomal recessive; XR: X-linked recessive.

Table 2 Vascular Ehlers-Danlos syndrome: Villefranche diagnostic criteria

Major diagnostic criteria	Minor diagnostic criteria
Arterial, digestive or uterine fragility or rupture	Positive family history
Thin, translucent skin	Sudden death in a close relative
Extensive bruising	Acrogeria
Characteristic facial appearance	Hypermobility of small joints
	Tendon and muscle rupture
	Talipes equinovarus (clubfoot)
	Early onset varicose veins
	Spontaneous pneumo or hemothorax

It's adapted from Germain *et al*^[5] and Beighton *et al*^[6].

an autosomal dominant inherited disease caused by one allele mutation of the *COL3A1* gene, which encodes type III procollagen. This mutation results in qualitative and quantitative abnormalities of mature type III collagen. Systemic arteries that are rich in type III collagen may undergo dissection, aneurysm, or rupture. In addition to vascular complications, ruptures of hollow organs that are rich in type III collagen, *i.e.*, intestines and uterus, are also characteristic^[8]. Pneumothorax is also a frequent complication, as the pleura also contains a high degree of type III collagen. While rare in childhood, EDS type IV complications occur in approximately 25% of 20-year-old diagnosed with vascular EDS^[3]. Further, by age 40, 80% of diagnosed individuals have no less than one complication^[9]. The median age of death is estimated to be 50 years, with the most common cause of death being arterial rupture. Pepin *et al*^[1] reported that the likelihood of death was greatest after organ rupture (45%) and least after bowel rupture (2%). In view of the multitude of clinical presentations, symptoms, natural history and prognosis, EDS type IV should be assessed separately within the group of EDS.

Understanding the GI manifestations of EDS type IV is necessary for both surgeons and gastroenterologists. The two main complications are perforation and bleeding. *In vitro* electromyographic studies of the colonic tissue suggest a possible link between abnormal myogenic

activity and colonic perforations^[10]. Of the perforations, most occur within the colon, more specifically the recto-sigmoid junction. Leake *et al*^[11] reported that bleeding into the wall of the gut might precede local necrosis and subsequent perforation. This hypothesis was supported by microscopy findings of submucosal edema in small bowel sections, vascular dilatation with focal hemorrhage, perforation, and organized inflammation in the serosal surface^[11].

Our case posed an endoscopic and surgical dilemma due to the complicated history of the patient. There is very limited data available concerning the safety of GI procedures in patients with EDS. Although some reports suggest avoiding elective procedures such as endoscopy, colonoscopy, angiography, nasogastric tube placement, and enema administration due to perforation or dissection^[12,13], there are also case reports of performing upper endoscopy and endoscopic retrograde cholangiopancreatography (ERCP) safely^[14,15]. In our patient, who had overt bleeding with significant hemodynamic instability, we believed that potential risk of ileoscopy was justified. Given the fact that our index case was a classical EDS type IV with complicated surgeries in the past, safety and caution were our paramount concerns. While the rarity of this syndrome precludes an evidence-based approach to management, previous cases served as a guide in the clinical care of this patient. We performed upper GI endoscopy uneventfully and in spite of using minimal air for luminal distension; the patient developed tachycardia and severe abdominal pain during ileoscopy, prompting early termination of the procedure. Abdominal CT scan revealed free air and extravasation of oral contrast into the peritoneum, confirming the diagnosis of ileal perforation. These events and findings served to emphasize the tissue fragility in EDS patients due to the collagen deficiency and the high risk of serosal tears that can occur upon minimal handling, as noted by many operating surgeons. For our patient, conservative care proved to be the best course of action. The overt bleeding was self-limited and the perforation was managed with bowel rest induced by antibiotics and total parental nutrition (Table 3).

In conclusion, our case highlights the clinical dilem-

Table 3 Endoscopic procedures reported in Ehlers-Danlos syndrome patients

Ref.	Age/sex	Procedure	Outcome/treatment
Hawk <i>et al</i> ^[15]	41/F	ERCP Sphincterotomy	No complication Non-pulsatile bleeding (conservative management)
Kahn <i>et al</i> ^[19]	45/F	ERCP	Bile duct rupture (conservative management)
Rana <i>et al</i> ^[20]	33/M	Colonoscopy	Perforation (Surgical intervention)
Baichi <i>et al</i> ^[14]	51/F	Upper endoscopy	No complication
Present case	35/F	Upper endoscopy Ileoscopy	No complication Perforation (conservative management)

F: Female; M: Male; ERCP: Endoscopic retrograde cholangiopancreatography.

mas in the management of GI complications of EDS type IV and stresses the importance of conservative management. Surgical interventions should be reserved for hemodynamically/clinically unstable patients who fail to respond to supportive measures. Colonoscopy or small bowel enteroscopy carry a higher risk when compared to upper GI endoscopy, which can be safely performed. Angiography can be associated with arterial dissection^[16]. Endoscopists should be prepared for bleeding and perforations in these high-risk patients with appropriate pre-endoscopic surgical back up.

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Endoscopic closure of a gastrocolic fistula using the over-the-scope-clip-system

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Abstract

Gastrointestinal (GI) defects such as fistulas and leaks can be potentially closed endoscopically using hemoclips and loops. However, hemoclips may not allow for closure of large defects and they do not exert enough tensile force to keep fibrotic defects larger than 5 mm approximated. Herein we present a case of successful endoscopic closure of a gastrocolic fistula in a severely malnourished patient with complex post-surgical upper GI anatomy. We strongly believe that this device is a major breakthrough for the management of various types of discontinuity defects or fistulas. In addition, we show the usefulness of placing a direct jejunostomy using the double balloon enteroscopy (DBE) technique during the same procedure. The concept of providing direct jejunal feedings while allowing for upper gastrointestinal bowel rest to promote the healing of the minimally invasive endoscopic operation is novel. Thus, our case is unique and exemplifies the utility of mini-

mally invasive endoscopic endoluminal surgery.

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Key words: Over-the-scope-clip; Bear claw; Fistula; Endoscopic closure; Gastrocolic fistula; Over the scope clip; Clip

Core tip: Herein we present the endoscopic closure of a gastro-colic fistula in a severely malnourished patient with complex post-surgical upper Gastrointestinal anatomy using the over-the-scope-clip (OTSC-system). The OTSC-system is an endoscopic clipping device made of Nitinol, which allows for treatment of peptic ulcer bleeding and the closure of perforations, anastomotic leaks and fistulas. In addition, we show the usefulness of placing a direct jejunostomy using the double balloon enteroscopy technique during the same procedure.

Mönkemüller K, Peter S, Alkurdi B, Ramesh J, Popa D, Wilcox CM. Endoscopic closure of a gastrocolic fistula using the over-the-scope-clip-system. *World J Gastrointest Endosc* 2013; 5(8): 402-406 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i8/402.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i8.402>

INTRODUCTION

The major endoscopic devices utilized to provide hemostasis and to close mucosal or luminal gastrointestinal (GI) defects are hemoclips and loops^[1-3]. However, hemoclips may not allow for closure of large defects and they do not exert enough tensile force to keep fibrotic defects larger than 5 mm approximated^[3]. In addition, partial and full-thickness defects resulting from perforations, fistulas and leaks may have irregular, thick and friable edges limiting the deployment of hemoclips and/or loops^[4]. Recently, a new endoscopic closure device called

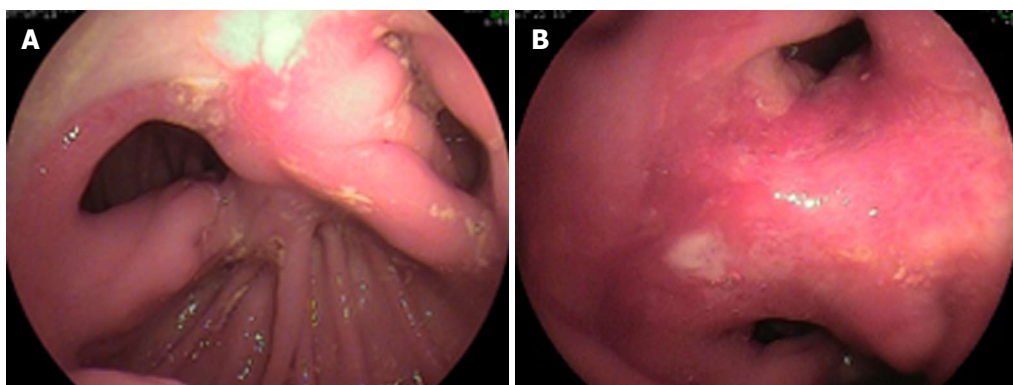


Figure 1 Billroth II anatomy. A clean-based ulcer is present at the anastomosis (A), the lumen to both the afferent and efferent limbs is patent (A); the gastrocolic fistula opening was located at the upper end of the anastomosis (B).

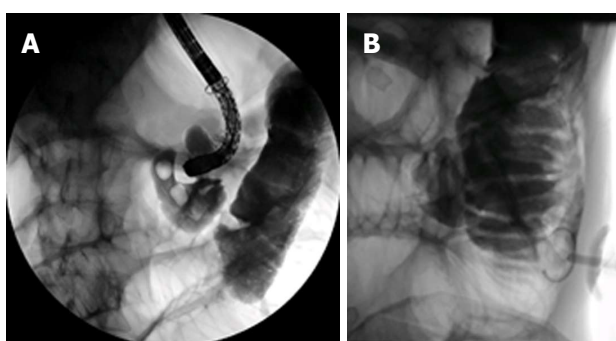


Figure 2 Insertion of the scope through this orifice lead to the colon (A), after placing the jejunostomy, water soluble contrast was injected confirming its perfect intra-jejunal position (B).

the over-the-scope-clip (OTSC)-system (Ovesco Endoscopy, Tübingen, Germany) or “bear claw” became available^[5,6]. The OTSC-system is an endoscopic clipping device made of Nitinol, which allows for treatment of peptic ulcer bleeding and the closure of perforations, anastomotic leaks and fistulas^[7-9]. The majority of information on the OTSC device stems from animal studies but data on the usefulness of the OTSC device in humans is increasingly recognized^[7-12]. The aim of this case report is to describe the effective endoscopic closure of a large gastrocolic fistula in an extremely malnourished patient with complex post-surgical upper GI anatomy.

CASE REPORT

A 47-year-old man with history of chronic pancreatitis, alcoholism and Billroth II gastrojejunostomy for perforated peptic ulcer presented with chronic diarrhea and severe weight loss of 32-kg over a 1 year-period. The diarrhea was watery and occurred up to 12 times per day, being worse after eating. His physical examination was remarkable for cachexia, his weight was 40 kg, his height was 170 cm (body mass index = 12.8). The laboratory data were remarkable for hypoalbuminemia (1.8 g/dL) and decreased hemoglobin (11 g/dL). An esophagogastroduodenoscopy (EGD) showed a clean based ulcer-

ration at the anastomosis and patent lumen to both the afferent and efferent limbs (Figure 1A). At the upper part of the anastomosis there was an additional orifice, which represented the fistula (Figure 1B). Insertion of the scope through this orifice lead to the colon. The patient was placed on bowel rest, NPO, total parenteral nutrition. Due to the patient's poor medical status no surgical intervention could be attempted to close the defect. The patient underwent a full GI evaluation (panendoscopy) to exclude a malignancy or inflammatory bowel diseases leading to fistula formation. An upper GI series using barium clearly demonstrated a communication between the stomach and the colon. A colonoscopy revealed a normal colon mucosa, but no clear fistula opening could be detected. Repeat EGD disclosed the three openings at the gastrojejunal (Billroth II) anastomosis. Both the afferent and efferent limbs were patent and had normal mucosa. The gastrocolic fistula measured about 10-12 mm in diameter (Figure 1B). The EGD was exchanged for a double balloon enteroscope. The overtube was positioned inside the stomach and the enteroscope was advanced through the fistula into the colon (Figure 2). Both the rectum and the cecum were reached. After re-examining the colon and ruling out malignancy and inflammation, the scope was brought back to the gastrojejunal anastomosis and both limbs were investigated using the double-balloon enteroscopy technique. The small bowel mucosa was normal, without evidence of obstruction, fistulization or inflammation. A direct percutaneous enteroscopic feeding jejunostomy was then placed using the double-balloon enteroscopy (DBE)-technique^[13]. Multiple biopsies of the gastrocolic fistula were negative for malignancy. Serum gastrin level was also within reference range.

Closure of the gastrocolic fistula

Before closing the fistula the entrance into the orifice was marked with India ink (SPOT INK, ultrasound Endoscopy, United States) (Figure 3). This intervention was performed in order to mark the area of interest, as the fistulous tract was somewhat friable and the occurrence of edema and oozing could potentially obscure visualization of the area once the OTSC-system was loaded on the tip of the endoscope. The gastrojejunostomy with the

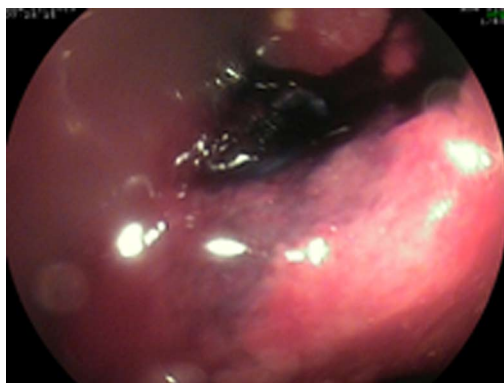


Figure 3 Before closing the fistula the entrance into the orifice was marked with India ink.

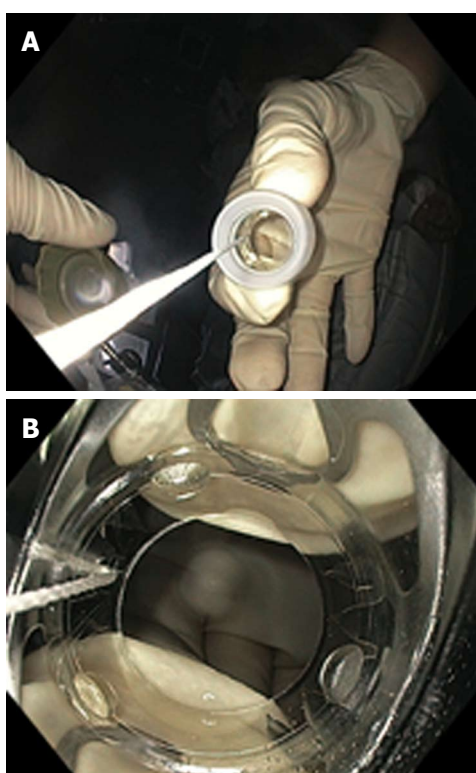


Figure 4 The over-the-scope-clip-system come loaded onto a transparent cap which is attached to the tip of the scope.

presence of two small bowel limbs made the endoscopic operation more challenging, as there is a previous report of complete small bowel obstruction resulting from the misapplication of this closure device^[10]. The atraumatic 11 mm diameter OTSC-system (“bear claw”) was applied (Figure 4). The OTSC cap was approximated into the fistula and suctioned was applied (Figure 5). To achieve definite closure, the edges of the fistula were approximated with a twin grasper (OTSC Twin Grasper; Ovesco Endoscopy AG, Tubingen, Germany) (Figure 5). In addition, an ongoing effort was made to aspirate (*i.e.*, “suck”) tissue into the distal transparent cap. Once enough tissue was trapped, the OTSC was released (Figures 6 and 7).

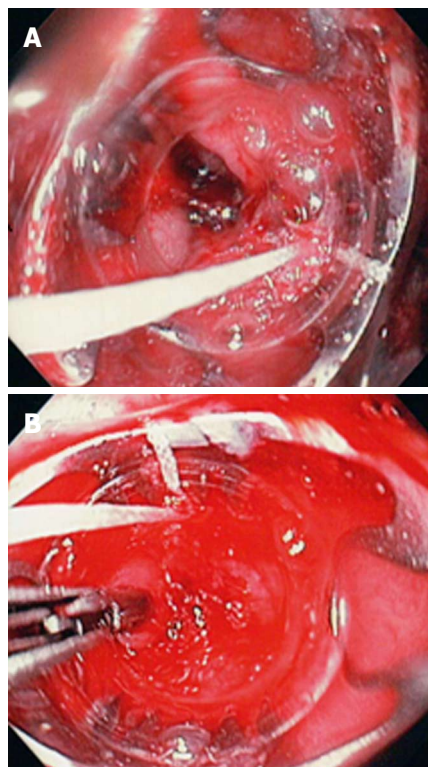


Figure 5 The over-the-scope-clip-system was approximated to the fistula (A) and the proximal edge of the fistula was pulled inside the transparent cap of the over-the-scope-clip-system using the Twin Grasper (B).

The patient was continued on high dose proton pump inhibitors (esomeprazole 40 mg *po* bid), kept NPO and 24 h later the feedings were started through the DPEJ. On the third post-operative day an upper GI study using barium was performed, documenting complete closure of the gastrocolic fistula (Figure 8). Closure was also confirmed by performing an EGD with direct visual inspection and Indigo carmine dye instillation during a simultaneously performed colonoscopy. No dye escaped into the colon from the stomach during the procedure. On day four after endoscopic closure the patient was started on a liquid diet, which was then slowly advanced to soft. Due to his poor nutritional status it was elected to keep the jejunostomy tube feedings until he has regained more weight and his condition has markedly improved. The patient was discharged home in stable condition 7 d after initial presentation and remains well one month after the procedure.

DISCUSSION

To the best of our knowledge this is the first case of successful endoscopic closure of a gastrocolic fistula in a patient with complex post-surgical upper GI anatomy. The additional challenge in this patient was his poor clinical status and hence inability to benefit from a surgical intervention. The case stands out for several reasons. First we show that this tissue-suturing device is also useful to accomplish endoscopic closure of a complex

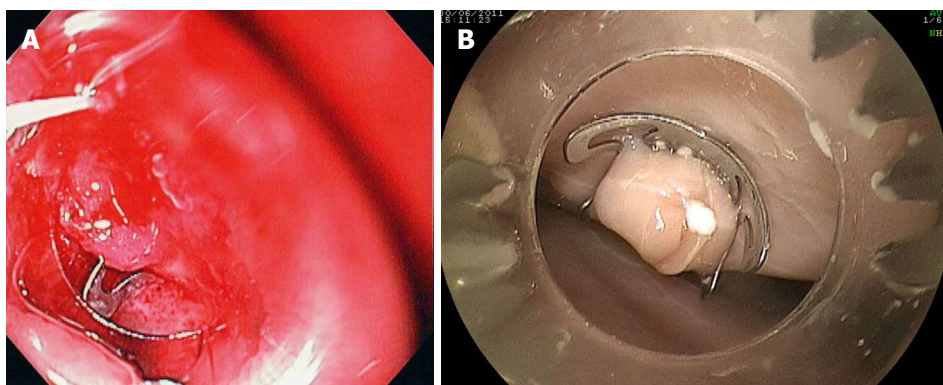


Figure 6 Once enough tissue was present inside the cap the over-the-scope-clip device was released. (A) Example of deployed over-the-scope-clip -system in experimental perforation in an *ex-vivo* pig stomach (B).



Figure 7 Radiologic view of the over-the-scope-clip -system ("bear trap").

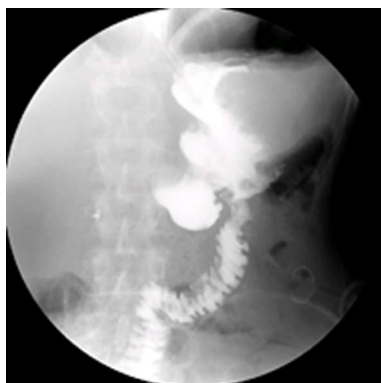


Figure 8 Barium study documents complete closure of the fistula. The contrast flows into the jejunal limbs.

fistula, located in an awkward anatomic position. We also provide useful tips and information on the utilization of this device, which is becoming more widely available. The OTSC-system is a quite innovative endoscopic suturing device made of superelastic biocompatible Nitinol, which allows for the entrapment of larger amount of tissue, allowing closure of fistula holes, and, as shown in these cases, hemostasis^[7-12]. The ability to grasp and pull and/or "suck" a relative large volume of tissue into the distal transparent cap allows for potential closure

of defects ranging from 10 to 20 mm in size, a situation which is usually not possible using traditional clipping devices^[7-12]. Second, we also demonstrate how panendoscopic evaluation using EGD, colonoscopy and DBE was fundamental to thoroughly examine the GI tract for malignancy and inflammatory conditions. Whereas a capsule endoscopy may have also been helpful to evaluate the small bowel, its utility in patients with deranged upper GI anatomy is questionable as there is no guarantee that both limbs are examined. In addition, DBE allowed us to inspect the colon through the fistula located in the transverse colon and perform a right and left colon inspection, including the ileocecal valve. Furthermore, DBE permitted for a direct placement of a jejunal feeding tube, which was essential to aid in the enteral feeding of this severely malnourished patient. Third, this case adds to the growing evidence that the OTSC-system is a useful device to treat clinically significant endoluminal GI defects. These GI scenarios include leaks, GI bleeding, stent anchoring, fistula closure and resection of submucosal lesions^[7-12].

The potential imitations of the OTSC-system should be acknowledged. Its application in tubular or torqued parts of the luminal GI tract may be difficult or impossible. In areas of curves or partially closed lumen, adequate apposition of the OTSC system against the defect may be impossible. If the defect is located in a tubular structure such as the esophagus adequate apposition of the device in a tangential manner to the defect may be more difficult. Thus, the closing forces of the OTSC-system may grasp and engulf the wrong part of the defect or normal tissue, as the vectorial forces are deranged due to the angulated position of the device against the defect. Indeed, a crucial element to technical success of OTSC system placement is to accurately position the lesion within the transparent OTSC cap^[10]. The misapplication of a clip to one side of such a lesion may interfere with the successful deployment of a second clip over the defect. Nonetheless, multiple OTSC applications in a single session may still be useful and allow approximation of tissue to facilitate subsequent closure^[10]. Nevertheless, and as shown in our case and experience, if the defect is visible and reachable a successful application can always

be successfully accomplished^[11,12]. Using marking with chromoendoscopy may improve visualization and recognition of the defect while the OTSC-system is being applied. Because the device is new it is not known how long it remains attached after deployment. A potential complication of the OTSC system is that once it is deployed it cannot be removed. We have recently demonstrated two techniques to remove the “bear claw” using the wire technique^[14] or resecting the OTSC system using endoscopic mucosal resection techniques^[15]. In addition, the OTSC system can be removed using Nd-YAG Laser or argon plasma coagulation^[10,16].

In summary, we have presented a case of successful endoscopic closure of a gastrocolic fistula in a severely malnourished patient with complex post-surgical upper GI anatomy. Panendoscopy using EGD, colonoscopy and DBE allowed for detailed examination of the GI tract and direct DPEJ placement before endoscopic closure with the OTSC. We strongly believe that this device is a major breakthrough for the management of various types of discontinuity defects or fistulas of the GI tract. Thus, the OTSC system should be incorporated into the therapeutic armamentarium of the advanced endoscopist. In addition, we show the usefulness of placing a direct jejunostomy using the DBE technique during the same procedure. The concept of providing direct jejunal feedings while allowing for upper gastrointestinal bowel rest to promote the healing of the minimally invasive endoscopic operation is novel. Thus, our case is unique and exemplifies the utility of minimally invasive endoscopic endoluminal surgery.

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Malignant peritoneal mesothelioma presenting umbilical hernia and Sister Mary Joseph's nodule

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Core tip: Malignant peritoneal mesothelioma is a rare aggressive tumor of the peritoneum. We performed laparoscopy which showed specific laparoscopic findings, and the pathological findings of the biopsy specimen led to the diagnosis. This case was associated with umbilical hernia and umbilical metastasis, which is also called as Sister Mary Joseph's nodule.

Tsuruya K, Matsushima M, Nakajima T, Fujisawa M, Shirakura K, Igarashi M, Koike J, Suzuki T, Mine T. Malignant peritoneal mesothelioma presenting umbilical hernia and Sister Mary Joseph's nodule. *World J Gastrointest Endosc* 2013; 5(8): 407-411 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i8/407.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i8.407>

Abstract

Malignant peritoneal mesothelioma is a rare aggressive tumor of the peritoneum. An increasing number of malignant mesothelioma cases have been reported in recent years. We report here a very rare case of malignant peritoneal mesothelioma with both umbilical hernia and umbilical metastasis which is also called Sister Mary Joseph's nodule. We performed laparoscopy which showed specific laparoscopic findings, and the pathological findings of the biopsy specimen led to the diagnosis. This case was associated with umbilical hernia which could be induced by massive ascites. A newly developed abdominal hernia should be noted as a primary symptom of malignant peritoneal mesothelioma, as shown in the present case.

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Key words: Malignant peritoneal mesothelioma; Umbilical hernia; Sister Mary Joseph's nodule; Umbilical metastasis; Laparoscopy

INTRODUCTION

Malignant mesothelioma is arising from the mesothelium lining of a body cavity and is associated with asbestos exposure. An increasing number of malignant mesothelioma cases have been reported in recent years. In malignant peritoneal mesothelioma, abdominal hernias are a common complication, probably due to massive ascites accompanying the disease. Most are inguinal hernias but the development of an umbilical hernia is very rare. Umbilical metastasis, which is also called Sister Mary Joseph's nodule, is a rare complication of malignant peritoneal mesothelioma. We are reporting a very rare case of malignant peritoneal mesothelioma with both umbilical hernia and umbilical metastasis.

CASE REPORT

A 64-year-old man visited our hospital for further examination of a moderate amount of ascites and multiple peritoneal masses observed during an annual health

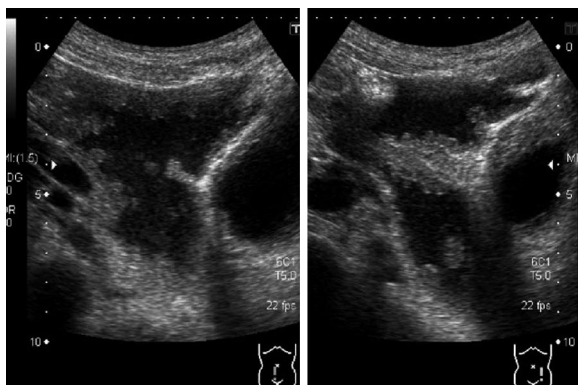


Figure 1 Abdominal ultrasonography. Moderate amount of ascites, irregular thickening of the mesentery and peritoneum, and multiple nodules were observed.

check. There was nothing noteworthy in his medical history and family history. He had no clear history of asbestos exposure. Physical examination demonstrated moderate abdominal distension with fluctuation and umbilical hernia. Bowel sounds were reduced and there was no abdominal pain or tenderness. Laboratory investigations revealed hypoalbuminemia (35 mg/L), a high level of C-reactive protein (3.5 mg/L), and levels of CEA and CA19-9 were within the normal range. No neoplastic lesions were observed by upper and lower gastrointestinal endoscopy. Abdominal ultrasound showed moderate ascites, irregular thickening of the mesentery and the peritoneum, and numerous nodules present (Figure 1). Contrast enhanced computed tomography showed a moderate amount of ascites and enhanced multiple nodules on the thickened peritoneum and mesenterium (Figure 2). By ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET), mild accumulation of FDG was observed over the entire abdominal region, but no localized strong accumulation suggesting this was the primary lesion (Figure 2C). Aspirated ascites was cloudy and a muddy yellow color with increased cell populations present (7660/ μL), most of which were histiocytes (93%) with some mesothelial cells (6%). Protein concentration of the ascites reached levels as high as 41 mg/L, indicating that the ascites was exudative. The hyaluronic acid concentration of the ascites was very high (436000 ng/L). Cytology indicated atypical mesothelial cells. These data strongly suggested malignant peritoneal mesothelioma and therefore, laparoscopy was performed. Laparoscopic observation showed multiple whitish nodules on the peritoneum and the mesenterium including falciform ligament of the liver with a slightly cloudy yellow ascites (Figure 3). Biopsy of the nodular lesions was performed. Additionally, Umbilical hernioplasty was performed owing to avoidance of the risk for incarceration and the pathological assessment of the umbilical region was also done. According to the histopathological findings of the nodular lesion, hematoxylin and eosin (HE) staining showed the infiltration of many tumor cells having acidophilic cytoplasm with large nuclei (Figure 4A). A mucus-like substance in the tumor background was positive by alcian blue staining, and was

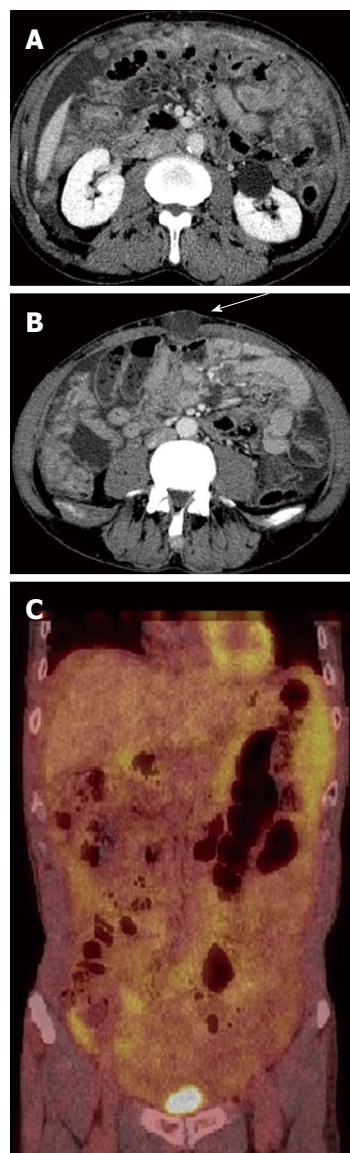


Figure 2 Contrast enhanced computed tomography and ^{18}F -fluorodeoxyglucose-positron emission tomography. A: Thickened peritoneum and mesentery with multiple nodules were positively enhanced by the contrast material; B: An umbilical hernia is also evident (arrow); C: A coronal image of ^{18}F -fluorodeoxyglucose-positron emission tomography (FDG-PET) showed no localized areas of high accumulation of FDG, but mild accumulation of FDG was observed over the entire abdominal region.

negative after hyaluronidase treatment, which suggested the presence of accumulated hyaluronic acid. Immunohistochemical stainings of calretinin, D2-40, and CK5/6, which are markers for mesothelial cells, were all positive, while Ber-EP4 and MOC31, which are markers for adenocarcinomas, were negative (Figure 5). Therefore, the final diagnosis was epithelioid type of malignant peritoneal mesothelioma. Umbilical hernia was repaired by surgery and the infiltration of tumor cells into the dermis was observed in the resected specimen of the umbilical region (Figure 4B).

The patient transferred to another hospital of his own will. According to the response mail from the hospital, he received a radical operation in which the peritoneal

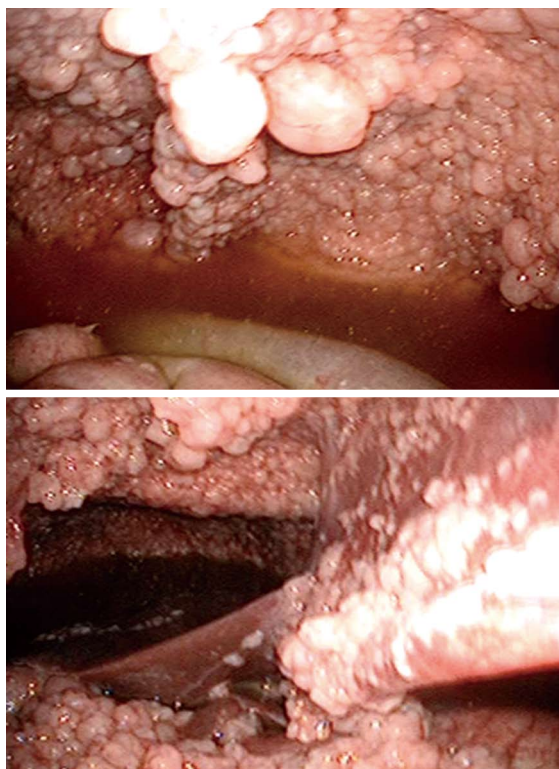


Figure 3 Laparoscopy. Multiple whitish nodules were observed on the peritoneum and the mesentery including falciform ligament of the liver with slightly muddy yellow ascites.

nodules were removed as much as possible, however, he got debilitated after the surgery which did not permit further chemotherapy. He died 6 mo after the diagnosis due to the progression of the malignancy.

DISCUSSION

Malignant mesothelioma originates in the pleura, peritoneum, pericardium and tunica vaginalis^[1], where a lining of mesothelial cells is present. The main causes of mesothelioma are known to include exposure to asbestos^[2] and erionite (natural mineral fiber). In Japan, a large amount of asbestos was used for buildings during the high-growth period (1950-1990). It is believed that the incubation period is approximately 30-40 years and it is estimated that the number of mesothelioma cases will therefore reach a peak between 2020-2030.

It has been reported that 85.5% malignant mesothelioma occurs in the pleura, 13.2% in the peritoneum, 0.8% in the pericardium, and 0.5% in the testicular tunica vaginalis^[3]. According to the histological classification, malignant mesothelioma can be classified as 3 types: epithelioid type, sarcomatoid type, and biphasic type. The frequencies of the 3 types of pleural mesothelioma, epithelioid, sarcomatoid, biphasic type, and unknown classification were reported to be 53.6%, 23.3%, 18.3%, and 4.8%, respectively^[3]. In Japan, the frequencies of peritoneal mesothelioma including epithelioid, sarcomatoid, biphasic type, and unknown classification were reported to

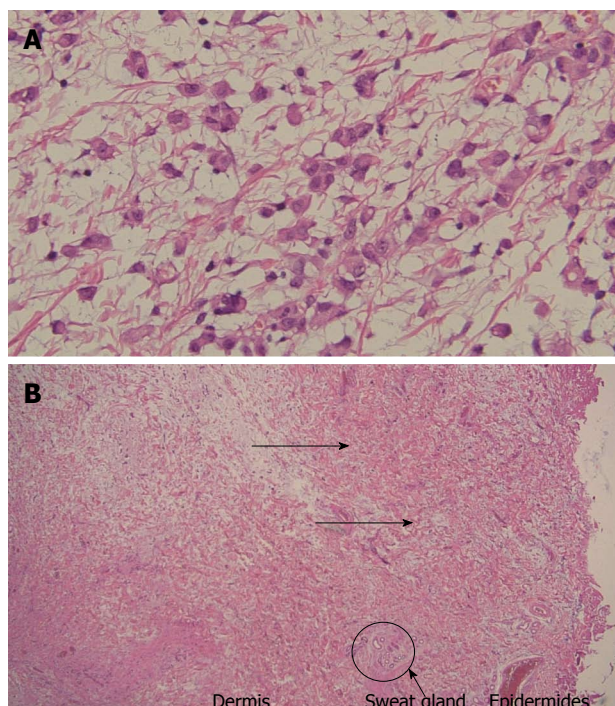


Figure 4 Pathological findings of the nodular lesion and the umbilical region. A: Diffuse infiltration of oval or polygon cells with acidophilic cytoplasm was observed [hematoxylin and eosin (HE), × 200]; B: Histopathology of the umbilical region showed the invasion of tumor cells into the dermis (arrows) (HE, × 40).

be 71.6%, 11.6%, 12.6%, and 4.2%, respectively^[3]. In the United States, Yan *et al*^[4] reported that there were no sarcomatoid type cases, and that the incidence of epithelioid and biphasic type were 92% and 8%, respectively. In both reports, fewer sarcomatoid type and increased epithelioid type cases were observed in malignant peritoneal mesothelioma, compared with pleural mesothelioma.

The clinical symptoms associated with malignant peritoneal mesothelioma include abdominal distention, abdominal pain, abdominal mass, a loss of appetite, weight loss, fever and diarrhea, but there are no disease specific symptoms^[5]. Abdominal hernia was reported to occur in 6%-12% of patients with malignant peritoneal mesothelioma^[6,7], but the majority of these were in the inguinal region. According to a report by Acherman *et al*^[6], the primary symptoms in 51 cases of malignant peritoneal mesothelioma included 17 cases (33%) of abdominal pain, 5 cases (10%) of abdominal pain and distention, 16 cases (31%) of abdominal swelling, and 6 cases (12%) with the new onset of hernias. Among these, 5 of the hernias occurred in the inguinal region while one occurred in the umbilical region. Thus, although umbilical hernia is rare, a newly developed abdominal hernia should be noted as a primary symptom of malignant peritoneal mesothelioma.

Moreover, the present case was associated with umbilical invasion of the tumor. Metastasis of malignant tumors to the umbilicus is also known as Sister Mary Joseph's nodule^[8]. The vascular system around the um-

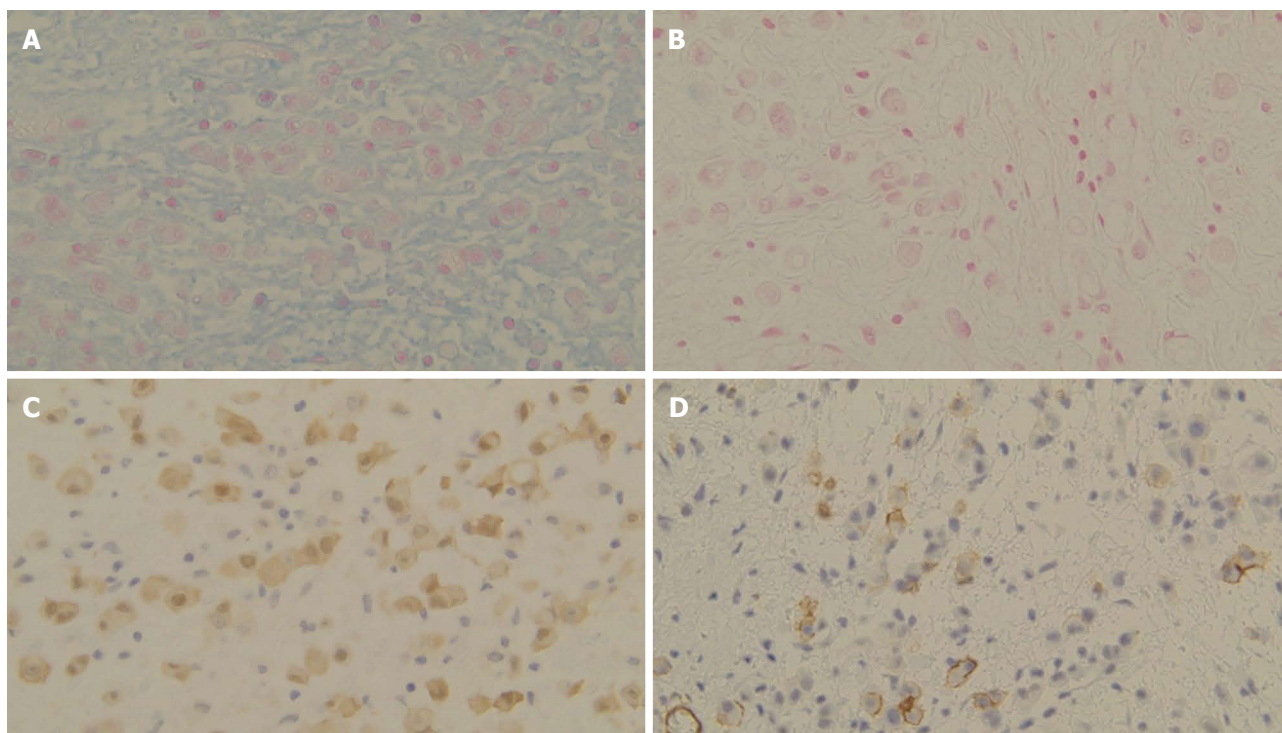


Figure 5 Immunohistochemical staining results. A mucus-like substance was stained positive by alcian blue staining, and was negative after hyaluronidase treatment. Staining of calretinin and CD146 (MCAM) were positive. A: Alcian blue; B: Alcian blue (after hyaluronidase treatment); C: Calretinin; D: CD146 (MCAM).

bilicus forms an arteriovenous loop and lymphoid vessel network, which continues to the round ligament of the liver. Regarding the metastasis pathway to the umbilicus, lymphogenous and hematogenous metastasis, and direct invasion from the surrounding tumor or along the round ligament of the liver have been reported^[9-11]. In the present case, laparoscopy revealed numerous thick nodules growing on both the parietal peritoneum and the round ligament of the liver next to the umbilical region. Thus, direct invasion by either or both of the above pathways was most likely. Boyde *et al.*^[12] reported 4 cases (3.4%) of umbilical metastasis in 89 cases of malignant peritoneal mesothelioma. In all 4 cases, the histological types were epithelioid type and the present case was similar. The umbilicus is one of the weakest regions in the abdominal wall, where the umbilical cord was previously penetrated and aponeurosis and subcutaneous fat are lacking. It is thought that umbilical hernia occurs in adults when the abdominal pressure increases due to pregnancy, obesity, large abdominal tumor, ascites, or peritoneal dialysis^[13,14]. In the present case, we observed umbilical metastasis, which might have weakened the surrounding connective tissue, and caused high intraabdominal pressure due to massive ascites. Both factors might contribute to the development of the umbilical hernia.

In summary, we experienced an extremely rare case of malignant peritoneal mesothelioma associated with umbilical metastasis and umbilical hernia. The incidence of malignant peritoneal mesothelioma is expected to increase in the near future. Although it is rare, a newly developed abdominal hernia should be noted as a pri-

mary symptom of malignant peritoneal mesothelioma, as shown in the present case.

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Dilation of a severe bilioenteric or pancreatoenteric anastomotic stricture using a Soehendra Stent Retriever

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Key words: Bilioenteric anastomotic stricture; Soehendra Stent Retriever; Dilation; Pancreatoenteric anastomotic stricture; Double-balloon enteroscopy

Core tip: The Soehendra Stent Retriever can be useful for the dilation of severe, tight bilioenteric or pancreatoenteric anastomotic strictures over a guidewire, and it is available for endoscopic dilation even under short double-balloon enteroscopy for patients with surgically altered anatomies.

Tsutsumi K, Kato H, Sakakihara I, Yamamoto N, Noma Y, Horiguchi S, Harada R, Okada H, Yamamoto K. Dilation of a severe bilioenteric or pancreatoenteric anastomotic stricture using a Soehendra Stent Retriever. *World J Gastrointest Endosc* 2013; 5(8): 412-416 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i8/412.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i8.412>

Abstract

Bilioenteric or pancreatoenteric anastomotic strictures often occur after surgery for a pancreaticobiliary disorder. Therapeutic endoscopic retrograde cholangiopancreatography using balloon enteroscopy has been shown to be feasible and effective in patients with such strictures. However, when a benign anastomotic stricture is severe, a dilation catheter cannot pass through the stricture despite successful insertion of the guidewire. We report on the usefulness of the Soehendra Stent Retriever over a guidewire for dilating a severe bilioenteric or pancreatoenteric anastomotic stricture under short double-balloon enteroscopy, in two patients with surgically altered anatomies.

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INTRODUCTION

Bilioenteric or pancreatoenteric anastomotic strictures often occur after surgery for a pancreaticobiliary disorder. For the management of these benign strictures in patients with surgically altered anatomies, push enteroscopes and pediatric colonoscopes have been used, but their failure rates have been high. Due to advances in endoscopy, therapeutic endoscopic retrograde cholangiopancreatography (ERCP) including the dilation of a bilioenteric or pancreatoenteric anastomotic stricture by balloon enteroscopy has been shown to be feasible and safe for these patients^[1], and has been commonly performed as the initial attempt to manage various postoperative disorder.

However, when a benign anastomotic stricture is severe, a dilation catheter cannot pass through the stricture, and it may not be possible to accomplish dila-

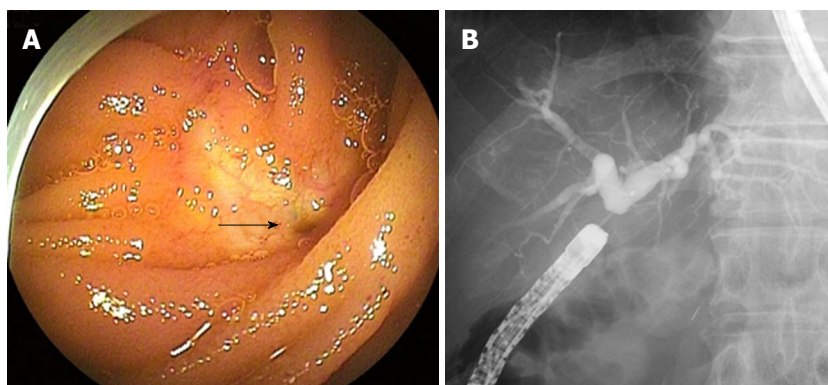


Figure 1 Endoscopic view and cholangiography by short double-balloon enteroscopy in a 66-year-old male. A: Bilioenteric anastomotic stricture looking like a pinhole (arrow); B: Dilated bilateral intrahepatic bile ducts were revealed.

tion despite successful insertion of the guidewire. Here we provide two case reports that involved the use of the Soehendra Stent Retriever (Cook Medical Inc., Winston-Salem, NC, United States), which was designed to facilitate the removal of a biliary or pancreatic plastic stent^[2]. We found that this stent retriever was useful for dilating procedures in such difficult situations, in two patients treated with short double-balloon enteroscopy (DBE).

CASE REPORT

Case 1

A 66-year-old male had undergone pylorus-preserving pancreatoduodenectomy (PPPD) by modified Child method due to an ampulla of Vater adenoma. Three years later, fever and elevated serum transaminase occurred. Regarding the cause of the cholangitis, we suspected a bilioenteric anastomotic stricture because magnetic resonance cholangiopancreatography (MRCP) imaging revealed dilation of the intrahepatic bile ducts.

For the resolution of the cholangitis, we performed endoscopic retrograde cholangiography with short DBE (EC-450BI5; Fujifilm, Tokyo, Japan). When the DBE reached the bilioenteric anastomosis, the benign severe anastomotic stricture, which looked like a pinhole, was revealed (Figure 1A). The cholangiography showed dilated bilateral intrahepatic bile ducts due to the stricture (Figure 1B). For the endoscopic dilation of this stricture, a 0.035-inch angled guidewire was advanced across the stricture, but a tapered 5.5-Fr catheter would not pass the tight stricture. Thus, the catheter was removed, and the guidewire was left in place. A 7-Fr Soehendra Stent Retriever (SSR) was introduced to the anastomosis over the guidewire and turned clockwise carefully with pressure to advance through the stricture into the bile duct (Figure 2A and B). Following this procedure and the removal of the SSR by counter-clockwise rotation, a 5.5-Fr catheter was allowed to pass the stricture (Figure 2C). In addition, an 8-mm dilation balloon catheter passed easily through the stricture, and consequently further dilation was achieved (Figure 2D and E).

In this case, direct cholangioscopy with an ultraslim

enteroscope (EG-530NW; Fujifilm) using overtube guidance was subsequently performed to ascertain whether any hepaticolithiasis existed; none was seen. No relevant complications, such as hemorrhage and perforation, were encountered. No recurrent cholangitis occurred within the 10-month period after the dilation.

Case 2

A 78-year-old female had undergone PPPD with Roux-en Y reconstruction by modified Child method due to an ampulla of Vater adenocarcinoma. One year after the PPPD, she reported abdominal pain and her serum pancreatic enzymes were elevated. Computed tomography imaging showed pancreatitis and marked diffuse dilation of pancreatic duct. Regarding the cause of the pancreatitis, MRCP imaging suggested a pancreatoenteric anastomotic stricture with pancreatic stone.

For resolution of the pancreatitis, endoscopic retrograde pancreatography (ERP) with a short DBE (EC-450BI5) was attempted. Although the anastomosis was cicatricial and obscure, pancreatic juice flowing out slightly from the pinhole-like anastomosis was identified (Figure 3A), and cannulation to the pancreatic duct by a tapered 5.5-Fr catheter was barely achieved with preceding 0.018-inch angled guidewire insertion. The ERP showed a dilated pancreatic duct due to the stricture and pancreatic stone (Figure 3B). For the dilation of this stricture, a 0.035-inch angled guidewire was advanced across the stricture into the pancreatic duct, but a 7-Fr Soehendra Biliary Dilation Catheter (SBDC) and a balloon dilation catheter whose top was non-tapered could not pass the tight stricture despite several attempts. Therefore, the catheter was removed and the guidewire was left in place. Here the 7-Fr SSR was used in the same manner as that described above for Case 1 (Figure 4A and B). Following this procedure and removal of the SSR, a 7-Fr SBDC and balloon dilation catheter easily passed through the stricture and dilation to 6-mm diameter was obtained (Figure 4C-E).

Lastly, 7-Fr × 7-cm Geenen pancreatic stent (Cook Medical) was inserted into the pancreatic duct proximal to the stricture to prevent pancreatic stone impaction.

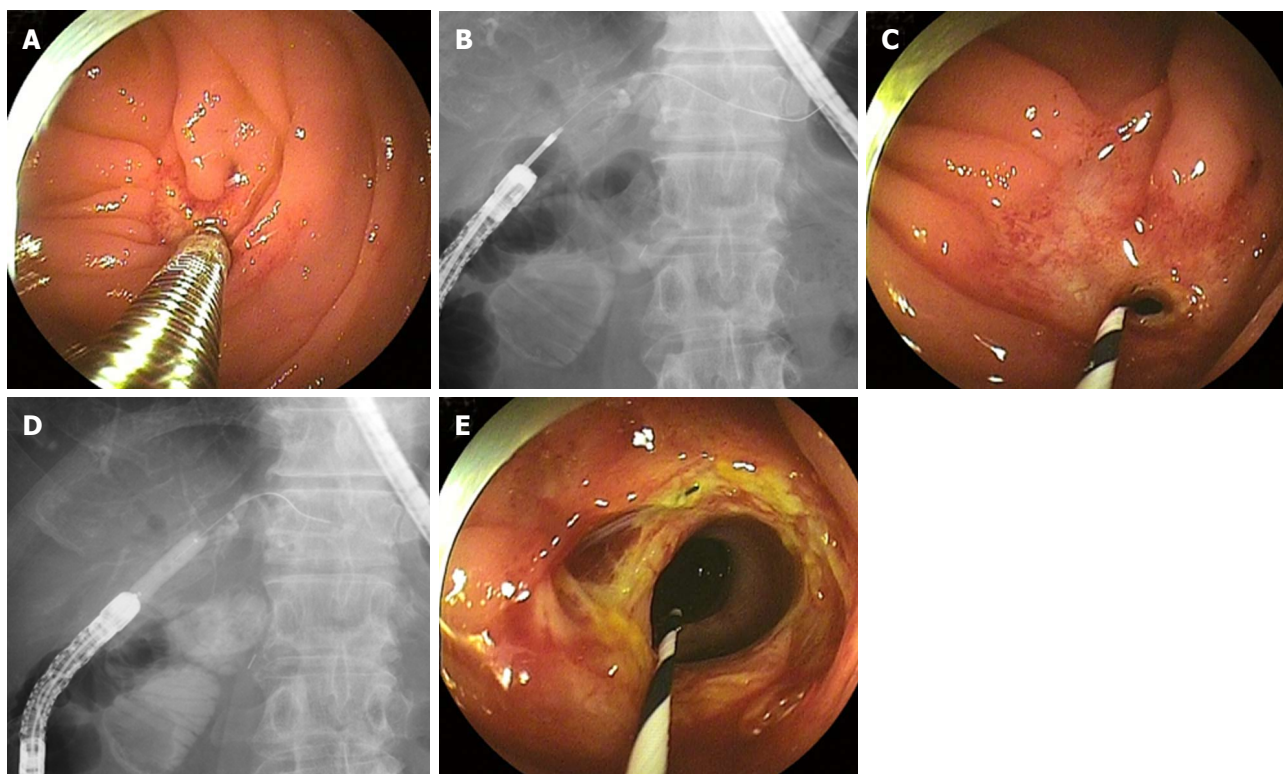


Figure 2 Dilation of the severe bilioenteric anastomotic stricture using a 7-Fr Soehendra Stent Retriever. A: The Soehendra Stent Retriever (SSR) was introduced to the anastomosis over the guidewire, and turned clockwise carefully with pressure to advance through the stricture into the bile duct; B: Fluoroscopic view showing dilation for the stricture by the SSR; C: Endoscopic view showing the dilated anastomosis by the SSR; D: Fluoroscopic view showing subsequent balloon dilation to 8-mm dia; E: Conclusive endoscopic view after balloon dilation for this severe bilioenteric anastomotic stricture.

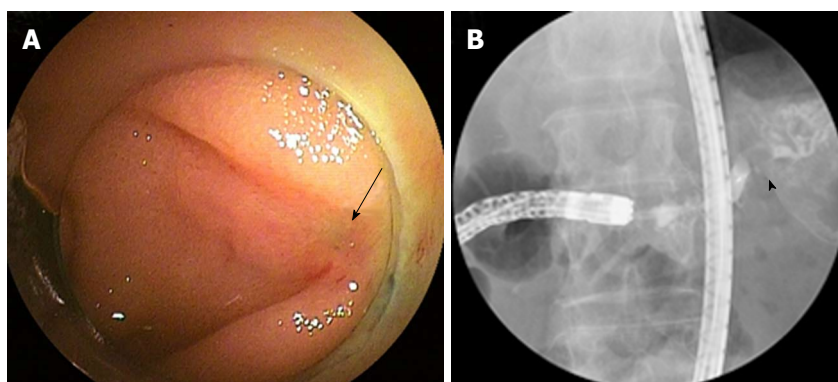


Figure 3 Endoscopic view and pancreatography by short double-balloon enteroscopy in a 78-year-old female. A: Pancreatoenteric anastomotic stricture looking like a pinhole with pancreatic juice flowing out slightly (arrow); B: Dilated pancreatic duct and pancreatic stone (arrowhead) were revealed.

No relevant complications occurred. A follow-up ERP 3 mo later showed improvement in the stricture, and the stone was removed after additional dilation.

DISCUSSION

In recent years, balloon enteroscopy has enabled endoscopists to access bilioenteric and pancreatoenteric anastomoses in patients with surgically altered anatomies, more definitively and safely^[1]. Thus, therapeutic ERCP including endoscopic dilation for these anastomotic strictures using balloon enteroscopy (particularly a short

DBE which makes almost all conventional accessories) has been commonly performed in initial attempts to manage various postoperative disorder.

As a matter of course, the successful endoscopic management of bilioenteric or pancreatoenteric anastomotic strictures requires the identification of the choledochojejunostomy or pancreaticojejunostomy, the insertion of a guidewire through the narrowed region, and the passage of a dilation catheter through it, followed by balloon dilation. However, anastomoses and the degree of stricture vary. Practically, the anastomosis is sometimes nowhere to be found because of marked stricture, localization at an ob-

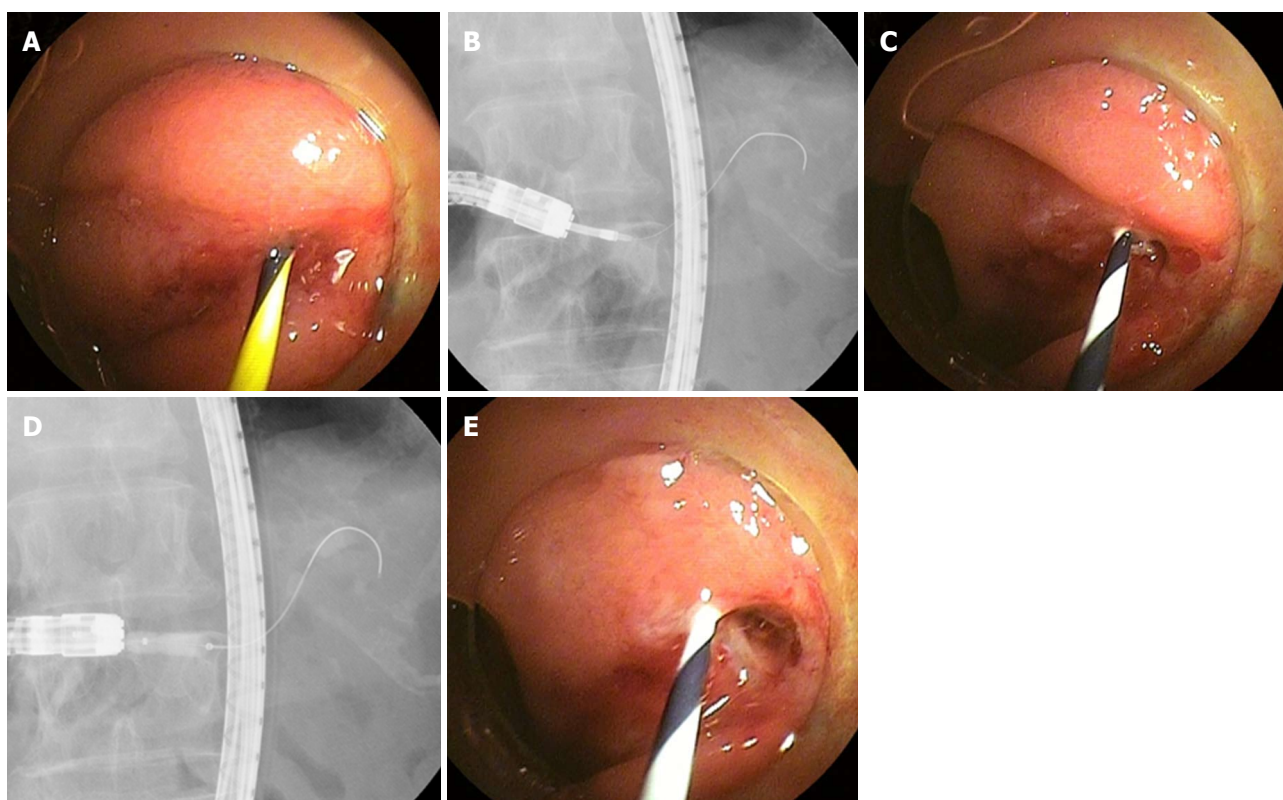


Figure 4 Dilation of the severe pancreatoenteric anastomotic stricture using a 7-Fr Soehendra Stent Retriever. A: The Soehendra Stent Retriever (SSR) was introduced to the anastomosis over the guidewire, and turned clockwise carefully with pressure to advance through the stricture into the pancreatic duct; B: Fluoroscopic view showing dilation for the stricture by the SSR; C: Endoscopic view showing the dilated anastomosis by the SSR; D: Fluoroscopic view showing subsequent balloon dilation to 6-mm dia; E: Conclusive endoscopic view after balloon dilation for this severe pancreatoenteric anastomotic stricture.

scure area, or mucosa-to-mucosa anastomosis, especially in pancreaticojejunostomy. Chahal *et al*^[3] reported that the success rate of cannulation and endoscopic therapy was significantly lower for pancreatic indications (3/37, 8%) than biliary indications (37/44, 84%) due to the above reasons. Therefore, if the guidewire insertion is achieved across a severe stricture, a dilation catheter could somehow be introduced to the bile or pancreatic duct through it. Our results indicate that the SSR was useful in dilating these strictures and subsequently allowing a dilation catheter to pass them to achieve sufficient dilation under a short DBE.

The 7-Fr SSR used in the present cases is a metal device comprised of a 180-cm-long, 7-Fr coiled cable with a 4-mm-long threaded tip of 4- to 6-Fr tapered calibers. The use of the SSR with its “self-tapping” screw design has been described for malignant biliary strictures as well as benign biliary and pancreatic duct strictures, and for the treatment of impacted bile duct stones^[4]. In addition, the SSR has been used successfully in many advanced therapeutic applications, including the expansion of mesh holes of metallic stents for bilateral biliary stenting^[5] and the dilation of a transduodenal or transgastric fistula for the endoscopic ultrasonography (EUS)-guided biliary or pancreatic pseudocyst drainage^[6,7]. In all of these studies, no occurrence of complications was reported. The present report is the first about the use

of the SSR for dilating severe bilioenteric or pancreatoenteric anastomotic stricture under a short DBE in two patients with surgically altered anatomies.

In cases in which it is impossible to insert a dilation catheter or guidewire through the stricture using a standard technique (including the use of a variety of tapered catheters and guidewires) due to severe stricture or complete obstruction, there is a report describing a direct incision for a short cicatricial ring at the anastomosis by needle knife^[8], but safety considerations indicate the need for further studies of this method. Accordingly, a percutaneous or EUS-guided approach is considerable as an alternative, excluding surgical approaches^[9-11]. A rendezvous or antegrade technique is also available by using these approaches. However, the EUS-guided procedure needs advanced expertise, and approaches to the pancreatic duct by these alternatives are especially challenging. In addition, these rendezvous techniques are complicated and require very careful maneuvers. Therefore, the SSR with its ability to stretch and lacerate the tissue bluntly seems to be the device of choice in situations in which a dilation catheter will not pass through a severe anastomotic stricture despite the successful insertion of a guidewire.

In conclusion, the SSR can be useful for the dilation of severe, tight bilioenteric or pancreatoenteric anastomotic strictures over a guidewire, and it is available for endoscopic dilation even under short DBE used for pa-

tients with surgically altered anatomies.

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Endoscopic management of Dieulafoy's lesion using Isoamyl-2-cyanoacrylate

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Abstract

Dieulafoy's lesion (DL) is a rare but important cause of obscure gastrointestinal bleeding that may be overlooked during diagnostic endoscopy. Mortality rates are similar to those of other causes for gastrointestinal bleeding. Diagnosis by upper endoscopy is the modality of choice during acute bleeding. In the absence of active bleeding, the lesion resembles a raised nipple or visible vessel. There are no guidelines regarding effective selective therapy for DL, when diagnosed, endoscopist experience is the major determinant of the treatment strategy. Following our strategy, an expert endoscopist with a skilled assistant should have a high rate of successful DL diagnosis when an obscured gastrointestinal lesion is suspected. Cyanoacrylates compounds have been used successfully in management of Gastric varices and DLs. To our knowledge, there have been no previous reports regarding use of isoamyl-2-cyanoacrylate (AMCRYLATE®; Concord Drugs Ltd.,

Hyderabad, India) as an effective therapy for gastric DL without serious complications. In our case study, Isoamyl-2-cyanoacrylate (AMCRYLATE®) was effective and safe for treating DL. Surgical wedge resection of the lesion should be considered as a therapeutic option if endoscopic therapy fails.

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Key words: Dieulafoy's lesion; Isoamyl-2-cyanoacrylate; Gastrointestinal bleeding; Endoscopy; Stomach

Core tip: The etiology of Dieulafoy's lesion (DL) is unknown. The hemorrhage is often torrential and life threatening. Diagnosis by upper endoscopy is the modality of choice during acute bleeding. In the absence of active bleeding, the lesion resembles a raised nipple or visible vessel. There are no guidelines regarding effective selective therapy for DL. When diagnosed, endoscopist experience is the major determinant of the treatment strategy. To our knowledge, there have been no previous reports regarding use of isoamyl-2-cyanoacrylate (AMCRYLATE®; Concord Drugs Ltd., Hyderabad, India) as an effective therapy for gastric DLs without serious complications.

Abd Elrazek AEMA, Yoko N, Hiroki M, Afify M, Asar M, Ismael B, Salah M. Endoscopic management of Dieulafoy's lesion using Isoamyl-2-cyanoacrylate. *World J Gastrointest Endosc* 2013; 5(8): 417-419 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i8/417.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i8.417>

INTRODUCTION

Dieulafoy's lesion (DL) is an important cause of obscure gastrointestinal bleeding that may be overlooked during diagnostic endoscopy or even laparotomy. The hemor-

rhage is often torrential and life threatening. The French pathologist Dieulafoy, who described three cases, discovered the lesion in 1889, although the first case was actually reported by Gallard in 1884. DLs can occur in any part of the gastrointestinal tract with a tendency toward the lower end of the esophagus, cardia, lesser curvature of the stomach, and caecum^[1].

The etiology of DL is unknown. Patients who bleed from DLs are typically males with comorbidities including hypertension, diabetes or alcohol abuse. The use of nonsteroidal anti-inflammatory drugs is also common among patients with bleeding, although many patients have no triggering events. DLs can appear any time between 20 mo and 92 years of age^[2,3].

Diagnosis by upper endoscopy is the modality of choice during acute bleeding. In the absence of active bleeding, the lesion resembles a raised nipple or visible vessel. In massive bleeding, active arterial pumping can be visualized in an area without an associated ulcer or mass lesion, although the aberrant vessel is often not seen. Endoscopic ultrasonography is useful for confirmation of the diagnosis^[4].

There are no guidelines regarding effective selective therapy for DL. When diagnosed, endoscopist experience is the major determinant of the treatment strategy. Many therapeutic approaches exist, including endoscopic hemostasis with a combination of epinephrine followed by bipolar probe coagulation; heater probe thermal coagulation; hemoclip placement; band ligation; argon plasma coagulation; arterial angiographic embolization; endoscopic sclerotherapy using ethanolamine oleate, polidocanol, or *N*-butyl-2-cyanoacrylate; and surgical wedge resection of the lesion, which is now rarely performed due to the availability of more advanced endoscopic technologies and increased operator experience^[5].

In the 1940s, various surgical cyanoacrylate adhesives were developed; these are a series of homologous alkyl-cyanoacrylate compounds. These compounds polymerize on contact with common substances, such as blood and water, at room temperature without requiring a solvent or catalyst. Adhesive glue is particularly useful for day surgeries, *e.g.*, circumcision. Cyanoacrylate is superior to sutures and its clinical use is becoming increasingly common due to its ease of application, decreased scarring, decreased pain, and superior cosmetic results with no discomfort, as can occur due to sutures snagging clothing and/or the dressing^[6-8]. Many authors have reported the disadvantages of *N*-butyl-2-cyanoacrylate as a treatment of choice for DL because of serious complications of extravasation, rebleeding due to massive ulceration, and even gastric perforation^[9]. Radiographically evident Pulmonary Embolism was reported after endoscopic injection sclerotherapy (EIS) for gastric variceal bleeding using *N*-butyl-2-cyanoacrylate^[10].

To our knowledge, there have been no previous reports regarding use of isoamyl-2-cyanoacrylate (AMCRYLATE®; Concord Drugs Ltd., Hyderabad, India) as an effective therapy for gastric DLs without serious complications.

CASE REPORT

A 29-year-old male patient was admitted with hematemesis with no history of the use of nonsteroidal anti-inflammatory drugs, aspirin, paracetamol, caffeine or alcohol abuse. There was no family history of bleeding disorders. The patient denied having taken medications for any illness, and no abnormalities were detected on ultrasound examination. Upper endoscopy revealed no masses, ulcers, varices, or any lesions. Six hours later, the patient developed massive hematemesis following the administration of 500 mL of packed red blood cells. Upper endoscopy was repeated, but no lesion was seen. The patient was administered hemostatic medications. One day after discharge, a massive attack of hematemesis recurred 48 h after the previous attack. The patient was transferred to our clinic, where upper endoscopy was repeated for the third time. A gastric wash was performed and an endoscopy expert was called. Upper endoscopy revealed a nipple-like protrusion on the greater curvature just 5 cm below the cardia. Touching the lesion with the blind, smooth end of a probe led to massive hemorrhage (Figure 1). The gastric wash was repeated with the administration of another 500 mL of packed red blood cells. Endoscopic sclerotherapy was performed using 1 mL of isoamyl-2-cyanoacrylate (AMCRYLATE®) in 1 mL of Lipidol in a 1:1 ratio. The bleeding was stopped (Figures 2 and 3). Post-endoscopic erect abdominal X-ray showed no extravasation. The caliber of the Dieulafoy's arteriole was relatively large; it opened directly into the stomach without branching, making it more than ten times larger than other gastric capillaries (Figure 4). Follow-up 3 mo later showed no complications due to the therapy and no extravasations, ulcerations or any other hemostatic disorders.

DISCUSSION

The use of isoamyl-2-cyanoacrylate (AMCRYLATE®) could be an effective treatment for gastric DLs because the viscosity and adhesive problems that can occur with *N*-butyl-2-cyanoacrylate are significantly reduced by use of isoamyl-2-cyanoacrylate (AMCRYLATE®). We expect fewer complications with almost identical results. Another advantage is that AMCRYLATE® is significantly more cost-effective than *N*-butyl-2-cyanoacrylate, especially when large amounts are required.

According to our experience, it is convenient to use isoamyl-2-cyanoacrylate as effective endoscopic management for gastric varices. The use of isoamyl-2-cyanoacrylate significantly reduced post endoscopic ulceration compared to *N*-butyl-2-cyanoacrylate.

In summary, DL is an infrequent but severe and obscure cause of gastrointestinal hemorrhage, which occurs predominantly in males. Repeated endoscopy is often required to determine the diagnosis. An expert endoscopist with a skilled assistant should have a high rate of successful diagnosis of DL. Thus, use of isoamyl-2-cyanoacrylate (AMCRYLATE®) seems effective and safe for treatment of gastric DLs. Surgical wedge resection should be reserved



Figure 1 Dieulafoy's lesion in male patient presented with active haematemesis. Note the haemorrhagic arteriole in greater gastric curvature.



Figure 3 Successfully Injected dieulafoy (arrow) and no more bleeding.



Figure 2 Injection of Dieulafoy's lesion with 1 cm Isoamyl 2-Cyanoacrylate dissolved in 1 cm Lipidol, 1:1 ratio.

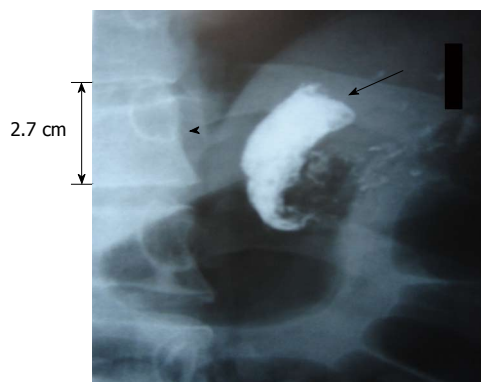


Figure 4 Erect X-ray, showing Dieulafoy large Arteriole after Iso Amyl-2-cyanoacrylate injection. It opens directly into the gastric cavity. Note the large caliber of the Arteriole (arrow) corresponding to the adjacent Lumbar Vertebra (arrow head).

for difficult-to-control bleeding. Death may occur if bleeding is not controlled.

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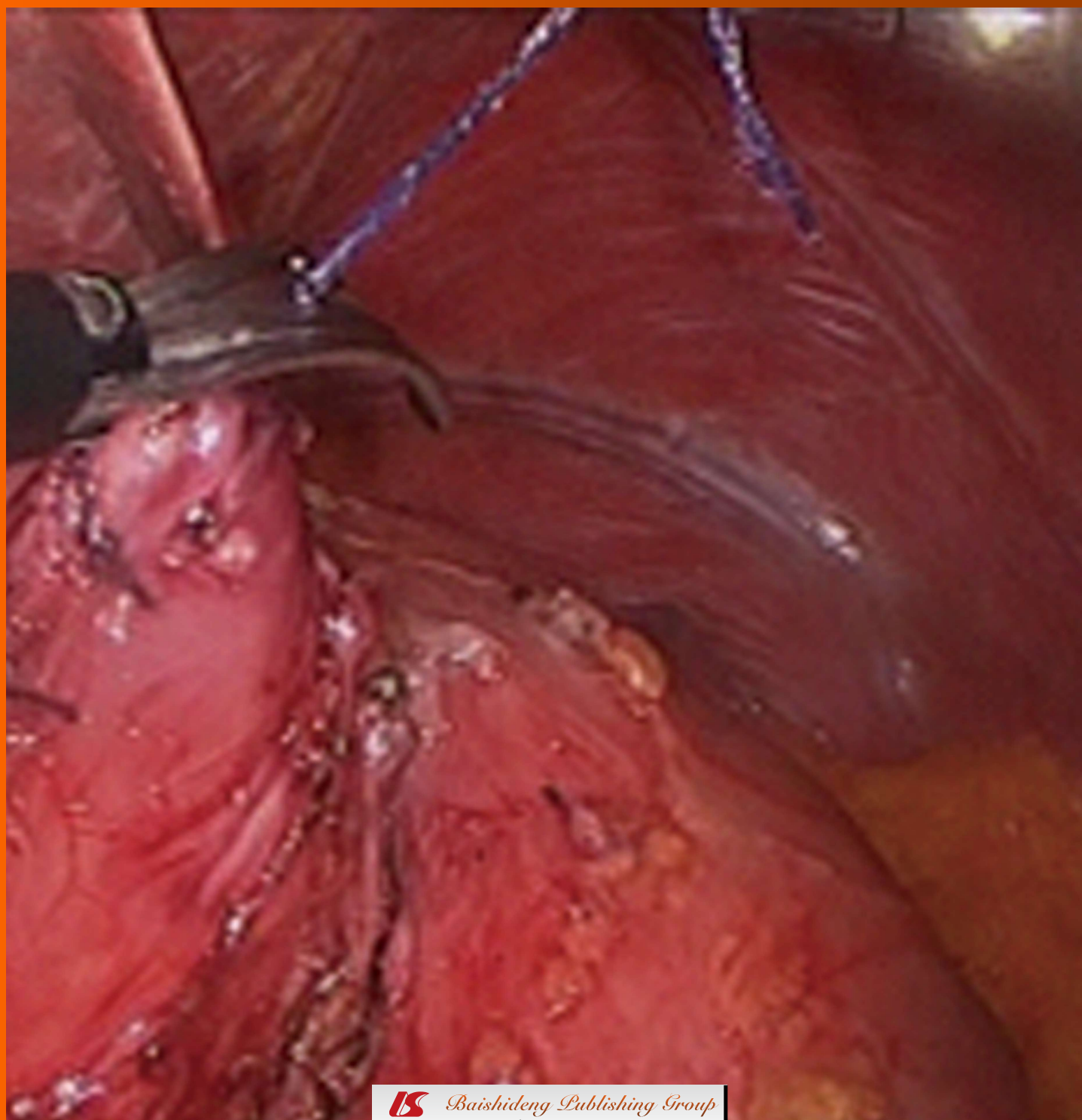
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Per-oral endoscopic myotomy for achalasia: An American perspective

David Friedel, Rani Modayil, Shahzad Iqbal, James H Grendell, Stavros N Stavropoulos

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Abstract

Achalasia is an uncommon esophageal motility disorder characterized by the selective loss of enteric neurons leading to absence of peristalsis and impaired relaxation of the lower esophageal sphincter. Per-oral endoscopic myotomy (POEM) is a novel modality for the treatment of achalasia performed by gastroenterologists and surgeons. It represents a natural orifice transluminal endoscopic surgery (NOTES) approach to Heller myotomy. POEM has the minimal invasiveness of an endoscopic procedure that can duplicate results of the surgical Heller myotomy. POEM is conceptually similar to a surgical myotomy without the inherent external incisions and post-operative care associated with surgery. Initial high success and low complications rates promise a great future for this technique. In fact, POEM has been successfully performed on patients with end-stage achalasia as an initial treatment reserving esophagectomy for those without good response. The volume of POEMs performed worldwide has grown exponentially. In fact, surgeons who have performed Heller myotomy have embraced POEM as the preferred intervention for

achalasia. However, the niche of POEM remains to be defined and long term results are awaited. We describe our experience with POEM having performed the first POEM outside of Japan in 2009, the evolution of our technique, and give our perspective on its future.

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Key words: Per-oral endoscopic myotomy; Achalasia; Heller myotomy; Natural orifice transluminal endoscopic surgery; Per-oral endoscopic myotomy; Minimally invasive surgery

Core tip: Per-oral endoscopic myotomy (POEM) is a minimally invasive endoscopic procedure that duplicates results of the surgical Heller myotomy. This innovative technique has been performed by both gastroenterologists and surgeons. POEM has been shown to be safe and effective in patients with classic achalasia and modest follow-up data. POEM has also been successfully applied in patients with hypertensive esophageal motor disorders as well as end-stage achalasia. It is recommended that prior to performing POEM, operators should have experience in endoscopic submucosal dissection or substantial training in animal models.

Friedel D, Modayil R, Iqbal S, Grendell JH, Stavropoulos SN. Per-oral endoscopic myotomy for achalasia: An American perspective. *World J Gastrointest Endosc* 2013; 5(9): 420-427 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/420.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.420>

INTRODUCTION

Achalasia is an esophageal motility disorder where there is aperistalsis of the distal one-third of the esophageal body and the lower esophageal sphincter (LES) fails to

relax in response to swallowing. Achalasia is noted equally in both genders with prevalence that ranges up to 1 per 10000 persons and it occurs across the age span, though diagnosis is usually made in middle age or later^[1]. The majority of cases are idiopathic, but the syndrome can be associated with malignancy (especially involving the gastro-esophageal junction) and as a part of the spectrum of Chagas disease. Rarely, achalasia is genetically transmitted^[2]. Achalasia is an uncommon prototypical esophageal motility disorder with characteristic clinical and esophageal manometry findings. The cardinal presenting symptom is dysphagia; usually for both solids and liquids. Other symptoms can include chest pain, regurgitation, heartburn, cough related to aspiration, and weight loss. Advanced cases can result in malnutrition. Achalasia is suggested by characteristic contrast imaging demonstrating a dilated esophagus with smooth distal narrowing that can resemble a “bird’s beak”, but formal diagnosis requires esophageal manometry. The necessary feature on manometry is a LES that does not consistently relax after swallowing. Common but more variable features are a hypertensive LES and disordered peristalsis in the esophageal body. High resolution manometry has refined the delineation of various subtypes of achalasia as defined by the more variable features^[3]. The classification has therapeutic importance as those with “classical” (aperistalsis of esophageal body) respond better to endoscopic and surgical interventions than those with “vigorous” achalasia^[4].

PRIOR CONVENTIONAL TREATMENTS FOR ACHALASIA

Medical treatment of achalasia with calcium channel blockers and other agents is considered to be ineffective. Therapy instead is directed towards disrupting or weakening the LES. Diminution of LES pressure after therapy is paramount in attaining relief from dysphagia^[5,6]. Until recently, the three traditional options for this were botulinum (Botox) injection (BTI) into the LES, pneumatic dilation (PD) of the LES and surgical myotomy (often with subsequent fundoplication to minimize reflux). BTI has been well validated as therapy for achalasia with good short-term benefit, but has poor long-term efficacy at diminishing dysphagia^[7,8]. However, it is a safe and effective treatment option for the infirm and elderly^[9]. Pneumatic dilation has a well validated track record in relieving dysphagia in achalasia, though repeated dilations are often needed and some require sequentially larger balloons^[10,11]. A pivotal study demonstrated therapeutic equivalence between PD and laparoscopic Heller myotomy with Dor’s fundoplication at 43 mo post-intervention in terms of LES pressure and relief from dysphagia^[12]. Despite this, surgical myotomy remains the preferred modality for achalasia in the United States; perhaps because of medical-legal concerns related to PD perforation and the usual more durable response with myotomy^[13]. The degree of esophageal dilation of the achalasia esophagus is less of a concern to the surgeon than previously, but the operator

must ensure an adequate myotomy and distal esophagectomy (6+ cm), and up to 20% of patients may require repeat intervention^[14].

EMERGENCE OF PER-ORAL ENDOSCOPY MYOTOMY

Per-oral endoscopic myotomy (coined “POEM”) developed as an offshoot of a technique to access the mediastinum in Natural Orifice Transluminal Endoscopic Surgery (NOTES)^[15]. The POEM technique was first tested in a porcine model^[16]. A key feature was creation of a submucosal tunnel with closure of mucosal entry site a distance away from the myotomy. Inoue extrapolated this method to perform the first POEM in humans^[17]. We performed our first POEM in 2009 (the first outside Japan) as part of an IRB-approved prospective trial protocol at Winthrop University Hospital^[18]. We have integrated our series data into a comprehensive international POEM (IPOEMS) survey that was completed in July 2012^[19]. The volume of POEMs performed worldwide has increased dramatically but appears to be concentrated at several select centers and literature concerning this new modality has also been increasing; albeit at a slower pace.

INDICATIONS AND CONTRAINDICATIONS FOR POEM

Patients considered candidates for POEM must have a confirmed diagnosis of achalasia *via* manometry and secondary achalasia related to malignancy must be excluded. Consensus contraindications to POEM include severe pulmonary disease, significant coagulation disorder and prior therapy that compromise esophageal mucosal integrity including endoscopic mucosal resection (EMR), radiofrequency ablation (RFA) and radiation. With experience, operators have been more liberal in performing POEM in a variety of achalasia subtypes as well as hypertensive esophageal motility disorders. The technique was used successfully on a patient with diffuse esophageal spasm^[20]. Patients with longstanding achalasia may develop a markedly dilated (“sigmoid”) esophagus that can require esophagectomy^[21]. Despite this, Inoue described POEM performed in 16 such patients in his series^[22]. POEM offers a minimally invasive treatment option that can be used initially, reserving esophagectomy for failures.

POEM TECHNIQUE

The technique of POEM is centered on creation of a submucosal tunnel within the distal esophagus where a myotomy is performed within this tunnel with dissection of the inner circular muscle of the esophagus and minimally dissection of the LES circular muscle. Equipment required for POEM is readily available and compatible with existing endoscopy instruments^[23] (Table 1). Endotracheal intubation is performed and it is paramount to

Table 1 Per-oral endoscopic myotomy equipment

High-definition diagnostic gastroscope
Transparent 4 mm distal cap attachment
Electrosurgical device for injection of saline, incision and cautery (T-type HK hybrid knife- with Erbe jet pump)
Electrosurgical device for incision and cautery (Triangle tip knife) and injection of saline with Injector force Max 4 mm, 23-gauge injection needle
Electrosurgical high frequency generator (<i>e.g.</i> , ERBE VIO 300D)
Coagulation 5 mm grasper (Olympus)
Endoscopic clips (Boston-Scientific, Olympus, Wilson-Cook)
Needle or trocar for potential decompression of capnoperitoneum (angiocatheter, Veress needle 120 mm)
Endoscopic dilating balloons- CRE balloon dilator (5.5 cm, 10-11-12 mm) multiple manufacturers (rarely required)
Submucosal injection: Methylene blue or indigo carmine diluted in saline

CRE: Controlled radial expansion.

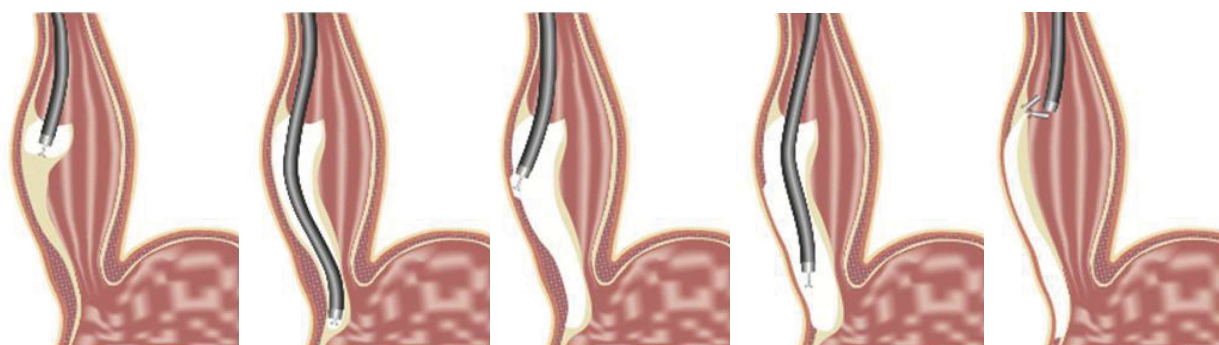


Figure 1 Per-oral endoscopic myotomy technique (© Winthrop University Hospital, 2012). A mucosal incision is performed after submucosal injection. Then, dissection of the submucosal tunnel is initiated and extended into the gastric cardia. Myotomy is performed of the circular layer and extended 2 cm into the gastric cardia. Finally, the entrance to the submucosal tunnel is closed with endoclips.

use carbon dioxide for endoscopic insufflations to minimize the risk of mediastinal emphysema and minimize barotrauma if pneumoperitoneum occurs. Endoscopy is performed on the fasted patient and the esophagus is cleared of any residual contents. Liquid antibiotic (gentamicin) is used to lavage the esophagus. The sequence of POEM is (1) submucosal injection, mucosal entry; (2) creation of the submucosal tunnel with subsequent; (3) distal esophageal circular muscle dissection; (4) LES myotomy; and (5) finally closure of the mucosal incision (Figure 1).

A submucosal injection of saline is used to expand the submucosal space ten to fifteen cm proximal to the LES and a two cm incision is then made (Figure 2A and B). The diagnostic gastroscope with cap is inserted into the submucosal space. The submucosal tunnel is extended with cautery and further injection. The submucosal tunnel located on the right side of the esophagus is extended to 2-3 cm distal to the LES and into the gastric cardia (Figure 2C). During dissection, if there is significant bleeding or the presence of larger vessels within the submucosa, the Olympus Coagrasper is employed to coagulate. The gastroscope is repositioned 2-3 cm distal to the initial mucosal incision site prior to initiating the myotomy. Dissection of the esophageal wall is performed with an electrical knife but actual dissection of the circular muscle is not performed until the plane between the inner circular and outer longitudinal esophageal muscles are clearly delineated (Figure 2D). The circular muscle myotomy is performed by hooking the inner muscle fibers with the knife and cutting them (Figure 2E

and F). This dissection of muscle is continued distally until it is extended 1-2 cm into the cardia. This extension (cardiomyotomy) is partially based on the surgical myotomy experience where there is greater treatment efficacy with such extension^[21]. This was also validated in a porcine POEM study^[24]. The recognition of the LES in the tunnel can be quite challenging; especially for the inexperienced POEM operator. There may be cues such as submucosal palisading vessels (with less vasculature in the cardia) and widening of the submucosal space^[20]. This can be correlated with tactile feedback of the endoscope entering the stomach. After the myotomy is completed with circular muscle excision from the mucosal entry to the cardia 1-2 cm distal to the LES, the endoscope is withdrawn into the esophageal lumen. The mucosal defect is closed with endoscopic clips (*e.g.*, Boston Scientific Resolution) (Figure 2G and H). It is important to realize that the integrity of the esophageal mucosa is the barrier against mediastinal soiling after the procedure. Thus, it should not be breached during the tunnel creation and the entry site securely closed.

EVOLUTION OF OUR POEM TECHNIQUE

There has been significant evolution of our technique due to our experience, newly available instruments and the experience of others worldwide (Table 2). We did not have access to endoscopic submucosal dissection (ESD) knives initially because they were not available in the United States. We partially overcame this by obtaining

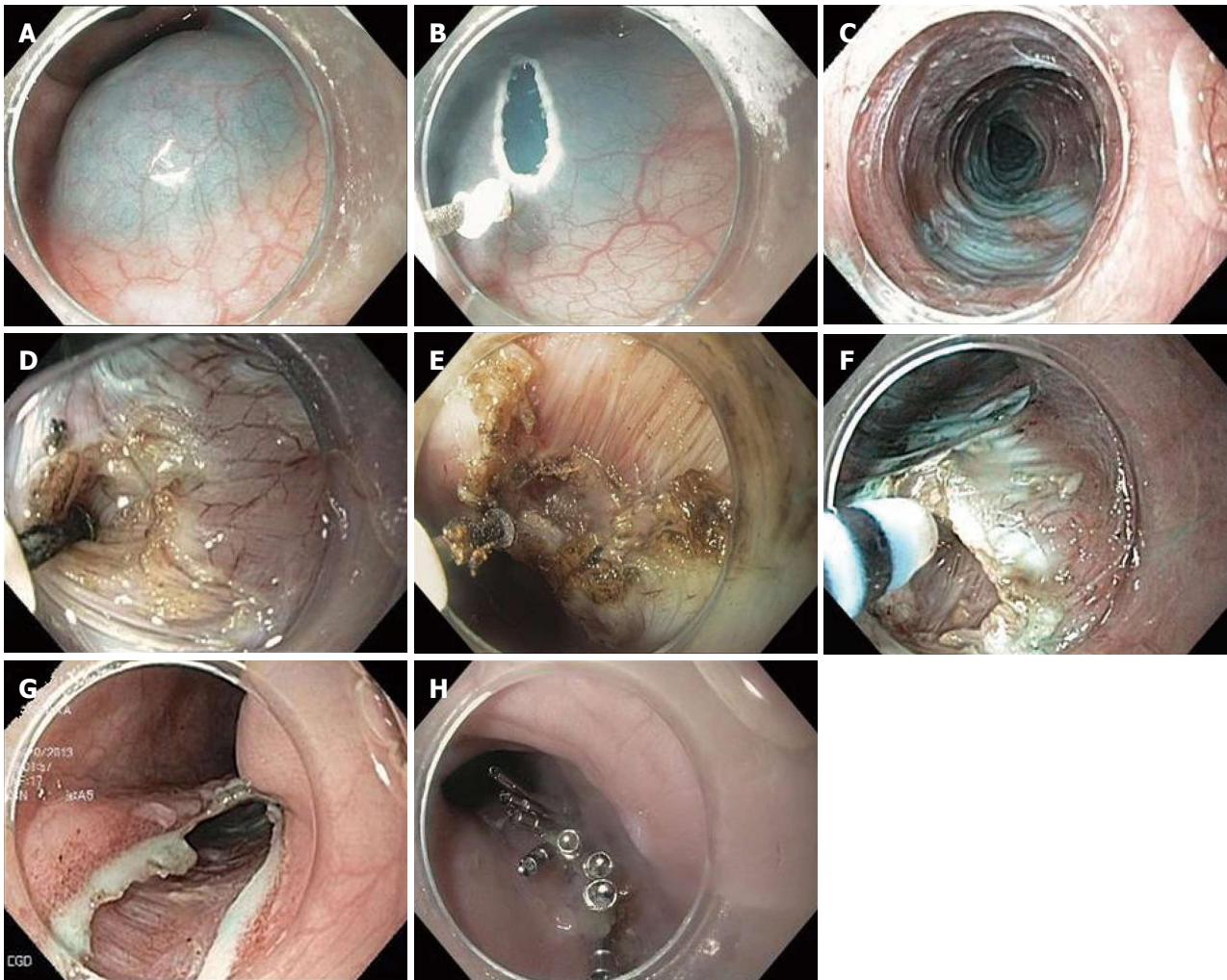


Figure 2 Per-oral endoscopic myotomy technique. A: Submucosal injection; B: Mucosal incision; C: Submucosal tunnel; D: Myotomy initiation; E: Dissection of the circular layer with longitudinal layer intact; F: Hooking of circular muscle layer with hybrid knife; G: Entrance to the submucosal tunnel; H: Closure.

Table 2 Evolution of per-oral endoscopic myotomy: A single center experience

Initial	Subsequent	Rationale
Performed in operating room with surgeon present	Performed in endoscopy suite with surgeon available	Demonstrated to be a predictable and safe procedure. Moderate procedural time
Selected patients had no prior achalasia intervention	Selected patients include those with prior intervention (BTI, PD, HM)	POEM results here and elsewhere
Use of dilation balloons to dissect submucosal tunnel	No or little use of balloon. Evolution from needle knife to IT knife and now hybrid knife	Experience. More reliable dissection with knives. Hybrid knife with flushing capability
Variable orientation of initial incision site	Preference for 5 o'clock position	Improved dysphagia relief
Short myotomy-less than 6 cm	Myotomy tailored to manometry findings and components of Eckardt score	POEM results here and elsewhere
Partial LES myotomy of circular muscle only	Preference for complete myotomy unless low LESP on manometry	Concern for POEM efficacy. Post-POEM GERD usually manageable with medication

POEM: Per-oral endoscopic myotomy; BTI: Botulinum (Botox) injection; LESP: Lower esophageal sphincter pressure; PD: Pneumatic dilation; HM: Heller myotomy; GERD: Gastroesophageal reflux disease.

prototypes of ESD knives and using them in our animal lab, and thus are familiar with them prior to human use. We did our first POEM procedures with the tunnel created by a dilating balloon (often a biliary balloon). There is concern with the blunt dissection caused by the balloon in terms of possible mucosal damage. The myotomy was performed with a needle knife^[17]. We used the triangular

tip knife (Figure 3) when it became available and as described by Inoue^[16]. Now, we employ the T-type hybrid knife (Figure 4) and avoid use of the balloon. Thus, submucosal injection can be made without need for exchanging devices. One POEM center (Shanghai group) touted the hybrid knife as superior to other knives and also used it in humans^[25].

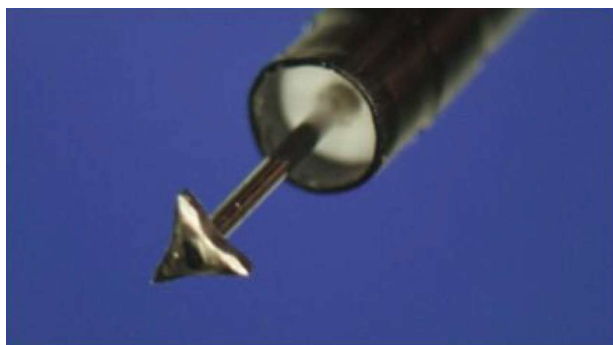


Figure 3 Triangular tip knife (Olympus) Courtesy Haruhiro Inoue.



Figure 4 T-type hybrid knife (ERBE Elektromedizin GmbH). Courtesy John Day, ERBE (Marietta, GA).

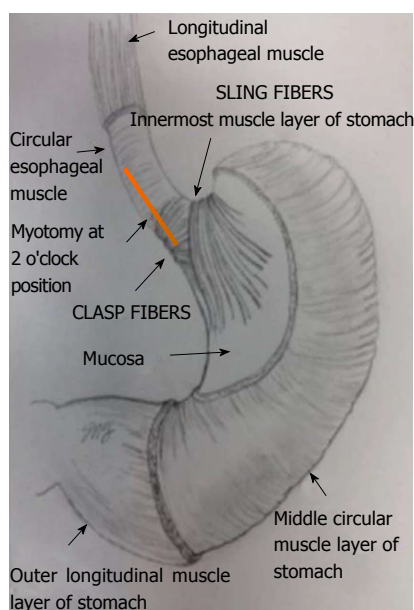


Figure 5 Human lower esophageal sphincter anatomy in relation to per-oral endoscopic myotomy myotomy orientation (© S.N. Stavropoulos, Winthrop University Hospital, 2012).

LOWER ESOPHAGEAL MYOTOMY: ORIENTATION, DEPTH AND LENGTH

The LES in humans has multiple components that include a weaker thinner clasp (circular) part on the gastric lesser curvature centered at 2 o'clock with 12 o'clock de-

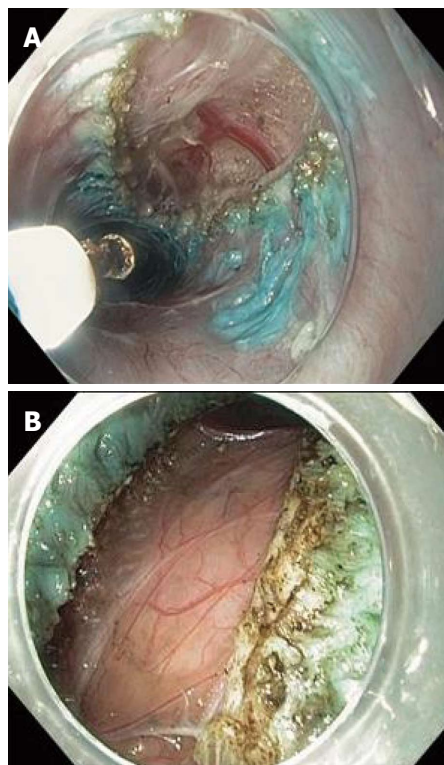


Figure 6 Full-thickness myotomy.

defined as the most anterior point and a sling (oblique) fiber part centered on the left posterior lateral wall of the LES at 7 o'clock and draping over the anterior and posterior walls at 5 and 11 o'clock respectively^[26] (Figure 5). The sling fibers represent a significant barrier to reflux. Laparoscopic Heller Myotomy usually involves transection of the sling fibers at 11 o'clock and thus reflux symptoms are common after laparoscopic heller myotomy (LHM). On the other hand, most POEM operators begin the SM tunnel at 2 o'clock which may minimize post-procedure reflux, but the tradeoff is with less than optimal efficacy because LES disruption is the key factor in achalasia intervention. We and others (Shanghai group) that employ a predominant 5 o'clock for the mucosal entry point and submucosal tunnel may have better relief of dysphagia because of dissection of the sling fibers but at the expense of mild reflux. At our center, patients with gastroesophageal reflux disease after POEM respond well to medical therapy. Conceivably, the decision regarding the mucosal entry site may be based on manometry findings where those achalasia patients with a normal or low LES pressure may receive a myotomy in the 2 o'clock while the majority of the other achalasia patients would be best served by a 5 o'clock incision. We can assess the quality of the myotomy by visualization and tactile assessment of the LES pressure by passage of the gastroscope. We and others assess the esophagogastric junction distensibility quantitatively with the EndoFlip system during POEM^[27]. In one patient from our series, we were dissatisfied with the results of gastro esophageal junction distensibility after the 2 o'clock position myotomy was

Table 3 Per-oral endoscopic myotomy experience: Series data

No. of patients	45
No. of completed POEMs	45
Age (mean, yr)	53 (23-93)
Achalasia by HRM subtype	
I	12%
II	83%
III	5%
Esophageal dilation > 6 cm or sigmoid	27%
Percent of patients who failed prior conventional achalasia treatment (Endoscopic balloon dilation, Botulinum toxin injection, Heller myotomy)	35%
Pre/Post Eckardt score (mean)	7.8/0.4
Percent of patients with clinical success at 3 mo (Eckardt score \leq 3)	95%
Myotomy length (mean, centimeter)	9
Percent of technical errors	
Minor mucosal perforations requiring clip closure	20%
Needle decompression of capnoperitoneum	13%
Percent of adverse events	
Surgical intervention/conversion	0%
ICU or step down unit stay	0%
Prolonged hospital stay > 5 d	0%
Significant blood loss or blood transfusion	0%
POEM related readmission	0%

POEM: Per-oral endoscopic myotomy; HRM: High resolution manometry; ICU: Intensive care unit.

performed, so it was followed by a second complete myotomy at the 5 o'clock position with good results.

We, like Inoue, were conservative with our initial POEM patients, performing a myotomy less than 6 cm in length^[16]. We have subsequently followed the consensus in the POEM literature where our myotomy usually is 8-10 cm. As with the mucosal incision site, we anticipate manometry findings to guide us in determining which patients would not require such a long myotomy (*i.e.*, a patient with non-spastic achalasia). We tend to perform a full-thickness myotomy of the LES (Figure 6) because (1) we are concerned about relief of dysphagia; (2) the residual longitudinal layer seems flimsy and is easily disrupted after the circular muscle is resected; and (3) the longitudinal layer usually plays a lesser role in the barrier mechanism. Most POEM operators perform only a partial LES myotomy leaving the outer longitudinal muscle layer intact, but one group transitioned to a full-thickness myotomy and reported significant better esophageal emptying in treated patients after the transition^[28].

POSTOPERATIVE CARE

All patients are hospitalized after POEM. A gastrografin swallow study is performed within 24 h to assess for leaks and gauge early efficacy. Antibiotics are often administered. The patient is usually given a liquid diet which is advanced and the patient is usually discharged within one-two days. Pain requiring narcotics is rarely reported and it seems less common than with LHM. A "second-look" endoscopy is usually not performed.

OUR POEM EXPERIENCE

We have performed POEM on 45 achalasia patients and have one year follow-up in more than half these patients

(Table 3). These patients had a wide age range and many had significant co-morbid disease. The POEM is usually completed within two hours though additional time antecedent to the POEM is sometimes necessary to clear the esophagus. We have not excluded patients with prior intervention and have concluded like others that prior botulinum toxin injection creates more challenges for the POEM operator than prior pneumatic dilation in terms of scarring and that POEM can be performed successfully after laparoscopic Heller Myotomy^[20]. We have performed POEM in patients with varying degrees of esophageal dilation including end-stage achalasia. Over 90% of our patients had relief of their dysphagia and improvement in global assessment (Eckardt scores). We are attempting to capture data recording post-therapy manometry. Data to date demonstrates at least 50% reduction in LES pressure post-myotomy. Other POEM groups have also generated excellent therapeutic results^[29,30]. POEM failures were defined as patients with Eckardt scores > 4. There were two patients early in our experience that met this criterion and had salvage PD. Follow up Eckardt scores at one year post salvage PD for these patients are zero.

We had an excellent safety record thus with our POEM patients with no life-threatening complications (Table 3). There were several patients with capnoperitoneum early in the series possibly related to mucosal flap injury, but these were easily treated with needle decompression. We emphasized the necessity of carbon dioxide during POEM. One POEM group had an unduly high rate of subcutaneous and mediastinal emphysema and pneumothorax that may relate to room air used in POEM^[31]. We are not aware of any documented POEM mortality. Published data on complications is sparse and the IPOEMS database infers a low rate (< 5%) of complications which include the above and bleeding within

the submucosal tunnel and one reported para-esophageal abscess^[18].

FUTURE PERSPECTIVES

There is a paucity of literature on POEM and to date only series from five centers^[26-28,32,33]. We are unique in that our POEM operator is a gastroenterologist and procedures are now done in the endoscopy suite. In spite of our success with POEM, some insurers have not sanctioned the use of the procedure-some terming it “experimental.” We anticipate consensus guidelines in the near future to deal with the issues mentioned about variability of technique as well training and credentialing guidelines. Training will likely include an animal model due to the low incidence of achalasia^[34]. A comparative trial between POEM and LHM yielded similar results for both arms^[35] and we expect further such studies.

As mentioned, POEM was originally developed as an innovation for NOTES and this work continues^[36]. The submucosal tunnel endoscopic resection technique (STER) is an offshoot of POEM, and allows removal of lesions in the muscularis propria and submucosa^[37].

CONCLUSION

POEM for esophageal achalasia is a novel and seemingly effective technique. Further validation is expected, but it appears already to have carved a niche in the armamentarium for achalasia. There are some controversies regarding technique that need to be resolved. There may be obstacles in the future concerning available training and availability of skilled operators.

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Hybrid natural orifice transluminal endoscopic surgery in gastric subepithelial tumors

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Abstract

Diagnosis of gastric subepithelial tumor (SET) has shown a rapid increase worldwide. Although, until now, endoscopic ultrasound guided procedures such as fine needle aspiration have shown relatively high accuracy in diagnosis of SET, the most important modality for diagnosis and treatment of SETs is complete resection such as endoscopic or surgical resection. However, endoscopic resection or laparoscopic wedge resection alone also has some limitations. Endoscopic resection is difficult to perform in cases of gastric SET located within deep portion of the gastric layer or a relatively large (larger than 25 mm diameter). On the other hand, gastric SET in a difficult location, such as the gastroesophageal junction or pyloric ring is challenging for laparoscopic surgical resection. The hybrid natural orifice transluminal endoscopic surgery (NOTES) technique is a combined method, including the advantages of both laparoscopic resection and endoscopic resection for gastric SETs. This method may be performed safely with reasonable operation times, less bleeding, and adequate resection margin and regardless of tumor size. In particular, in the case of a difficult location for resection, such as the esophagogastric junction or pyloric ring, hybrid NOTES is currently believed to be an ideal

treatment method.

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Key words: Subepithelial tumor; Hybrid natural orifice transluminal endoscopic surgery; Endoscopic ultrasound

Core tip: Hybrid natural orifice transluminal endoscopic surgery is thought to be an ideal method for treatment of gastric subepithelial tumor with adequate resection margin, regardless of tumor size and location, such as the esophagogastric junction or pyloric ring.

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INTRODUCTION

Diagnosis of gastric subepithelial tumor (SET) has shown a rapid increase worldwide in accordance with increasing performance of endoscopy for screening. The SETs occupy approximately 5% of total gastric tumors, showing various aspects from benign, such as lipoma, to malignancy, such as gastrointestinal stromal tumor^[1].

For diagnosis of SETs, the use of endoscopic ultrasonography (EUS) and EUS guided fine needle aspiration or Tru-Cut biopsy has shown a recent increase. However, the average accuracy rate of EUS guided fine needle aspiration (EUS-FNA) for diagnosis of SETs is only 60% to 80%. In a recent study, Mekky *et al*^[2] reported on the diagnostic utility of EUS-FNA in gastric SETs. The sampling adequacy was 83%, with an average of 2.5 passes. EUS-FNA results were diagnostic in 43.3%, suggestive in 39% and non-diagnostic in 17.7%. EUS-FNA results showed 95.6%

accuracy in differentiation of potential malignant lesions. Another study validated the unroofing technique for diagnosis of SETs in 16 patients^[3]. Use of the unroofing technique provided specimens that were sufficient for diagnosis and assessment of risk for malignancy in 15 out of 16 cases [diagnostic yield 93.7% (95%CI, 80.4%-100.0%)]. However, the indication for use of the unroofing technique should be confined to liquid SETs, such as lipoma and cystic lymphangioma. In addition, EUS guided biopsy or unroofing technique is limited to use as a diagnostic tool rather than a treatment modality.

Therefore, until now, the most important modality for diagnosis and treatment of SETs has been complete resection. Because the characteristics of SETs are mostly benign in nature and are rarely malignant in nature with hematogenous spread rather than lymphatic metastasis, lymph node dissection is not necessary for treatment of SETs. Therefore, SETs are a good indication for resection of tumors using endoscopy or laparoscopy.

According to development of endoscopic technology, a non-invasive method is currently preferred. In this article, we will provide validation for endoscopic treatment, surgical treatment and hybrid natural orifice transluminal endoscopic surgery (NOTES) for treatment of gastric SETs.

ENDOSCOPIC TREATMENT AND LIMITATIONS

Various endoscopic resection techniques have recently been reported for treatment of SETs. However, there are two major limitations of endoscopic resection alone. One is for SETs originating within a deep portion of the gastric layer and another is for SETs of large size. Endoscopic mucosal resection (EMR), including EMR with a cap and eEMR with ligation is a simple method for resection of small SETs originating from the mucosal and submucosal layer with low complication rates. However, for lesions originating from the muscularis propria, endoscopic resection has a main drawback of a risk of perforation. Therefore, SETs located deeper below the submucosal lesion are usually managed by surgery.

To overcome this limitation, some new techniques have been developed. Endoscopic submucosal tunnel dissection was validated for upper gastric SETs. In 12 patients who presented with an upper gastrointestinal SET of ≤ 40 mm located in the esophagus or cardia, a submucosal tunnel was created endoscopically starting at approximately 5 cm proximal to the lesion. SETs had a mean size of 19.5 mm (range, 10-40 mm), eight were located in the esophagus and four in the cardia^[4]. SET resection was successful in 10 patients (83.3%) who underwent *en bloc* resection and the two remaining patients who underwent resection in two pieces. However, endoscopic tunnel dissection is difficult to perform for a large SET. The size of piecemeal resected SETs was 25 mm and 40 mm, which were larger than *en bloc* resected SETs (median 15 mm, range 10-25 mm). In addition, there is a

risk for perforation during or after treatment.

In another Chinese study, 26 patients with gastric SETs originating from the muscularis propria were treated by endoscopic full thickness resection (EFR)^[5]. Briefly, the EFR procedure is as follows: (1) a circumferential incision as deep as muscularis propria around the lesion by the endoscopic submucosal dissection (ESD) technique; (2) incision into the serosal layer around the lesion using a knife; (3) completion of full-thickness incision to the tumor, including the serosal layer using a knife or snare by gastroscopy without laparoscopic assistance; and (4) closure of the gastric-wall defect with metallic clips. The complete resection rate was 100%, and the mean resected lesion size was 2.8 cm (range, 1.2-4.5 cm). The key to the EFR procedure is the successful closure of wall defects after resection for prevention of peritonitis and surgical intervention. Because the size of a wall defect after resection should be smaller than the width of the open clips, performance of the EFR procedure for large SETs (large than 25 mm) is difficult.

In summary, endoscopic resection alone has a limitation of complete resection for gastric SETs located within a deep portion of the gastric layer and is difficult to perform for a relatively large size (larger than 25 mm diameter).

SURGICAL TREATMENT AND LIMITATIONS

Traditionally, the basis for complete resection of SETs has been surgical resection. Recently, laparoscopic wedge resection has commonly been used as a non-invasive modality^[6,7]. The surgical techniques can be selected according to location and characteristics of the tumor^[8,9]. The location and aspect of SETs is also a limitation of laparoscopic resection. The exogastric approach is the most popular technique for SETs located at the anterior wall, particularly those that exhibit extraluminal growth^[7,10]. However, because it is associated with excessive resection of healthy tissue of the gastric wall, there is a possibility of stenosis or deformity with this procedure^[9]. Therefore, this approach is not considered suitable for SETs at or near the gastric inlet or outlet, such as the area near the gastroesophageal junction and pyloric ring. Tumors located at the posterior wall of the stomach can usually be treated using a transgastric or intragastric approach^[8,9,11,12]. The intragastric approach is the preferred method for lesions located at the posterior wall and for the tumors of the esophagogastric junction^[13-16]. Use of this procedure carries little possibility of deformity and stenosis. However, it cannot be applied to anterior wall lesions or large tumors. In addition, after completion of this procedure, repair of two or three stab wounds of the anterior wall of the stomach must be performed.

Tumors located near the pylorus and the lesser curvature of the stomach are challenging. The usual approach to submucosal tumors of the stomach is wedge resection with an adequate margin. In order to ensure

Table 1 The published studies on hybrid natural orifice transluminal endoscopic surgery of gastric subepithelial tumors

Author, year and number of patients	Operation time, min	Intraoperative bleeding, mL	Tumor size, mm	Number of linear staplers used	Postoperative complications	Hospital stay, d	Tumor location	Type of growth	Pathologic diagnosis, n
Hiki <i>et al</i> ^[20] , n = 7	169.0 ± 17.0	7.0 ± 2.0	46.0 ± 3.0 (35-60)	2.2 ± 0.1	0	7.4 ± 8.1	U4 M1 L1 Remnant stomach, posterior 1	Extragastric type 1 Intragastric type 6	GIST, 6 Schwannoma, 1
Tsujimoto <i>et al</i> ^[21] , n = 20	157.5 ± 68.4 (89-316)	3.5 ± 6.4 (0-20)	37.9 ± 11.0 (18-63)	2.7 ± 0.5 (2-3)	0	11.6 ± 9.5 (6-13)	U8 (40%) M8 (40%) L4 (20%)	Extragastric type 2 (15%) Intragastric type 17 (85%)	GIST, 16 (80%) Inflammation for parasite, 1 (5%), leiomyoma, 1 (5%), glomus tumor, 1 (5%), aberrant pancreas, 1 (5%)
Abe <i>et al</i> ^[22] , n = 4	221.5 ± 129.4	38.0 ± 46.7	38.0 ± 7.1 (22-43)	NA	0	7.5 ± 0.7	U1 M3	NA	GIST, 1 Lipoma, 1 Ectopic pancreas, 1 Schwannoma, 1

Data are expressed as median ± SD (range). U: Upper portion; M: Middle portion; L: Lower portion; NA: Not available; GIST: Gastrointestinal tumor.

patency of the gastric lumen and to prevent vagus nerve injury, special precautions must be taken during resection of tumors located near the pylorus and the lesser curvature of the stomach. A application of the intragastric or transgastric approach in this area is very difficult because of the small space available for handling or introduction of the instrument. Use of linear staplers in the prepyloric antrum is not recommended because surgeons cannot guarantee penetration to the luminal side and because the inevitable removal of healthy tissue from the gastric wall results in luminal compromise^[17].

HYBRID NOTES

NOTES implies the use of empty organs as an access to the peritoneal cavity using an endoscope, completely avoiding skin incisions^[18]. In order to overcome current technical limitations, investigators have combined NOTES with the conventional laparoscopic approach in the so-called hybrid NOTES technique.

Wilhelm *et al*^[19] reported that three different methods are available for laparoscopic-endoscopic “rendez-vous” resection. In the case of laparoscopic assisted endoscopic resection, the lesion is resected with diathermy; larger lesions demand that resection be performed as a wedge resection for tumors located in the anterior aspect of the stomach and as a transgastric resection for posterior wall lesions.

Hiki *et al*^[20] reported on 7 cases of laparoscopic and endoscopic cooperative surgery using endoscopic submucosal dissection with laparoscopic wedge resection as the technique developed for hybrid NOTES. The procedure for hybrid NOTES was as follows: both mucosal and submucosal layers around the tumor were circumferentially dissected using endoscopic submucosal dissection *via* intraluminal endoscopy. Subsequently, the seromuscular layer was laparoscopically dissected on the exact three-fourths cut line around the tumor. The sub-

mucosal tumor was then exteriorized to the abdominal cavity and dissected using a standard endoscopic stapling device (Figure 1). Endoscopic approach using the ESD technique can provide the precise cut line as a marker for laparoscopic resection. During performance of the resection, use of an intragastric endoscopic and extragastric laparoscopic approach can allow for observation of both sides of the resection margin. These dual approaches can allow for attainment of an appropriate resection margin. In addition, this method can provide an easy approach for the difficult location of SET resection and minimize the stricture or deformity after resection of gastric SETs at the esophagogastric junction or pyloric ring. In addition, as always, hybrid NOTES has the advantage of external wedge resection for large sized subepithelial tumors.

In the study reported by Hiki *et al*^[20], in all cases, the laparoscopic and endoscopic cooperative surgery (LECS) procedure was successful for dissecting out the gastric submucosal tumor. In four of seven cases, the tumor was located in the upper gastric portion near the esophagogastric junction. The three remaining tumors were located in the posterior gastric wall. In two cases, the tumors were more than 5 cm in diameter, and one was a gastrointestinal tumor (GIST) of the remnant stomach. The mean operation time was 169 ± 17 min, and the estimated blood loss was 7 ± 2 mL. The postoperative course was uneventful in all cases. In another study, 20 consecutive patients underwent LECS for resection of gastric SETs. In all cases, dissection of the gastric SET was successful using the LECS procedure. The tumor was located in the upper third of the stomach in eight cases, in the middle third in eight cases, and in the lower third in four cases^[21]. A summary of some published series on hybrid NOTES is shown in Table 1^[20-22].

The hybrid NOTES procedure for treatment of gastric SET should be performed carefully. Accidental rupture of a gastric SET, such as GIST, during resection with

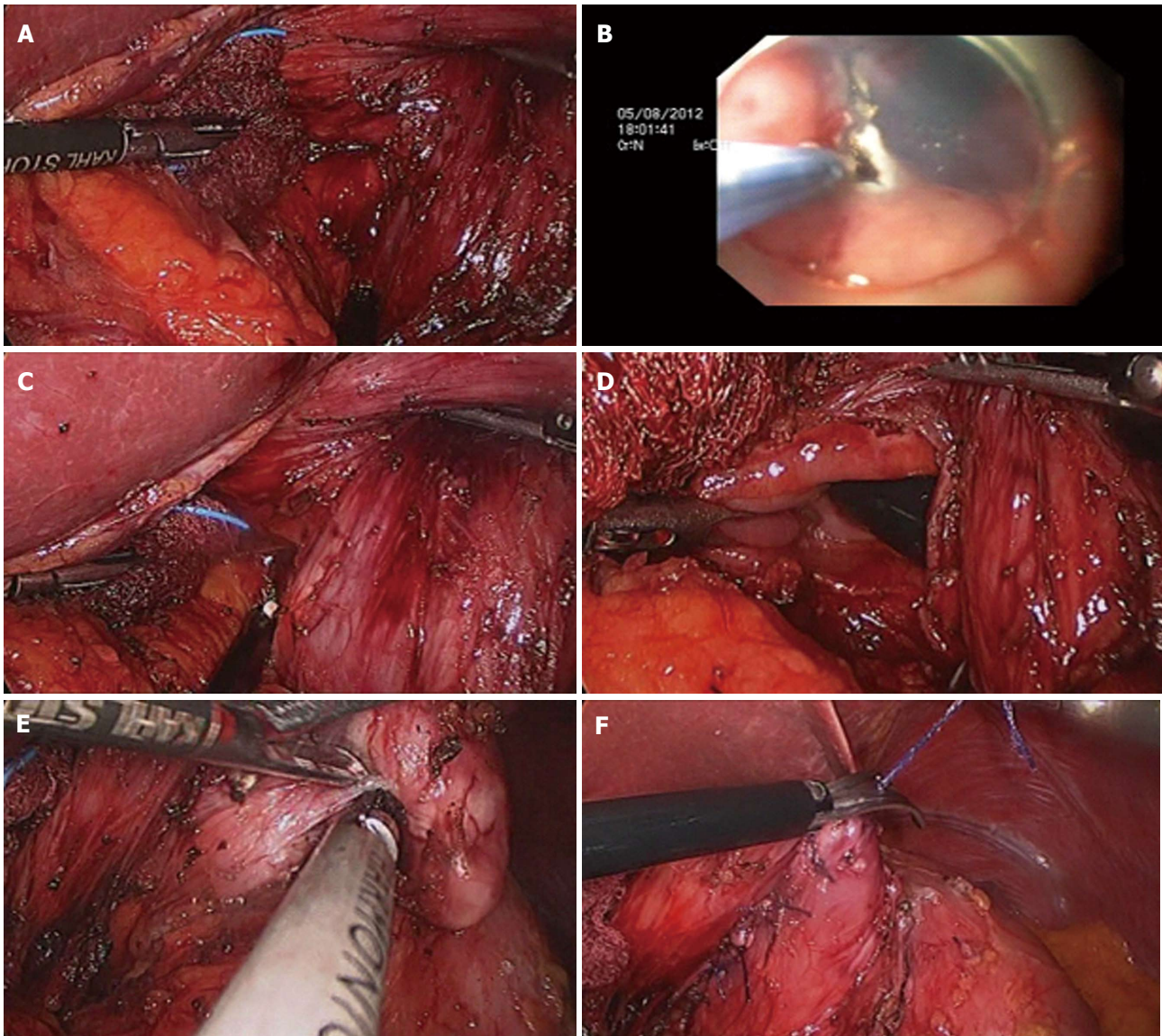


Figure 1 Procedures for hybrid natural orifice transluminal endoscopic surgery (laparoscopic assisted endoscopic full-thickness resection). A: Laparoscopic view during dissection of the attachment of the lesser omentum around the tumor site; B: Endoscopic view during precutting around the tumor using an O type knife (Finemedix, Daegu, South Korea); C, D: Laparoscopic view of a full-thickness incision from inside the stomach using the same knife; E: Laparoscopic view of the remaining full thickness incision from outside the stomach using a HARMONIC ACE® (Ethicon Endo-Surgery); F: Laparoscopic view after laparoscopic handsewn closure of the gastric wall defect.

peritoneal seeding is theoretically possible. Therefore, hybrid NOTES may be contraindicated for ulcerated or bleeding tumor. Removal of tumors from the abdomen into a specimen retrieval bag is also important for prevention of seeding of the tumor to the peritoneum and port-site wound.

CONCLUSION

The hybrid NOTES technique is a combined method including the advantages of laparoscopic resection and endoscopic resection for gastric SETs. This method may be performed safely with reasonable operation times, less bleeding, and adequate resection margin regardless of tumor size. In particular, in cases of difficult location for resection, such as the esophagogastric junction or

pyloric ring, hybrid NOTES is currently believed to be an ideal treatment method.

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Same-day 2-L PEG-citrate-simethicone plus bisacodyl vs split 4-L PEG: Bowel cleansing for late-morning colonoscopy

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Abstract

AIM: To evaluate the efficacy, tolerability, acceptability and feasibility of bisacodyl plus low volume polyethyleneglycol-citrate-simethicone (2-L PEG-CS) taken the same day as compared with conventional split-dose 4-L PEG for late morning colonoscopy.

METHODS: Randomised, observer-blind, parallel group, comparative trial carried out in 2 centres. Out patients of both sexes, aged between 18 and 85 years, undergoing colonoscopy for diagnostic investigation, colorectal cancer screening or follow-up were eligible. The PEG-CS group received 3 bisacodyl tablets (4 tablets for patients with constipation) at bedtime and 2-L PEG-CS in the morning starting 5 h before colonoscopy. The control group received a conventional 4-L PEG formulation given as split regimen; the morning dose was taken with the same schedule of the low volume preparation. The Ottawa Bowel Preparation Scale (OBPS) score was used as the main outcome measure.

RESULTS: A total of 164 subjects were enrolled and 154 completed the study; 78 in the PEG-CS group and 76 in the split 4-L PEG group. The two groups were comparable at baseline. The OBPS score in the PEG-CS group (3.09 ± 2.40) and in the PEG group (2.39 ± 2.55) were equivalent (difference $+0.70$; 95%CI: $-0.09-1.48$). This was confirmed by the rate of successful bowel cleansing in the PEG-CS group (89.7%) and in the PEG group (92.1%) (difference -2.4% ; 95%CI: $-11.40-6.70$). PEG-CS was superior in terms of mucosa visibility compared to PEG (85.7% vs 72.4%, $P = 0.042$). There were no significant differences in caecum intubation rate, time to reach the caecum and withdrawal time between the two groups. The adenoma detection rate was similar (PEG-CS 43.6% vs PEG 44.7%). No serious adverse events occurred. No difference was found in tolerability of the bowel preparations. Compliance was equal in both groups: more than 90% of subjects drunk the whole solution. Willingness to repeat the same bowel preparations was about 90% for both regimes.

CONCLUSION: Same-day PEG-CS is feasible, effective as split-dose 4-L PEG for late morning colonoscopy and does not interfere with work and daily activities the day before colonoscopy.

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Key words: Bowel preparation; Polyethyleneglycol; Simethicone; Ottawa Bowel Preparation Scale; Colonoscopy

Core tip: The timing of bowel preparation is fundamental for high quality colonoscopy and also for patient satisfaction. Split-dose preparation improves the rate of adequate cleansing and patient compliance. This study shows that the same-day low volume polyethyleneglycol-citrate-simethicone (PEG-CS) plus bisacodyl tablets is feasible, and as effective as split 4-L PEG. The low volume bowel preparation taken the same day of the exam may be an attractive option for late morning

colonoscopy as it reduces the overall time for bowel preparation with no loss of work time and impact on daily activities the day before the exam.

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INTRODUCTION

Optimal bowel preparation is an essential component of high quality colonoscopy. A clean colon free of residual stool or brown liquid over the mucosa minimizes the risk of missing a flat adenoma or other small lesions^[1,2].

The ideal preparation for colonoscopy should effectively and rapidly remove all residual content from the large bowel, without inducing macroscopic or histologic alterations of the colonic mucosa. It should be safe with no risk for causing significant shifts in fluids or electrolytes, easy and pleasant to take in terms of volume and taste and should minimally interfere with daily activities.

To date, no bowel preparation meets all the requirements though important, advancements have been made with the low-volume^[3-7] and split-dose bowel preparations. There is still a need to increase the overall acceptability of bowel preparation for colonoscopy and reduce the burden and impact on productivity and daily living with the ultimate objective to improve the attitude toward colonoscopy within the colon cancer screening programs^[8].

A new low volume isotonic sulphate-free formulation of polyethyleneglycol-citrate-simethicone (PEG-CS) plus bisacodyl tablets has been designed to be as effective as high volume conventional PEG bowel preparation before colonoscopy and to improve patient satisfaction and compliance. Split-dose administration has been shown to provide better cleansing and reduce patient discomfort compared with a traditional administration on the day before^[9-13]. Same-day low volume bowel preparation may provide a further option for people who desire no or minimum impact on their work and daily activities on the day before the endoscopic procedure.

The present study was intended to compare the same-day PEG-CS with the split-dose conventional 4-L PEG for late morning colonoscopy. The primary endpoint was to compare the efficacy and the feasibility of both regimens. The secondary endpoints included adverse events, tolerability, acceptability and compliance and colonoscopy quality indicators.

MATERIALS AND METHODS

This was a randomised, observer-blind and parallel

group trial. Data were collected over an 11-mo period (from April 2011 to March 2012) at two Endoscopy Units. The trial was registered at Clinical Trials Gov site with number NCT01685853. The study was performed in accordance with the Declaration of Helsinki. The protocol was carried out according to the general principles of Good Clinical Practices and was approved by the Local Ethical Committee.

Study population

Adult out-patients of both sexes, aged between 18 and 85 years, undergoing colonoscopy for diagnostic investigation, colorectal cancer screening or follow-up were eligible. Patients with known or suspected gastrointestinal obstruction or perforation, severe acute inflammatory bowel disease or toxic megacolon, ileus or gastric retention, ileostomy, hypersensitivity to any of the ingredients, pregnancy and lactation and/or at a risk of becoming pregnant, were excluded. Patients unable to reach the Endoscopy Units in less than 1 h were not included in the study.

Enrolment

Eligible patients were informed about the aims, procedures, benefits and possible risks of the study prior to signing the informed consent form from day -30 to day -3. In the same visit a baseline evaluation, including medical history, physical examination and collection of demographic data, was performed by a study physician other than the study endoscopist (blinded for patient's preparation). The same physician instructed the patients how to take the preparation in both oral and written forms and gave to the patient a diary to record the timing of preparation intake, the number and the time of bowel movements, any adverse event, impact of daily life and any additional comments. In the last three days before colonoscopy, patients had to follow a free fibre diet, *i.e.*, without pasta, rice, bread, vegetables and fruits (fruit juices allowed). They could eat meats, fish, eggs and dairy products. The day before the examination, the subjects had to follow a clear liquid diet (*e.g.*, tea, milk, coffee, fruit juices, soft drinks and soup).

Bowel preparation methods

Patients were assigned to receive one of the two bowel preparations according to a computer generated block-randomisation list. One group received PEG-CS (2-L Lo-VOL[®]-esse) + bisacodyl tablets (Lovel-dyl[®]). The main active ingredient of the new formulation is macrogol 4000. The other important ingredients are citric acid, sodium citrate and simethicone. The product is available as sachets containing powder for oral solution. Each sachet must be dissolved in 500 mL of water and taken every 30 min. The dosing schedule in detail was as follows: (1) 3 bisacodyl tablets (4 tablets for patients with an history of chronic or occasional constipation) at bedtime; and (2) 2-L PEG-CS in the morning of colonoscopy – starting 5 h before colonoscopy. It was estimated that about 3 h were

needed for drinking the solution and for bowel movements, up to an 1 h for the journey to hospital and 30 min in the waiting room). The control group received a conventional PEG-ELS formulation (SELG® 1000) given as split regimen: 2-L + 2-L with the morning dose taken with the same schedule of the low volume preparation. The main active ingredients are macrogol 4000 and sodium sulphate. Each sachet of powder must be dissolved in 1L of water and taken as 250 mL every 15 min. The dosing schedule in detail was as follows: (1) 2-L at 6:00 pm the evening before the exam; and (2) 2-L the morning of colonoscopy, starting 5 h before colonoscopy.

Day of colonoscopy

Patients returned to the Endoscopy Unit for colonoscopy and gave back the completed diary to the Physician who asked them about tolerability, adverse events, acceptance compliance and impact on daily activities. The colonoscopy was performed by experienced Endoscopists who perform more than 500 colonoscopy/year and have familiarity with the bowel preparation scoring scale used in this study [the validated Ottawa Bowel Preparation Scale, Ottawa Bowel Preparation Scale (OBPS)]^[14]. The endoscopists were unaware of the bowel preparation taken by the patient and scored the colon cleansing according to the aforementioned scale.

Colon cleansing efficacy measures

The cleanliness of each section of the colon, *i.e.*, the right, the mid and the rectosigmoid colon was rated according to the 5-point Ottawa scale. The overall colonic fluid was rated according to a 3-point scale. The total score (bowel cleansing total score; primary endpoint) may range from 0 (best) to 14 (worst).

A total OBPS score < 7 was considered a successful bowel preparation.

In addition, we also measured the amount of foam and bubbles in terms of overall impact on mucosal visibility, as follows: (1) Excellent: clear imaging, no or minimal amount of bubbles or foam, which can be easily removed = 0; Fair: modest amount of bubbles and foam, which can be cleared, with loss of some time = 1; and (2) Insufficient: a great amount of foam and bubbles, which reduce significantly the clear visualization of the mucosa = 2.

Tolerability

The occurrence, time of onset and severity of gastrointestinal (GI) symptoms, *i.e.*, nausea, bloating, abdominal pain/cramps, anal irritation, during and after bowel preparation were collected by means of a 3-point Likert scale (2 = severe distress, 1 = mild distress, 0 = no distress).

Patient acceptability

Pre-determined questions were addressed to each patient with regard to: (1) difficulty to take the preparation within scheduled times; (2) urgency and incontinence episodes during the trip to the hospital; (3) sleep lost (yes/no); (4) ease of taking the preparation (none, mild and severe distress); and (5) patient preference as com-

pared to previous bowel preparations [willingness to use the same product in the future (yes/no)].

Compliance

Compliance was scored on a 3-grade scale specifying the percentage of drunk solution: (1) Optimal: intake of the whole solution = 0; (2) Good: intake of at least 75% of the solution = 1; and (3) Poor: intake of < 75% of the solution = 2.

Adverse events

Any adverse event reported by any subject or observed by the Physician, independently from its seriousness and its relation to the study formulations, were recorded including time of onset, nature, duration, severity and any action taken.

Colonoscopy quality indicators

Caecum intubation rate, time to reach the caecum (intubation time), withdrawal time and adenoma detection rate were recorded.

Statistical analysis

Taking into account a drop-out rate of 15%, 164 patients (82 per treatment group) had to be enrolled and randomised to obtain 138 evaluable subjects. Such sample size was determined assuming a standard deviation value for the bowel cleansing score equal to 3 points and using an equivalence margin of 1 point, so that the two-sides 95%CI of the mean score difference was expected to lie between ± 1.5 points with 80% power. The data were summarized by treatment using classical descriptive statistics: mean, standard deviation, minimum and maximum values (for quantitative variables) and by frequencies and percentages (qualitative variables). The efficacy analysis was performed on both intention to treat (ITT) and per protocol (PP) populations (patients having drunk at least 75% of the solution) by building the 95%CI for the difference of the mean Ottawa bowel cleansing score in the two groups. Other analysis were performed on ITT populations.

Treatments were compared using *z* test for bowel cleansing score and other quantitative variables while using chi-square test for qualitative variables. All tests were considered two-tailed with significance level set to 5%.

RESULTS

One hundred and sixty-four subjects were enrolled and randomly assigned to the two groups: seven subjects were excluded before colonoscopy (5 for consent withdrawal, 2 for adverse events before starting the treatment). A total of 157 patients underwent colonoscopy (ITT), 78 randomized to PEG-CS and 79 to PEG (Figure 1). The demographic data of the two groups at baseline were comparable (Table 1).

Efficacy

The mean OBPS score was 3.09 ± 2.40 in the PEG-CS

Table 1 Patients characteristics

Variable	PEG-CS + Bis (n = 78)	PEG (n = 79)
Male	30 (38.5)	27 (34.2)
Age (yr)	61.8 ± 10.8	60.9 ± 12.0
Height (cm)	166.2 ± 9.1	165.0 ± 8.1
Weight (kg)	68.4 ± 14.5	68.6 ± 13.4
BMI (kg/m ²)	24.6 ± 3.8	25.1 ± 4.1

Data are expressed as absolute numbers (percentage) or mean ± SD. PEG-CS + Bis: Polyethyleneglycol-citrate-simeticone+ bisacodyl; PEG: Polyethyleneglycol; BMI: Body mass index.

Table 2 Efficacy results

	PEG-CS + Bis (n = 78)	PEG (n = 76) ¹
Overall OBPS score	3.09 ± 2.40	2.39 ± 2.55
Caecal intubation rate	76 (97.4)	75 (98.7)
Time (min) to reach the caecum	10.90 ± 6.1	9.80 ± 3.6
Adenoma detection	34 (43.6)	34 (44.7)

Data are expressed as absolute numbers (percentage) or mean ± SD. ¹Three patients did not complete the study (see Figure 1). PEG-CS + Bis: Polyethyleneglycol-citrate-simeticone+ bisacodyl; PEG: Polyethyleneglycol.

group and 2.39 ± 2.55 in the PEG group. The difference between the mean OBPS score in the two groups was not statistically significant for both PP (+0.70; 95%CI: -0.09-1.48) and ITT populations (+0.63; 95%CI: -0.18-1.43). As the confidence intervals are within the predefined interval range (-15%-15%), the two bowel preparations were equivalent for efficacy (Table 2). The rates of successful bowel preparation (OBPS < 7) were similar between the two groups (89.7% *vs* 92.1%). The rate of excellent visibility (no or minimal amount of bubbles or foam) was greater in the PEG-CS group (85.7%) as compared with 72.4% in the split PEG 4-L group (*P* value = 0.042) (Figure 2). There were no significant differences in the caecum intubation rate, time to reach the caecum and withdrawal time between the two groups (Table 2).

A significant association between subjects aged > 60 years and adenoma detection rate was found (*P* = 0.04).

Adverse events and tolerability

No serious adverse event occurred and no subject discontinued bowel preparation for an adverse event or poor tolerability. No difference was found in terms of tolerability between bowel preparations. There was no significant difference in terms of GI symptom associated with bowel preparation (Table 3).

Compliance and acceptability

Ninety percent of subjects, in both groups of treatment, drank the whole solution with no difference in compliance. The majority of subjects in both groups had no distress during bowel preparation, was willing to repeat the future colonoscopy with the same bowel preparation and preferred the present preparation

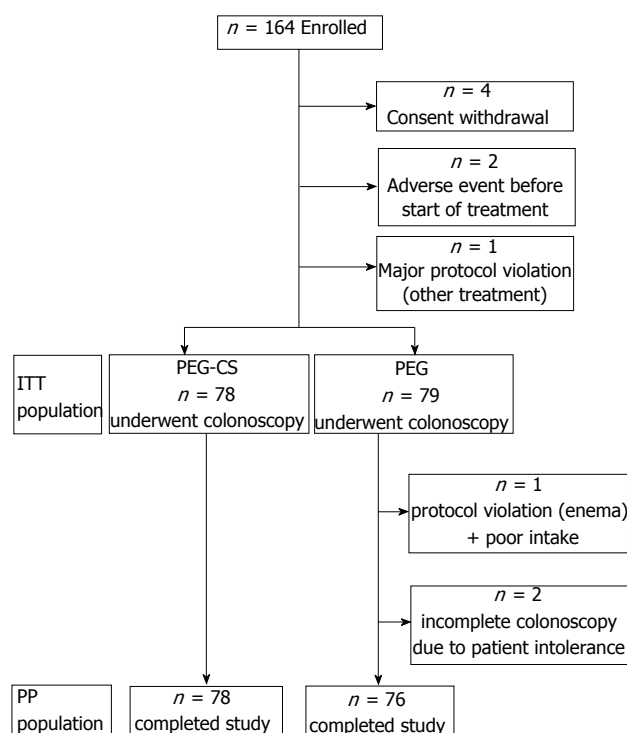


Figure 1 Study population flow chart. PEG-CS: Polyethyleneglycol-citrate-simeticone; PEG: Polyethyleneglycol; ITT: Intention to treat; PP: Per protocol.

to the previous one with no significant difference between the two preparations. No patient had severe urgency or a need to stop for bowel movement or incontinence during the journey to the hospital. Only few subjects reported moderate to severe interference with sleeping, with no significant difference between the two groups (Table 3).

DISCUSSION

In this trial the combined regimen of bisacodyl tablets given at bedtime the day before and 2-L of the new isotonic sulphate-free PEG-CS taken in the morning 5 h before the scheduled colonoscopy was compared with the split-dose 4-L PEG in which the morning dose was given with the same timing. We have shown that the same day schedule is feasible and as effective as the split-dose conventional PEG regimen for late morning colonoscopy.

As a matter of fact, the means of Ottawa Bowel Cleansing Score of the two treatment groups were statistically equivalent. This finding was confirmed by the rates of patients with successful bowel preparation, which were similar between the two preparations. Similarly, the adenoma detection rate and caecum intubation rate, two indicators of the quality of colonoscopy, were comparable between PEG-CS and PEG. It is important to note that PEG-CS was superior than PEG in terms of mucosal visibility. This is explained by the anti-foam action of simeticone^[15-18] which is contained only in PEG-CS.

Table 3 Tolerability and acceptability *n* (%)

	PEG-CS + Bis (<i>n</i> = 78)	PEG (<i>n</i> = 79)
GI tolerability		
Nausea (no or mild)	73 (93.6)	72 (91.1)
Bloating (no or mild)	77 (98.7)	78 (98.7)
Abdominal pain/cramps (no or mild)	73 (93.6)	77 (97.5)
Anal irritation (no or mild)	75 (96.1)	77 (97.5)
Adverse events		
Vomiting	6 (7.7)	2 (2.5)
Sweating	2 (2.6)	0 (0.0)
Headache	3 (3.8)	3 (3.8)
Shivering	2 (2.6)	1 (1.3)
Pre-syncope	2 (2.6)	0 (0.0)
Acceptability		
Easy of intake (no distress)	51 (65.4)	48 (60.8)
Willingness to repeat the same regimen	67 (85.9)	71 (89.9)
Preference to current regimen ¹	23 (28.1)	26 (32.9)
Urgency during the journey (no or mild)	78 (100.0)	79 (100.0)
Interference with sleeping (no or mild)	71 (91.0)	76 (96.2)

¹Excluding patients with first colonoscopy, missing data or unable to remember the first preparation. PEG-CS + Bis: Polyethyleneglycol-citrate-simeticone+ bisacodyl; PEG: Polyethyleneglycol; GI: Gastrointestinal.

The clinical rationale of same-day bowel preparation is the same as that of split-dosing, *i.e.*, to shorten the interval between the completion of bowel preparation and colonoscopy^[19]. It has been demonstrated that the quality of bowel preparation improves when the interval between the last dose of bowel preparation and colonoscopy does not exceed 8 h^[20-22]. After that period a viscous bile-stained mucous enters the colon and distributes over the colonic mucosa of the right colon with the potential to cover small or flat lesions containing high dysplasia. These lesions are considered a great challenge for the endoscopist having a high potential to remain missed at colonoscopy^[23,24]. The morning dose of the same day as well as split dose clears away this material and may increase the performance rate of colonoscopy in terms of detection of small adenomas.

Our study shows that same-day bowel preparation with a low-volume PEG-CS plus bisacodyl tablets is feasible and well accepted by subjects who are referred for colonoscopy. No subject had to stop the journey to hospital for urgency or arrived late in the hospital.

There was no significant difference for sleep interference between the two preparations. No patient in the PEG-CS group (and in the PEG group) complained nocturnal awakenings for bowel movements or pain/cramps. This suggests that sleep difficulty is more likely to be attributed to the anxiety for the day-after procedure. Bowel movements induced by bisacodyl taken at bedtime occurred after the wake-up.

We were unable to find differences for tolerability and acceptability between the two bowel preparations even if the new PEG-CS solution was considered in a panel of subjects more palatable than conventional PEG, which contains sodium sulphate. The subjects in our study were thoroughly instructed how to use the

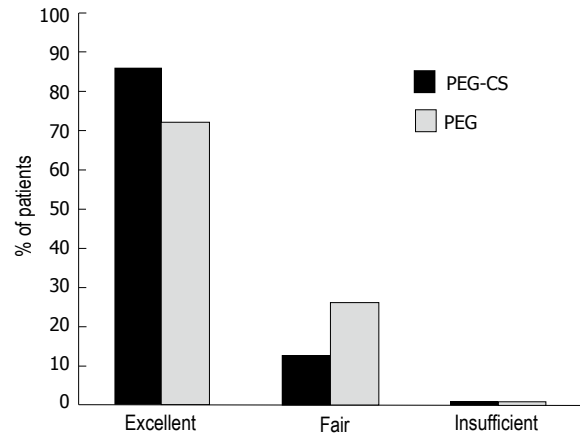


Figure 2 Mucosa visibility. PEG-CS: Polyethyleneglycol-citrate-simeticone; PEG: Polyethyleneglycol.

bowel preparation and its importance for a quality colonoscopy. This increased the motivation of the patients in the study and contributed to the high compliance rates in both groups. In routine clinical practice the motivation and compliance to the high volume PEG solution appear to be lower.

In addition to a 2-d low-fibre diet, the patients followed a clear fluid diet all the day before and this may have increased the rates of successful bowel cleansing. As the clear fluid diet is not well accepted, it would be interesting to evaluate whether same results can be obtained with a low-fibre diet extended to the day before, which is better accepted.

We were unable to show substantial advantages in terms of tolerability and acceptability for this new low volume bowel preparation which requires to drink only 2-L of bowel preparation solution: this was probably due to the low sensitivity of our measuring tools. We have shown that both PEG-CS and PEG bowel preparation can be used to substantially shorten the runway time, that is the time between the end of bowel preparation and colonoscopy.

A limit of this study was to evaluate only bowel preparation for late morning colonoscopy, *i.e.*, the period from 10:00-10:30 am and 1:00-1:30 pm. Therefore our results cannot be extrapolated to early morning colonoscopy. Another limit is that we did not randomize patients according to factors such as age, indication to colonoscopy, bowel habits or comorbidities (for instance diabetes) which may influence bowel cleansing. However the two groups were relatively comparable in terms of indications for colonoscopy and comorbidities. Patients with constipation received an additional tablet of bisacodyl. No differences were found in terms of colon cleansing between patients with constipation and those with normal habits. The most common co-morbidity was hypertension (controlled by drug therapy) followed by diabetes, both well balanced between the two groups. No patients had heart failure or renal failure or other conditions which predispose to electrolyte imbalance.

The age (cut-off 60 years) showed a significant association with adenoma detection rate; however this finding was largely expected because patients older than 60 years have a higher prevalence of adenomas.

The most important advantage of the PEG-CS preparation in comparison to the PEG regimen is the lack of any impact on work activity and quality of life the day before. This is important for the clinical practice as today healthy subjects have a full working and free time life and are reluctant to lose their time. A faster and easier bowel preparation method such as PEG-CS plus bisacodyl may increase the adherence to the colonoscopy.

In this study we maintained our current practice method, *i.e.*, 48-h low fibre diet, which is usually well accepted followed by 24-h clear fluid diet which is bothersome for most patients. Considering the high rates of successful bowel cleansing in our study, it is time to reconsider the value of this practice which was introduced long time ago. It is likely that with the improved bowel cleansing regimens which are performed more closely to colonoscopy, a more patient-friendly diet can be adopted. Only the low fibre diet for one day may be sufficient to achieve satisfactory bowel preparation^[25].

In our study bisacodyl was taken at bedtime and the PEG-CS preparation 5 h before the scheduled colonoscopy. Some patients started to take the morning dose as early as 5:00-5:30 am without great inconvenience. Most patients started drinking at 7:00 am to be ready for colonoscopy at 12:00 am. In all patients colonoscopy was performed no later than 3-4 h after finishing bowel preparation. Most colonoscopies were scheduled between 1:00 and 2:00 in patients who started taking PEG-CS at 7:00 am and finishing at 9:00 am.

We are aware that the same day dosing of low-volume PEG (as well as split-dosing) cannot be proposed for early morning colonoscopy (*e.g.*, before 10:00 am).

Our study has also implications for the organisation of Endoscopic Unit. Patients having a long journey to reach the hospital should be scheduled late in the morning or in the afternoon to exploit the advantage of the split or same day bowel preparation. This approach could be proposed for late morning and afternoon colonoscopies, especially within colorectal cancer screening programs, with the aim to increase the compliance to colonoscopy.

A relevant aspect of this study is that the proposed low-volume bowel cleansing regimen had a good acceptability by the patients. The low rate of mild adverse events, the high proportion of patients who drank the whole solution and the willingness to repeat the same modality of bowel preparation, suggest that the same day regimen can be proposed as an attractive alternative to the split high volume PEG. In this context the cooperation of the patient which is influenced positively by the extent and quality of oral and written instructions provided by health professionals and the patient preference for the type of bowel preparation remain important.

However future larger multicenter studies encom-

passing the evaluation of the patient characteristics are warranted to confirm our results and to establish if compliance to colonoscopy could be really increased.

COMMENTS

Background

Bowel preparation is fundamental for high quality colonoscopy. Colon cleansing varies inversely with the time interval between the end of bowel preparation and endoscopic examination. The split-dose preparation has demonstrated to significantly improve the rate of adequate cleansing and patient compliance. The disadvantages are represented by the ingestion of a high volume and the burden for the long bowel preparation.

Research frontiers

Same-day bowel preparations are recommended for afternoon colonoscopy. The low volume bowel preparation may also be used for late morning colonoscopy but no clinical studies are available.

Innovations and breakthroughs

The low volume polyethyleneglycol-citrate-simethicone (PEG-CS) given same-day plus bisacodyl is feasible and as effective as split PEG 4-L. PEG-CS plus bisacodyl may be an attractive option for late morning colonoscopy. It reduces the overall time for bowel preparation with no loss of work time and impact on daily activities the day before the exam.

Applications

PEG-CS plus bisacodyl may represent an attractive option compared to split-dose PEG 4 L for late morning colonoscopy.

Peer review

It is a good manuscript with a concise methodology and clearness of the results. A real difference between both preparations was not found but patient compliance. There seems to be no bias in the results and discussion.

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Diagnostic utility of small-caliber and conventional endoscopes for gastric cancer and analysis of endoscopic false-negative gastric cancers

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Abstract

AIM: To analyze the diagnostic utility of a small-caliber endoscope (SC-E) and clinicopathological features of false-negative gastric cancers (FN-GCs).

METHODS: A total of 21638 esophagogastroduodenoscopy (EGD) gastric cancer (GC) screening examinations were analyzed. Secondary endoscopic examinations ($n = 3352$) were excluded because most secondary examinations tended to be included in the conventional endoscopy (C-E) group. Detection rates of GCs and FN-GCs were compared between SC-E and C-E groups. FN-GC was defined as GC performed with EGD within the past 3 years without GC detection. Macroscopic types, histopathological characteristics and

locations of FN-GCs were compared with firstly found-gastric cancers (FF-GCs) in detail.

RESULTS: SC-E cases ($n = 6657$) and C-E cases ($n = 11644$), a total of 18301 cases, were analyzed. GCs were detected in 16 (0.24%) SC-E cases and 40 C-E (0.34%) cases ($P = 0.23$) and there were 4 FN-GCs (0.06%) in SC-E and 13 (0.11%) in C-E ($P = 0.27$), with no significant difference. FN-GCs/GCs ratio between SC-E and C-E groups was not significantly different ($P = 0.75$). The comparison of endoscopic macroscopic types of FN-GCs tended to be a less advanced type ($P = 0.02$). Histopathologically, 70.6% of FN-GCs were differentiated and 29.4% undifferentiated type. On the other hand, 43.0% of FF-GCs were differentiated and 53.8% undifferentiated type, so FN-GCs tended to be more differentiated type ($P = 0.048$).

CONCLUSION: The diagnostic utility of SC-E for the detection of GCs and FN-GCs was not inferior to that of C-E. Careful observation for superficially depressed type lesions in the upper lesser curvature region is needed to decrease FN-GCs.

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Key words: Gastric cancer; Small-caliber endoscope; False-negative gastric cancer

Core tip: This is the first study to reveal that the screening performance for gastric cancers by a small caliber-endoscope might not be inferior to that of conventional endoscope. Superficially depressed type lesions in the upper lesser curvature region should be carefully observed in gastric cancer screening in order to decrease false-negative gastric cancers.

Kataoka H, Mizuno K, Hayashi N, Tanaka M, Nishiwaki H, Ebi

M, Mizoshita T, Mori Y, Kubota E, Tanida S, Kamiya T, Joh T. Diagnostic utility of small-caliber and conventional endoscopes for gastric cancer and analysis of endoscopic false-negative gastric cancers. *World J Gastrointest Endosc* 2013; 5(9): 440-445 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/440.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.440>

INTRODUCTION

Currently, transnasal esophagogastroduodenoscopy (EGD) using a small-caliber endoscope (SC-E) is being widely carried out as a screening examination for gastric cancer (GC) because EGD with an SC-E appears to be less stressful to the cardiovascular system and has good patient tolerance in several comparative analyses^[1-5]. However, the diagnostic accuracy of SC-E has been thought to be low because of several weak points, including low resolution, low brightness and poor operational performance^[6,7].

In this study, the diagnostic utility of SC-E and conventional endoscopy (C-E) in GC screening health checkups were compared from the viewpoints of GC detection rates and false-negative gastric cancers (FN-GCs). Furthermore, the clinicopathological features of FN-GCs were analyzed.

MATERIALS AND METHODS

A total of 21638 patients who underwent EGD for screening of the upper gastrointestinal tract in Nagoya Toei Clinic from 2003 to 2011 were investigated. The SC-E group included 6831 subjects (4959 men, 1872 women; mean \pm SD age 50.98 ± 9.89 years) and the C-E group included 14807 subjects (11000 men, 3807 women; age 52.05 ± 10.44 years), as shown in Table 1. EGD examinations by SC-E were performed using an EG 530N or EG530NW (Fuji Film, Tokyo, Japan), whereas EGD examinations by C-E were performed using an XQ240 and H260 (Olympus, Tokyo, Japan). The outer diameters of these scopes were 5.9 mm for the EG530N and EG530NW, 9.0 mm for the XQ240, and 9.8 mm for the H260. Viewing angles were 120° for the EG530N and 140° for the EG530NW, XQ240 and H260.

FN-GC was defined as GC that was missed on EGD examination within the past 3 years. FN-GCs were categorized into 4 groups by analyzing the previous EGD images of FN-GC patients: (1) undetected error; (2) incomplete visualization; (3) misdiagnosis as a benign lesion; or (4) no findings.

Statistical analysis

Descriptive statistics and simple analyses were carried out using the statistical package R version 2.4.1 (www.r-project.org). In the comparisons between any two subject groups, Student's unpaired *t* test was used for continuous variables and the χ^2 test and Fisher's exact test were used to compare categorical variables. Analysis

Table 1 Patient demographics

	SC-E	C-E
Endoscopic examinations	6831	14807
Male/female	4959/1872	11000/3807 ^b
Age (yr) mean \pm SD	50.98 ± 9.89	52.05 ± 10.44^b

^b*P* < 0.01 vs small caliber-endoscope (SC-E). C-E: Conventional-endoscope.

Table 2 The detection rate of gastric cancer and false negative-gastric cancer *n* (%)

Scope examinations	Detected GCs	Detected FN-GCs	FN-GCs/GCs
SC-E (<i>n</i> = 6831)	16 (0.23)	4 (0.059)	25.0%
C-E (<i>n</i> = 14807)	94 (0.63)	13 (0.088)	13.8%
<i>P</i> value	0.01	0.48	0.27
SC-E ¹ (<i>n</i> = 6657)	16 (0.24)	4 (0.060)	25.0%
C-E ¹ (<i>n</i> = 11644)	40 (0.34)	13 (0.112)	32.5%
<i>P</i> value	0.23	0.27	0.75

¹3352 secondary endoscopic examinations that including 54 gastric cancer cases were excluded from a total 21638 endoscopic examinations because most of secondary endoscopic examinations tended to be performed by conventional-endoscope (C-E). GC: Gastric cancer; FN-GC: False negative-gastric cancer; SC-E: Small caliber-endoscope.

of variance was performed for comparisons among multiple groups. In all analyses, *P* values < 0.05 were considered significant.

RESULTS

As shown in Table 1, the SC-E group included 6831 subjects (4959 men, 1872 women; age 50.98 ± 9.89 years) and the C-E group included 14807 subjects (11000 men, 3807 women; age 52.05 ± 10.44 years); the SC-E group included more females and younger patients than the C-E group (*P* < 0.01).

GC and FN-GC detection rates

The GC detection rate was significantly lower by SC-E than by C-E (*P* = 0.01). However, the FN-GC detection rate and the ratio of FN-GCs/GCs were not significantly different between the two groups (*P* = 0.48, *P* = 0.27) (Table 2). We found that some of these patients had some abnormalities in the stomach checked by X-ray barium studies before EGD examination. Furthermore, the majority of secondary endoscopic checks were included in the C-E group. A total of 3352 patients underwent EGD as secondary checks; these patients were excluded and the detection rates were re-calculated. As shown in Table 2, the SC-E group included 6657 subjects and the C-E group included 11644 subjects; 16 GCs were detected in the SC-E group (detection rate, 0.24%) and 40 GCs were detected in the C-E group (detection rate, 0.34%). There were no significant differences in the GC detection rates, FN-GC detection rates and FN-GCs/GCs ratios between the two groups. Thus, the GC and FN-GC detection rates were not different between SC-E and C-E.

Table 3 Clinical characteristics of 17 patients of false negative-gastric cancer

Characteristics	Value
SC-E/C-E	4/13
Age (mean \pm SD)	57.6 \pm 9.4
Male/female	14/3
Duration ¹ (mean \pm SD)	14.6 \pm 8.2 (M) (m: 13.2 \pm 3.0, sm: 14.5 \pm 2.5)
Depth of invasion	m: 9, sm: 6, mp: 0, unknown: 2
Macroscopical types	Elevated type: 5, depressed type: 12
Histopathological types	tub1: 8, tub2: 4, por/sig: 5
Treatment	Endoscopic (EMR, ESD): 6 Surgical: 9 Unknown: 2
The previous endoscopic findings	Undetected error: 3 Incomplete visualization: 6 Misdiagnosis as benign: 7 No findings: 1

¹From the last time endoscopy to the day of cancer detected by endoscopy. SC-E: Small caliber-endoscope; C-E: Conventional-endoscope; m: Mucosal layer; sm: Submucosal layer; mp: Muscularis propria; tub1: Well differentiated tubular adenocarcinoma; tub2: Moderately differentiated adenocarcinoma; por: Poorly differentiated adenocarcinoma; sig: Signet ring cell carcinoma; EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

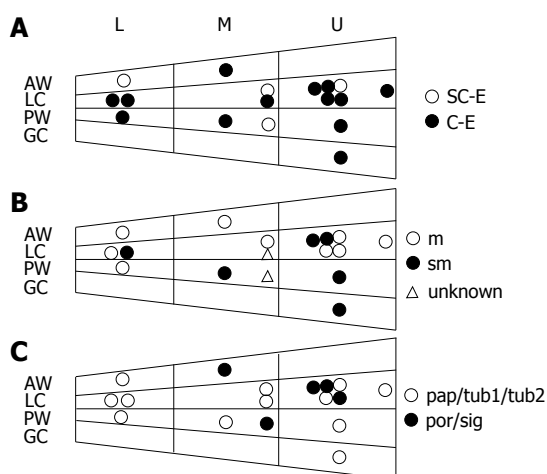


Figure 1 Locations of 17 false-negative gastric cancers. A: Open circles indicate the false-negative gastric cancer (FN-GC) lesions found by small-caliber endoscope (SC-E), and closed circles indicate the FN-GCs found by conventional endoscopy (C-E); B: Open circles indicate FN-GC lesions that invaded to the mucosal layer and closed circles indicate the FN-GC lesions that invaded to the submucosal layer. Open triangles indicate lesions with unknown depth; C: Open circles indicate the FN-GC lesions of pathologically differentiated types (papillary adenocarcinoma, well or moderately differentiated adenocarcinoma) and closed circles indicate the FN-GC lesions of pathologically diffuse types (poorly differentiated adenocarcinoma or signet ring cell carcinoma). m: Mucosal layer; sm: Submucosal layer; pap: Papillary adenocarcinoma; tub1: Well differentiated tubular adenocarcinoma; tub2: Moderately differentiated adenocarcinoma; por: Poorly differentiated adenocarcinoma; sig: Signet ring cell carcinoma; AW: Anterior wall; PW: Posterior wall; LC: Lesser curvature; GC: Greater curvature; U: Upper; M: Middle; L: Lower.

Clinical characteristics of FN-GCs

As a next step, 17 FN-GCs were analyzed in detail (Table 3). Four FN-GCs were detected with SC-E and 13 with C-E, but there were no significant differences between

Table 4 The comparison of endoscopic macroscopic types between false negative-gastric cancer and firstly found-gastric cancer

	FN-GC	FF-GC
Types		
I	0 (0)	7 (7.5)
II a	5 (29.4)	12 (12.9)
II b	1 (5.9)	0 (0)
II c	9 (52.9)	33 (35.5)
III	2 (11.8)	16 (17.2)
Advanced	0 (0)	20 (21.5) ^a
Unknown	0 (0)	5 (5.4)

^a $P < 0.05$. FN-GC: False negative-gastric cancer; FF-GC: Firstly found-gastric cancer.

the two groups in FN-GC detection rate and the ratio of FN-GCs/GCs, as shown in Table 2. The mean duration from the previous endoscopic examination to the day of cancer detection by EGD examination was 14.6 \pm 8.2 months (mean \pm SD). There were no significant differences in the mean duration between intramucosal GC cases (13.2 \pm 3.0) and GC with submucosal layer cases (14.5 \pm 2.5). Nine cases were intramucosal FN-GCs and 6 cases were FN-GCs with submucosal layer invasion, but there were no FN-GCs that invaded to the muscularis propria or deeper. Six cases were treated endoscopically (endoscopic mucosal resection and endoscopic submucosal dissection) and 9 cases were treated surgically. The previous endoscopic images were analyzed minutely and 3 cases were considered an “undetected error”, which means that the endoscopist missed the cancer lesion at the previous examination and the cancer lesions could be seen in the endoscopic images of previous EGD examinations. Six cases were considered “incomplete visualization”, which means that no images of the location of the cancer had been taken at the last examination or the image quality of the cancer location was low. Seven cases were considered “misdiagnosis as benign”. The endoscopic specimens of 7 cases were all re-checked by a pathologist and they were reconfirmed as benign. Thus, in the 7 “misdiagnosis as benign” cases, techniques of biopsy under endoscopy seemed to have been the major problem. There was only one case that was considered to be “no findings”. It was confirmed that there was no lesion in the previous clear image of the cancer location.

The locations of 17 FN-GC cases are shown in Figure 1. FN-GCs tended to be located in the upper (U) lesser curvature (LC) region. As shown in the lower panel (Figure 1C), GCs of differentiated type (pap/tub1/tub2) tended to be localized in the lower (L) region.

Finally, the macroscopic types of GCs were compared between the FN-GC group and the FF-GC group. As shown in Table 4, FF-GCs included more advanced type GCs ($P < 0.05$). In the early GCs, FN-GCs tended to include more II c types (superficially depressed types) than FF-GCs, but the difference was not significant.

Table 5 The comparison of histopathological types between false negative-gastric cancer and firstly found-gastric cancer

	Pap/Tub1/Tub2	Por/Sig	Unknown	Total
FN-GC	12 (70.6%)	5 (29.4%)	0 (0%)	17
FF-GC	40 (43.0%)	50 (53.8%)	3 (3.2%)	93

False negative-gastric (FN-GC) false negative-gastric cancer; Firstly found-gastric cancer (FF-GC) firstly found-gastric cancer. $P = 0.048$.

Histopathological characteristics of FN-GCs

Finally, the histopathological features (pap/tub1/tub2, por/sig, unknown) of FN-GCs [12 (70.6%), 5 (29.4%), 0 (0%)] and FF-GCs [40 (43.0%), 50 (53.8%), 3 (3.2%)] were compared; FN-GCs included significantly more differentiated type GCs (pap/tub1/tub2) than FF-GCs ($P = 0.048$) (Table 5).

DISCUSSION

GC is ranked as the second leading cause of global cancer mortality and the fourth most common cancer worldwide^[8,9]. Japan is known as one of the countries of highest incidence and mortality of GC; approximately 110000 people develop GC each year, with 65000 estimated deaths. Detecting mucosal GC in asymptomatic people by high quality endoscopic GC screening is important for decreasing mortality of GC.

This is the first study to compare the detection rates of GCs and FN-GCs between an SC-E group and a C-E group in GC endoscopic screening. For GC screening, radiographic screening using upper gastrointestinal series has been performed nationwide in Japan, but the GC screening rate has gradually decreased due to a lack of human resources. Thus, several new methods are anticipated as alternative approaches for GC screening. Prescreening of a high-risk group for GC by serological testing for pepsinogen and *Helicobacter pylori* (*H. pylori*) antibody is one of the alternative methods, especially for the population at high risk of GCs^[10-12]. Patients categorized as high-risk for GC are considered to be the candidates for endoscopic screening. Recently, although problems remain related to the confirmation of the validity of the evidence, several studies reported that endoscopic screening of the upper gastrointestinal tract significantly decreased the GC mortality rate^[13,14].

Transnasal EGD with SC-E has been used more for GC screening because the tolerability, acceptability and safety are better for SC-E than for C-E^[15,16]. However, the screening performance of SC-E for GC may be inferior to that of C-E due to low resolution, low luminous intensity and the narrow angle of view of SC-E.

In the present study, there were no significant differences in screening performance for GCs and FN-GCs between SC-E and C-E. Similar to the present results, some previous studies have reported that the diagnostic accuracy of SC-E is almost equivalent to that of C-E for the detection of upper gastrointestinal tract lesions, in-

cluding GCs^[17-21]. The present study has some weakness because it was a non-randomized retrospective study and the selection of endoscope (SC-E or C-E) was decided by patient's choice. Further randomized controlled studies need to be carried out to achieve precise conclusions. Nakata *et al*^[22] reported that the diagnostic performance of SC-E was inferior to that of C-E for GC screening, particularly in subjects with non-atrophic gastritis. In our study, the atrophic stages of the gastric mucosa were not significantly different between the FN-GC group and the FF-GC group. Between FN-GCs found by SC-E and FN-GCs found by C-E, there was no significant difference of gastric mucosal atrophic stages (data not shown).

Yoshida *et al*^[15] reported no significant differences in the detection of early GC and adenoma between SC-E and C-E, but they pointed out that GCs might be overlooked by SC-E when performed by less experienced endoscopists. In the present study, almost all EGD examinations were performed by experienced endoscopists (over 10 years experience) and there was no laterality of endoscopists in experience who performed previous EGD examinations of FN-GCs.

Hayashi *et al*^[23] analyzed the detection rates of early GCs and reported that SC-E was less efficient in screening for GCs located in the upper third of the stomach (U region) due to the narrower field of view and low luminous intensity. As shown in Figure 1A, although more FN-GC lesions tended to exist in the U region compared with the middle (M) and/or L regions, there was no laterality of FN-GCs in location detected by SC-E.

A literature search identified no previous studies that compared the detection rates of FN-GCs between an SC-E group and a C-E group. With respect to the ratio of FN-GCs/FF-GCs, Yoshimura *et al*^[24] reported a ratio of 28.2% and Yoshikawa *et al*^[25] reported 31.6% with SC-E; these are similar to the present false-negative rates (25.0% with SC-E and 32.5% with C-E). The clinicopathological features of FN-GCs detected by SC-E (4 cases) and FN-GCs by C-E (13 cases) were also investigated, but there were no significant differences between the two groups. However, in the previous endoscopic findings of FN-GC cases, 75% (3 out of 4 cases) of FN-GCs with SC-E was due to "incomplete visualization". This finding may imply that improvement of the image quality of SC-E is necessary to achieve greater accuracy of GC screening by SC-E. A future study with a larger number of patients should be performed to analyze FN-GCs with SC-E in endoscopic screening.

The necessity of annual GC endoscopic screening is debatable from the viewpoint of not only mortality and morbidity rates but also cost-benefit. Chung *et al*^[26] reported that endoscopic resection was performed more frequently in the annual screening group than in the biennial group (56.9% *vs* 33.3%; $P = 0.02$) in an endoscopic screening study of 58849 subjects. As shown in Table 3 of the clinicopathological analyses of FN-GCs, the mean duration from the previous endoscopy to the day of cancer detection by endoscopy was 14.6 ± 8.2 mo and that of FN-GCs with submucosal invasion was 1.3 mo longer

than that of FN-GCs *in situ*. These findings suggest that annual GC endoscopic screening is beneficial for decreasing the mortality rate of GCs by identifying FN-GCs in the early stages.

Finally, the histopathological analyses of FN-GCs revealed that differentiated type GC was significantly more common in the FN-GC group than in the FF-GC group. Yoshikawa *et al.*^[25] also reported that 66.6% of FN-GCs with SC-E were differentiated type GC. At this point, there is no apparent explanation for this result, but we should pay more attention to differentiated type GCs that are macroscopically superficial depressed type.

In conclusion, this is the first study to have compared the detection rates of FN-GCs and GCs between SC-E and C-E. The screening performance for GCs by SC-E might not be inferior to that of C-E. Superficially depressed type lesions in the upper lesser curvature region should be carefully observed in GC screening in order to decrease FN-GCs. In the near future, high-performance SC-E will surely be developed and used as the main endoscopy method for GC screening, with better tolerability, acceptability and safety than C-E.

COMMENTS

Background

Transnasal esophagogastroduodenoscopy (EGD) using a small-caliber endoscope (SC-E) is being widely carried out as a screening examination for gastric cancer (GC) because EGD with an SC-E appears to be less stressful to the cardiovascular system and has good patient tolerance in several comparative analyses. However, the diagnostic accuracy of SC-E has been thought to be low because of several weak points, including low resolution, low brightness and poor operational performance.

Research frontiers

In this study, the diagnostic utility of SC-E and conventional endoscopy (C-E) in GC screening health checkups were compared from the viewpoints of GC detection rates and false-negative gastric cancers (FN-GCs). Furthermore, the clinicopathological features of FN-GCs were analyzed.

Innovations and breakthroughs

The results have clearly demonstrated that the screening performance for GCs by SC-E might not be inferior to that of C-E. FN-GCs tended to be located in the upper lesser curvature region, more differentiated type, more superficial depressed type and less advanced type.

Applications

The diagnostic utility of SC-E for the detection of GCs and FN-GCs was not inferior to that of C-E. Careful observation for superficially depressed type lesions in the upper lesser curvature region is needed to decrease FN-GCs.

Peer review

This is a large monocentric retrospective study showing no difference for screening and diagnosis of gastric cancer between small-caliber and conventional endoscopes by expert endoscopists. Conclusions are nevertheless of great interest.

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Extremely rare case of primary esophageal mucous associated lymphoid tissue lymphoma

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Abstract

SJ is a 37-year-old male who presented with one year history of dysphagia, odynophagia and 15 pounds weight loss. He underwent endoscopic evaluation which showed mid esophageal ulcers. It was thought that the cause of the ulcer was the multivitamins and the patient was asked to stop them. Furthermore Esomeprazole therapy was also initiated. Patient's symptoms persisted but he did not seek any medical attention until about one year later. Meanwhile the patient reported additional 15 pounds of weight loss. We repeated upper endoscopy again which showed evidence of two chronic non bleeding irregular friable ulcerations seen in the mid esophagus, 31 cm from the incisors. Biopsies and frozen section were taken and sent for assessment to the Pathology lab. Immunoperoxidase studies on frozen sections showed the presence of IgM and for

most plasma cells IgG. The microscopic and histologic findings were consistent with mucous associated lymphoid tissue lymphoma with plasmocytic differentiation. Computed tomographic scan done showed no evidence of spread to adjacent structures. The patient was referred to oncology and several cycles of radiation and Rituximab therapy were initiated which cured the disease. Subsequent endoscopies with blind biopsies were done which were negative for any neoplastic process.

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Key words: Lymphoma; Mucous associated lymphoid tissue; Esophagus

Core tip: This is a case of a 37-year-old gentleman presenting with chronic esophageal ulcers. Endoscopic biopsy samples were taken. Immunohistochemistry and hematoxylin and eosin staining of the biopsy samples were consistent with mucous associated lymphoid tissue (MALT) lymphoma. There was no sign of disease process in the stomach, and radiological studies revealed no evidence of metastasis. In consideration of these findings a diagnosis of primary esophageal MALT lymphoma was made, which is an extremely rare occurrence. On the basis of our experiences we recommend keeping primary esophageal MALT lymphoma in the differential diagnosis of chronic esophageal ulcers that are resistant to conservative management.

Malik AO, Baig Z, Ahmed A, Qureshi N, Malik FN. Extremely rare case of primary esophageal mucous associated lymphoid tissue lymphoma. *World J Gastrointest Endosc* 2013; 5(9): 446-449 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/446.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.446>

INTRODUCTION

We present a very rare case of primary esophageal B cell mucous associated lymphoid tissue (MALT) lymphoma.



Figure 1 Photograph of esophagogastroduodenoscopy showing two ulcers at approximately 8 o'clock and 5 o'clock positions.

Gastrointestinal (GI) lymphoma is an uncommon disease but is the most frequently occurring extra nodal lymphoma and is almost exclusively Non-Hodgkin's type^[1]. Esophageal lymphomas occur most often secondary to cervical and mediastinal lymph node invasion or contiguous spread from gastric lymphoma^[1]. Primary esophageal lymphomas is a very rare condition accounting for less than one percent of GI lymphomas, with B cell lymphomas being the most common histological subtype^[2]. The predominant presentation is that of sub mucosal infiltration but the tumor can also manifest as a polypoid mass into the lumen, ulceration or nodularity^[3].

We report a very rare case of primary esophageal MALT lymphoma in a middle aged patient.

CASE REPORT

Clinical presentation

The patient is a 37-year-old Indian gentleman, who presented with complains of difficulty swallowing, which started about a year ago. Shortly thereafter he started experiencing pain with swallowing as well. He was treated for three months with Esomeprazole and had resolution of his symptoms. However his symptoms recurred 6 mo later. An endoscopy was performed, and biopsies were taken. These slides were sent to be reviewed by pathology which indicated focally dense lymphoplasmacytic infiltrate with Kappa light chain excess, most consistent with a B cell MALT lymphoma with plasmacytic differentiation.

Previous medical history was significant for hypertension and recurrent bouts of sinusitis. Surgical history was significant for endoscopic surgery for sinusitis and appendectomy done several years ago. The patient had recently travelled to Pakistan, and denied any substance abuse. Medications included nifedipine (calcium channel blocker) and Losartan (angiotensin receptor blocker) for hypertension. Furthermore the patient's father had died from Non-Hodgkin's lymphoma of unknown histologic subtype. The rest of his immediate family members were alive and healthy.

Endoscopic and microscopic findings

The endoscopy showed two superficial serpiginous fri-

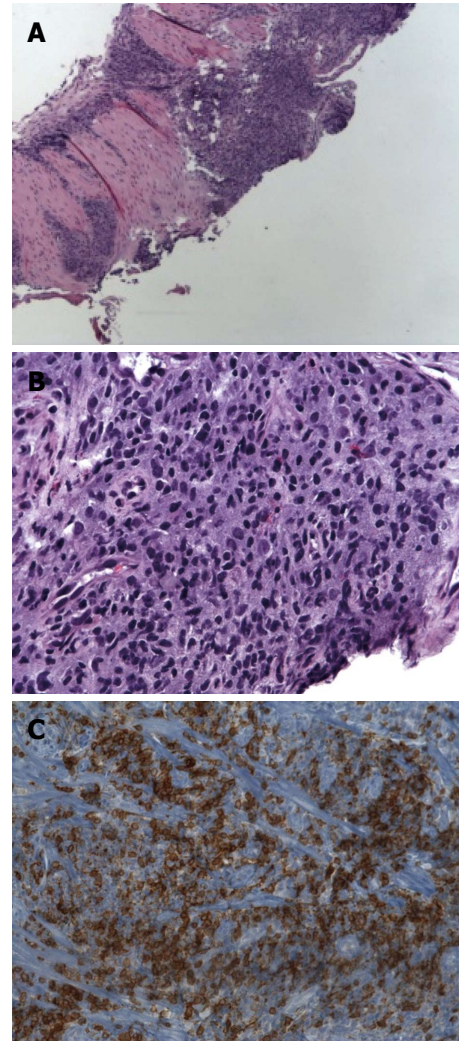


Figure 2 Photographs from the hematoxylin and eosin stain, and immunohistochemistry staining, of the biopsy samples. A: Photomicrograph shows atypical infiltrate under the mucosa of the esophagus $\times 40$ original magnification hematoxylin and eosin (HE) stain; B: The tumor cells are medium sized lymphocytes and have a round or slightly constricted nuclei, $\times 400$ original magnification, HE stain; C: Immunohistochemistry: CD20, CD3, CD43, Kappa and Lambda.

able chronic ulcers visualized 31 cm and 33 cm from the incisors, and measuring 1.2 cm and 1.5 cm respectively. Multiple core biopsies were taken from the affected region. The two ulcers seemed to be merged together with evidence of cicatrix formation between them. The gastro esophageal junction was at the level of 40 cm from the gums. The stomach, pylorus and the duodenum appeared to be normal. The endoscopic photograph of the ulcers is shown in Figure 1.

Hematoxylin and eosin (HE) staining of the cold biopsies, showed fragments of squamous epithelium with separate fragments of ulcer bed including acute and chronic inflammation with associated markedly atypical lymphoid infiltration. These findings were concerning for underlying lymphoma with superimposed ulcer bed. Photographs from the HE, and immunohistochemistry staining, of the biopsy samples are shown in Figure 2.

Additional immunoperoxidase staining showed small

aggregates of CD20 positive cells and a small number of CD3 positive cells within the nodules. Stains for immunoglobulin kappa and lambda light chains showed only very rare plasma cells positive for lambda, with the majority being positive for kappa. These microscopic and histological finding were most consistent with MALT lymphoma with plasmocytic differentiation.

A bone marrow biopsy and flowcytometry were also done, which were negative for any disease process.

Radiology findings

Computed tomography (CT) scan showed mild thickening of the mid esophagus, most likely suggestive of a neoplasm. Except for an incidental finding of an 8 mm parenchymal density within the posteromedial right lung base, there were no other positive findings. A thoracic esophagram was also performed which showed adequate primary contractions observed fluoroscopically. The contrast was noted to flow freely into the stomach.

An endoscopic ultrasound was also done which showed diffuse obliteration of normal echo architecture of esophageal layers 1-3. No mediastinal, celiac axis or peripancreatic lymphadenopathy was observed.

Diagnosis, treatment and follow up

The endoscopic findings were suggestive of esophageal ulcers with possible eosinophilic esophagitis. However Immunohistochemistry staining of the biopsy samples confirmed the diagnosis of MALT lymphoma and excluded eosinophilic esophagitis from the list of differentials. As there was no evidence of disease in the stomach on endoscopy, and in consideration of immunohistochemistry and HE staining a diagnosis of Primary Esophageal MALT lymphoma was made. EUS findings were in contrast to the usual presentation of esophageal lymphoma, that is a hypo echoic lesion^[4]. A possible reason for this could be that the MALT lymphoma was diagnosed at an early stage.

On the basis of radiological, bone marrow biopsy and microscopic findings the tumor was staged as 1A. The patient received a 4 cycles of 36 Gy external beam radiotherapy. After radiation therapy he received four doses of Rituximab, as consolidative treatment.

After the treatment complete remission was achieved. The patient is seen at our institute regularly. Follow up endoscopies every 6 mo over last three years with targeted biopsies at the site of previous ulcers as evidenced by cicatrix formation have been negative.

DISCUSSION

Lymphoid tissue neoplasms compromise a diverse yet closely related group of neoplasms, including hodgkin's lymphoma, non-hodgkin's lymphoma, multiple myeloma, MALT lymphomas and several other types.^[5] MALT lymphomas can arise in various anatomic locations where lymphocytes are usually absent due to acquisition of MALT, including the gut, lung, thyroid, sali-

vary glands and liver^[6]. Primary esophageal lymphoma is extremely rare^[7]. Esophageal involvement by lymphoma is usually secondary to local spread from the stomach or the mediastinum^[8]. Very few cases of primary esophageal lymphomas were reported in literature^[6-11]. There are many morphological variants with most of the common being large B cell type and Non-Hodgkin's lymphoma^[9]. We report a case of primary esophageal B cell MALT lymphoma in an immune competent patient. Only a few other cases of this particular morphological type of primary esophageal lymphoma have been reported in literature^[7,12].

Patients with acquired immunodeficiency syndrome (AIDS) are at an increased risk of developing malignant lymphomas, with the gastro intestinal tract being the most common site^[13]. Chronic immunosuppression has also been suggested to be linked with the development of primary esophageal lymphomas^[10]. MALT lymphomas of the stomach have closely been linked to Helicobacter Pylori infection, however no such relationship has been proven for primary esophageal MALT lymphoma^[14].

Esophageal cancer generally presents with symptoms of dysphagia and weight loss^[15]. There has been a trend of increased incidence of esophageal cancers in population less than 55 years^[15]. In the case that we report the patient presented with classical sign and symptoms but the rare nature of the histological classification of the disease made the diagnosis difficult to make.

In summation this case illustrates an instance of biopsy proven primary esophageal MALT lymphoma in a 37 years old man, with history of dysphagia, odynophagia and weight loss. The malignancy presented as persistent ulcers seen in mid esophagus, 31 cm from the incisors. Radiographic studies including CT scanning done at the time revealed localized disease without any spread to surrounding structures. The patient was referred to oncology where he received several cycles of radiation therapy. On subsequent follow ups the patient was found to be cured of the disease with normal endoscopic findings. Blind biopsy samples were taken from the esophagus which proved to be negative for any neoplastic process.

On the basis of our experience we suggest MALT lymphoma in the differential diagnosis of chronic esophageal ulcers that are resistant to conservative therapy.

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Pseudoachalasia: A peculiar case report and review of the literature

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Abstract

Pseudoachalasia is a rare secondary achalasia, which accounts for only a small subgroup of patients. We describe a 77-year-old woman with recent onset of dysphagia and typical esophageal manometric findings of achalasia. Moreover, esophageal manometric findings of vascular compression at 36 cm from the nose were associated with dysphagia. An upper endoscopy showed the absence of lesions both in the esophagus and gastro-esophageal junction, whilst a 15-mm ulcer on the gastric angulus was detected. The gastric ulcer resulted in being a diffuse signet ring cell carcinoma at histology, suggesting pseudoachalasia. An abdominal computed tomography scan showed an irregular concentric thickening of the gastro-esophageal junction

wall extending for 7 cm and a dilated ascending thoracic aorta with no presence of the inferior vena cava, with an enlarged azygos as the source of vascular compression of esophagus. Moreover, cardia involvement from diffuse signet ring cell carcinoma of the gastric angulus was also recognized as the cause of dysphagia. The cancer was not suitable for a surgical approach in an old patient with cardiovascular comorbidities and support therapy was started. In our ambulatory series, pseudoachalasia was eventually diagnosed in 4.7% of 234 consecutive patients with esophageal manometric finding suggestive of achalasia. We also reviewed cases in the literature and aimed to evaluate the reported causes of pseudoachalasia.

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Key words: Pseudoachalasia; Achalasia; Esophageal vascular compression; Thoracic aorta; Azygos vein

Core tip: Typical esophageal dysmotility can be observed in pseudoachalasia, a secondary form of achalasia mostly due to cancer or even benign tumors, post-operative complications or paraneoplastic syndromes. Dysphagia is frequently observed in subjects with pseudoachalasia. We describe a peculiar case where dysphagia could be due to a vascular compression of the esophagus rather than involvement of the esophagus at the gastro-esophageal junction from gastric neoplasia. The less invasive therapeutic option should be proposed in an old patient. The reviews of our cases of pseudoachalasia and the literature are included.

Campo SMA, Zullo A, Scandavini CM, Frezza B, Cerro P, Balducci G. Pseudoachalasia: A peculiar case report and review of the literature. *World J Gastrointest Endosc* 2013; 5(9): 450-454 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/450.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.450>

INTRODUCTION

Pseudoachalasia is a secondary form of achalasia which accounts for up to 4% of patients with achalasia-like syndrome, with symptoms, radiographic and esophageal manometric findings that mimic primary achalasia^[1]. It was first recognized by Ogilvie^[2] in 1947 as a form of achalasia due to involvement of the cardia region from gastric adenocarcinoma. Achalasia is a rare esophageal motor disorder with an estimated annual incidence of 1 per 100000 individuals. The pathophysiology of achalasia consists of loss of inhibitory neurons of the myenteric plexus in the esophageal wall^[3-7]. Likely, it is believed to be the result of a slowly progressive process affecting the neural control of lower esophageal sphincter (LES) relaxation, with consequent symptoms, dysphagia, regurgitation, chest pain and weight loss, indistinguishable from those in pseudoachalasia. Patients with idiopathic achalasia or pseudoachalasia are not rarely misdiagnosed as having other diseases, such as gastro-esophageal reflux or stricture^[8-11]. So far, Chaga's disease, intestinal pseudo-obstruction, amyloidosis, surgery (post vagotomy, post fundoplication), pancreatic pseudocyst and cardia cancer have been identified as types of pseudoachalasia^[12-15]. We describe a peculiar case of pseudoachalasia and review data reported in literature.

CASE REPORT

A 77-year-old woman, with previous acute myocardial infarction, was suffering with hypertension and mild depression for which she was taking angiotensin converting enzyme inhibitor, serum serotonin reuptake inhibitor and low-dose aspirin. Because of swallowing difficulties of solids and liquids for the last 3 mo, with recent recurrent vomiting episodes and a 9-kg weight loss, she underwent a barium study which showed an enlarged esophagus, with a characteristic tapered narrowing of the lower end, producing a "rat tail" appearance. However, an upper endoscopy showed an absence of lesions, both in the esophagus and gastro-esophageal junction, whilst a 15-mm ulcer on the gastric angulus was detected. While waiting for histological assessment of the gastric ulcer, a conventional esophageal manometric study was performed to rule out achalasia.

Esophageal manometry was done with a 8-lumen pneumo hydraulically infused catheter using external transducers with an ambulatory stationary recording system (Mui Scientific, Ontario, Canada), as previously described^[16]. Four distal radially oriented leads were used to identify and measure LES pressure by the use of the station withdrawal method. Peristalsis was considered absent if both extrapolated onsets and the peaks of waves at 5 cm, 10 cm and 15 cm above the LES after swallow of 5 mL water were not in sequence, *i.e.*, simultaneous contractions. The tracing was also examined for evidence of vascular compression, which may be diagnosed when a localized area of elevated intra-esophageal resting pressure of at least 4 mmHg with superimposed

cyclic pressure spikes with a frequency of 60-100/min is observed^[17]. This segment of vascular compression was also assessed for evidence of relaxation to resting intra-esophageal pressure in response to wet swallows.

In detail, manometric findings were typical of achalasia with LES pressure of 38 mmHg (range of normal values between 10 mmHg and 30 mmHg), decreased LES relaxation and the absence of peristalsis with simultaneous contractions in the esophageal body. Moreover, elevated intra-esophageal resting pressure of 22 mmHg at 36 cm from the nose with superimposed cyclic pressure spikes with a frequency of 88/min was registered (Figure 1). Absence of relaxation in response to swallows on manometric tracing with evidence of vascular compression of the esophagus was found in our patient and considered to be the cause of dysphagia^[17]. The gastric ulcer resulted in being a diffuse signet ring cell carcinoma at histology and a computed tomography (CT) scan disclosed a dilated ascending thoracic aorta with no presence of the inferior vena cava with azygos continuation (Figure 2) as the source of vascular compression of the esophagus. In addition, an irregular concentric thickening of the gastro-esophageal junction wall extending for 7 cm was documented and recognized as the cause of dysphagia from mechanical obstruction in the more distal esophagus. The tumor mass also involved the left diaphragmatic pillar with the adjacent adipose tissue. Such a feature was consistent with diagnosis of pseudoachalasia, as shown by esophageal manometry^[18]. The cancer was not suitable for a surgical approach in an old patient with cardiovascular comorbidities and support therapy was started.

Our ambulatory series

By reviewing medical records of outpatients with dysphagia referred to our ambulatory series to perform conventional esophageal manometry, we computed 234 consecutive patients with achalasia. Of these, 11 (4.7%) patients were eventually diagnosed with pseudoachalasia due to different causes (Table 1). No manometric findings of esophageal vascular compression were detected in the manometric tracings.

Literature review

A computer-assisted search was performed using PubMed, with the limitation of English language and from June 1968 to June 2012, by using the exploded medical subject heading term "pseudoachalasia". Boolean operators (NOT, AND and OR) also were used in succession to narrow and widen the search. Manual searches of reference lists from identified relevant articles were performed to identify any additional studies that might have been missed. Overall, we identified 155 publications reporting data of 302 patients diagnosed with pseudoachalasia. As shown in Table 2, primary malignancies of the esophagus or esophago-gastric junction accounted for 50% of cases of secondary achalasia. This was followed by secondary malignancies (18%), such as metastases

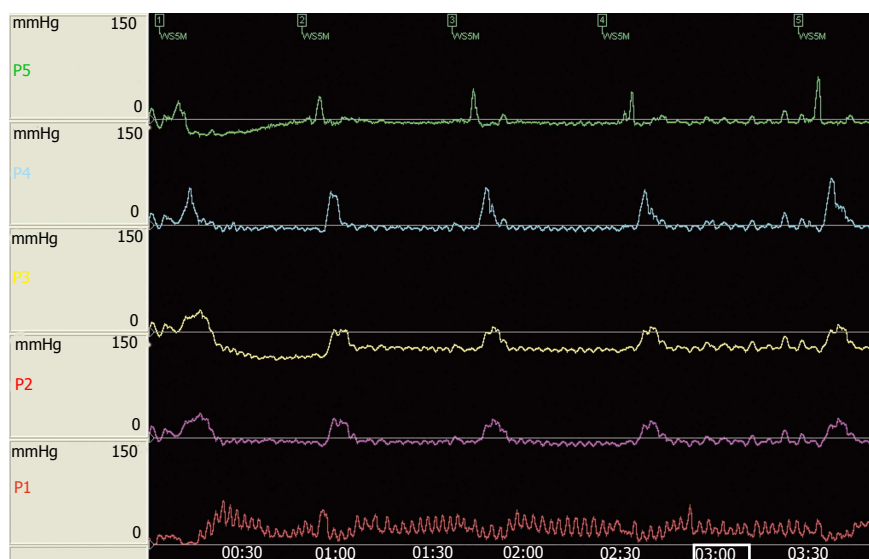


Figure 1 Esophageal manometric findings of elevated intra-esophageal resting pressure > 4 mmHg, localized at 36 cm from the nose, with superimposed cyclic pressure spikes with a frequency of 60-100/min with absence of relaxation in response to swallow (see P1 in the second swallow), typical of esophageal vascular compression.

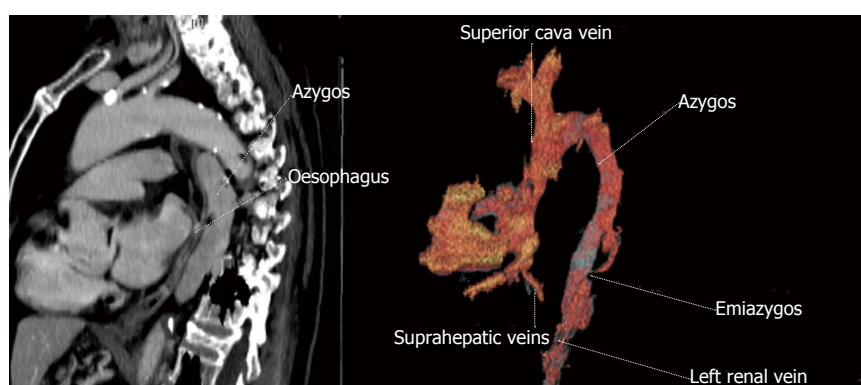


Figure 2 Computed tomography view of a dilated ascending thoracic aorta with no presence of the inferior vena cava with azygos continuation, cause of the vascular compression of esophagus.

Table 1 Clinical features in 11 patients with pseudoachalasia

Age (yr)	Sex	Duration of dysphagia (mo)	Etiology	Treatment
83	M	5	Esophageal adenocarcinoma	Radiotherapy
82	F	3	Cardia adenocarcinoma	Esophageal metal stent
79	M	7	Gastric carcinoma	Supportive therapy
77	F	2	Gastric carcinoma	Radiotherapy
75	M	8	Cardia adenocarcinoma	Chemotherapy
74	M	9	Gastric carcinoma	Surgery
71	M	4	Mediastinal tumor	Radiotherapy
69	F	5	Cardia carcinoma	Chemotherapy
69	M	3	Pancreatic tumor	Chemotherapy
68	M	6	Lung adenocarcinoma	Surgery
52	F	12	Stricture post-fundoplication	Surgery

M: Male; F: Female.

(12%), which primarily originated from lung and breast. Benign causes, including mesenchymal tumors, secondary amyloidosis and peripheral neuropathy accounted for 14% of patients with pseudoachalasia. In 12%, the motor abnormality occurred as a consequence of gastro-esophageal surgery, namely anti-reflux surgery. Rare causes of pseudoachalasia were neurological disorders (3.5%) or paraneoplastic syndromes (2.5%) in the context of small-

Table 2 Causes of pseudoachalasia reported in the literature

Cause	n (%)
Cardia-esophageal adenocarcinoma	156 (50)
Secondary malignancy	59 (19)
Benign lesions	45 (14)
Postoperative complications	35 (11)
Diseases of central nervous system	11 (3.5)
Paraneoplastic syndromes	7 (2.5)

cell carcinoma, bronchial carcinoid, gastric carcinoma and pleural mesothelioma. However, none of these paraneoplastic syndromes was associated with mediastinal or esophageal infiltration by the primary tumor.

DISCUSSION

Pseudoachalasia is a rare disease which accounts for only a small subgroup of patients with dysphagia. Owing to the lack of a large series, there are no reliable epidemiological data on the incidence and prevalence of the disease. In our series, 4.7% of patients who fulfil the manometric criteria of achalasia were eventually diagnosed with a malignant disease, directly or indirectly involving the cardia, or following anti-reflux surgery. Two patterns of tumor involvement have been described^[19]. The most

common type consists of malignant stricture of the cardia which acts as a physical barrier to the passage of food. A less frequent type is strictly related to the malignant submucosal infiltration with secondary impairment of inhibitory neurons of the esophageal myenteric plexus by tumor cells, which let the manometric pattern of achalasia be stable even after any treatment^[20]. Indeed, many malignancies as common causes of pseudoachalasia directly involve the esophageal myenteric plexus by neoplastic cells infiltrating the mucosa at the cardia as the main pathogenetic mechanism^[21-26]. Moreover, neuronal degeneration distant from the primary tumor site with reduction in ganglion cells in the dorsal nucleus of the vagal nerve or in the vagal nerve itself has been also proposed^[27]. This interaction of tumor factors with the esophageal neuronal plexus without a direct infiltration of the esophago-gastric junction, even infrequently, and serological antineuronal nuclear antibody can be detected in these patients, suggesting a paraneoplastic syndrome. Another form of pseudoachalasia occurs following anti-reflux surgery^[14]. Three explanations have been proposed: misdiagnosed idiopathic achalasia with evidence of dysphagia just after surgery, achalasia occasionally developing for the underlying gastro-esophageal reflux, and development of scar tissue and/or an overly tight fundic wrap.

Pseudoachalasia needs to be excluded in old patients (> 60 years) with a short duration of symptoms (< 1 year) and substantial weight loss. It might be difficult to diagnose in an early phase because of the low diagnostic yield of either barium and endoscopy studies, with a false-negative rate up to 25% for endoscopic biopsies to diagnose cancer being reported^[28,29]. Moreover, even although the role of the CT scan has been described as useful, the normal findings of either biopsy or CT scan results should not lead to complete reassurance of a benign etiology^[30]. Endoscopic ultrasound can provide the level of tumor invasion and possible spread to regional lymph nodes, but shows a low accuracy in differentiating mucosal from submucosal lesions at the lower esophagus or gastro-esophageal junction and only repeated studies or even surgical exploration may point to the diagnosis of pseudoachalasia^[31]. Esophageal manometry remains the current gold standard to diagnose esophageal motor disorder, both in idiopathic achalasia and pseudoachalasia, which includes an abnormal relaxation of the LES and absence of peristalsis in the esophageal body^[5].

Since the major mechanism producing pseudoachalasia is undoubtedly a mechanical obstruction of the distal esophagus which causes esophageal dilation, the removal of this obstruction either by surgery and/or chemotherapy and/or radiation can be the goal of treatment in some cases. It often allows the return of normal peristalsis into the esophagus^[32]. However, in many patients with pseudoachalasia, the esophageal motor abnormalities have been found to be stable even after a radical treatment of the neoplasia. Recently, the use of expandable metal stents has been proposed as an additional

therapeutic option in selected cases of pseudoachalasia when palliation is required in patients not suitable for surgery^[33-36].

We report a case of pseudoachalasia in an old woman with recent onset of symptoms with substantial weight loss. Barium study, esophageal manometric findings typical of achalasia and manometric findings of vascular compression at 36 cm from the nose were observed. Abdominal CT scan showed a dilated ascending thoracic aorta with no presence of the inferior vena cava with enlarged azygos. Moreover, an irregular concentric thickening of the gastro-esophageal junction wall from diffuse signet ring cell carcinoma of the gastric angulus was also documented, suggesting secondary achalasia.

Our patient represents a typical case of pseudoachalasia due to a gastric tumor. We considered it peculiar because dysphagia could be due to esophageal vascular compression with an elevated intra-esophageal resting pressure of 22 mmHg at 36 cm from the nose with absence of relaxation to resting intra-esophageal pressure in response to swallows. However, cardia involvement from the tumor mass originating from the gastric angulus, which resulted in being diffuse signet ring cell carcinoma, could also cause dysphagia. Moreover, no cases of pseudoachalasia have been described in the literature associated with esophageal vascular compression.

In conclusion, a secondary form of achalasia may diagnose a small subgroup of patients with dysphagia. Esophageal manometric study must be considered in conjunction with a careful barium study, CT scans and an accurate endoscopic examination in these subjects as diagnostic tests. A vascular compression of the esophageal body could cause dysphagia, which in our case was associated with mechanical obstruction of the cardia from a tumor mass originating from the angulus in the stomach. The less invasive therapeutic option should be proposed in an old patient with comorbidities with a short life expectancy in terms of acceptable quality of life and low risk procedure in respect to other more invasive and complex, even more appropriate treatments.

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Abdominal pain post endoscopic mucosal resection: Treat the patient not the CT scan

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Author contributions: Heerasing N was the primary author of the case; Dowling D and Alexander S were involved in editing the manuscript.

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Core tip: This report highlights the importance of correlating clinical findings with radiological ones in a patient who underwent endoscopic mucosal resection of a large ascending polyp. The computed tomography scan in this case reveals a colonic perforation but the patient was symptom free and was managed conservatively without needing surgery. Colonoscopists who undertake endoscopic mucosal resection (EMR) need to be aware that radiological features of perforation can be seen post EMR in the absence of an EMR associated perforation.

Abstract

An 85-year-old female, with hereditary nonpolyposis colorectal cancer syndrome, underwent a colonoscopy and endoscopic mucosal resection (EMR) of a 25-mm proximal ascending colon polyp (Paris classification 0-Is). Post-procedure, the patient developed abdominal pain in the right iliac fossa which settled 1 h later. An urgent computed tomography (CT) scan of her abdomen was organised which happened 6 h post onset of abdominal pain. She had radiological evidence of perforation on the CT scan but clinically remained well and was managed conservatively. The exact aetiology of this patient's symptoms is not known. We suspect the radiological findings are probably due to a combination of injectate within the colonic wall and leakage of insufflated air or CO₂ following transmural passage of the EMR needle. As EMR is becoming an increasingly effective treatment modality in the management of large sessile polyps, clinicians need to be aware of potential complications of treatment. It is also important to recognise that radiological features of perforation can be seen post EMR in the absence of an EMR associated perforation.

Heerasing N, Dowling D, Alexander S. Abdominal pain post endoscopic mucosal resection: Treat the patient not the CT scan. *World J Gastrointest Endosc* 2013; 5(9): 455-456 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/455.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.455>

INTRODUCTION

Endoscopic mucosal resection in a tertiary setting is a safe, efficient and effective minimally invasive outpatient therapy for large sessile polyps or laterally spreading tumors of the colon^[1]. In this case report, we describe a patient who, having developed abdominal pain post resection of a large colonic polyp, was managed conservatively.

CASE REPORT

An 85-year-old female, with hereditary nonpolyposis colorectal cancer syndrome, underwent a colonoscopy and endoscopic mucosal resection (EMR) of a 25-mm proximal ascending colon polyp (Paris classification 0-Is). Piecemeal resection after chromo-saline injection was undertaken.

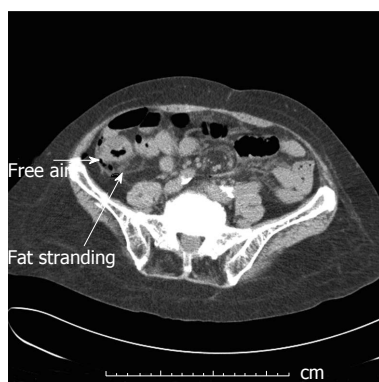


Figure 1 Computed tomography abdomen demonstrates free air and inflammatory fat stranding at the site of the polyp removal by endoscopic mucosal resection in the proximal ascending colon. Those features are consistent with a colonic perforation.

Post procedure, the patient experienced abdominal pain in the right iliac fossa and was monitored. An urgent computed tomography (CT) scan (Figure 1) of the abdomen was ordered but was delayed due to equipment malfunction. Whilst awaiting her scan, the patient's pain resolved (1 h post resection). Approximately 6 h post EMR, CT scan showed inflammatory stranding at the site of EMR and extra-luminal gas consistent with a colonic perforation. Despite these findings, the patient remained pain free and was discharged the following day.

DISCUSSION

Non-specific and usually self-resolving abdominal pain is reported to occur in around 2% of EMR procedures^[1].

EMR in the colon has become a commonly used technique and a viable alternative to invasive surgery for the treatment of large or complex pre-malignant lesions^[2]. The rate of perforation during EMR is estimated to be around 1.3%^[3]. In our patient, the radiological findings are probably due to a combination of injectate within the colonic wall and leakage of insufflated air or CO₂ following transmural passage of the EMR needle. To our knowledge, this has not been previously reported in the English literature. Our patient has remained well and she had a repeat colonoscopy six months later which showed no recurrent polyp.

Colonoscopists who undertake EMR need to be aware that radiological features of perforation can be seen post EMR in the absence of an EMR associated perforation. As usual, it is essential to treat the patient and not the CT scan findings.

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Gastric calcifying fibrous tumor removed by endoscopic submucosal dissection

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Author contributions: Ogasawara N, Izawa S and Tanabe A performed endoscopic submucosal resection of the submucosal tumor; Mizuno M, Ozeki T and Noda H managed the patient's condition during hospitalization; Takahashi E and Yokoi T pathologically diagnosed the SMT as a gastric calcifying fibrous tumor; Ogasawara N, Sasaki M and Kasugai K wrote the manuscript.

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Abstract

The World Health Organization describes calcifying fibrous tumors (CFTs) as rare, benign lesions characterized by hypocellular, densely hyalinized collagenization with lymphoplasmacytic infiltration. These tumors rarely involve the gastrointestinal (GI) tract. A routine endoscopic upper gastrointestinal screen detected a 10-mm submucosal tumor (SMT) in the lesser curvature of the lower corpus of the stomach of an apparently healthy, 37-year-old woman with no history of *Helicobacter pylori* infection. Endoscopic ultrasonography (EUS) localized the internally isoechoic, homogeneous SMT mainly within the submucosa. Malignancy was ruled out using endoscopic submucosal dissection (ESD). A pathological examination confirmed complete resection of the SMT, and defined a hypocellular, spindle-cell tumor with

a densely hyalinized, collagenous matrix, scattered lymphoplasmacytic aggregates as well as a few psammomatous, dystrophic calcified foci. The mass was immunohistochemically positive for vimentin and negative for CD117 (c-kit protein), CD34, desmin, smooth muscle actin (SMA) and S100. Therefore, the histological findings were characteristic of a CFT. To date, CFT resection by ESD has not been described. This is the first case report of a gastric calcifying fibrous tumor being completely resected by ESD after endoscopic ultrasonography.

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Key words: Calcifying fibrous tumor; Endoscopic submucosal dissection; Submucosal tumor; Endoscopic ultrasonography

Core tip: Calcifying fibrous tumors (CFTs) rarely involve the gastrointestinal tract. Resection of CFT by endoscopic submucosal dissection (ESD) has not been reported. This is the first case report of a gastric calcifying fibrous tumor being completely resected by ESD after endoscopic ultrasonography.

Ogasawara N, Izawa S, Mizuno M, Tanabe A, Ozeki T, Noda H, Takahashi E, Sasaki M, Yokoi T, Kasugai K. Gastric calcifying fibrous tumor removed by endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; 5(9): 457-460 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/457.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.457>

INTRODUCTION

Rosenthal originally identified benign, fibrous, calcifying fibrous tumors (CFTs) in soft tissues of the extremities in children^[1]. These tumors comprised hyalinized fibrous

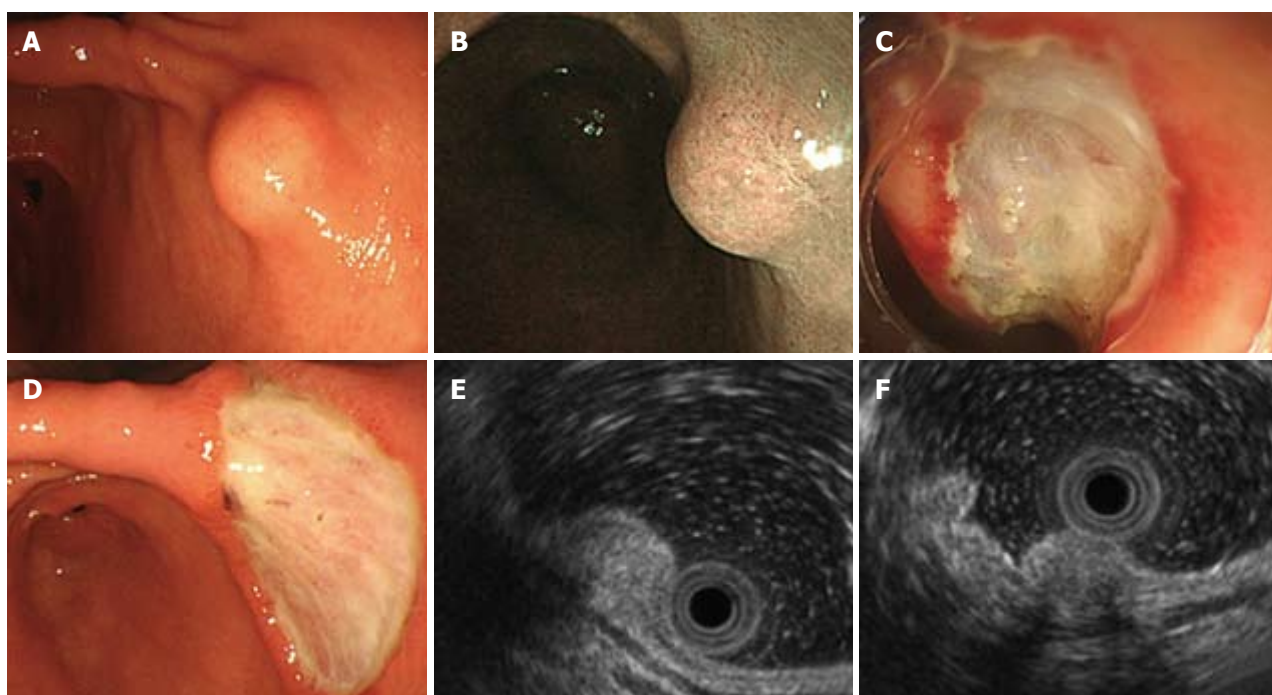


Figure 1 Endoscopic ultrasonography findings of visualized submucosal tumor. A: Endoscopy shows 10-mm shows submucosal tumor (SMT) in lesser curvature of lower corpus of stomach; B: Narrow-band endoscopic imaging SMT covered by normal gastric mucosa; C: Endoscopic submucosal dissection (ESD) for SMT; D: Stomach ulceration five days after ESD; E: Endoscopic ultrasonography (EUS) findings show internally isoechoic, homogeneous sub-mucosal tumor mainly localized within second and third layers, whereas first and fourth layers are preserved; F: Acoustic shadowing of hyperechoic foci inside lesion is consistent with calcifications. Fourth layer is obvious.

tissue interspersed with bland fibroblastic spindle cells, scattered psammomatous, and/or dystrophic calcifications and variably prominent mononuclear inflammatory infiltrates. CFTs have recently been identified in the mesentery and peritoneum^[2-4], mediastinum^[5], pleura^[6], lung^[7], adrenal glands^[8] and in the paratesticular and spermatic cord^[4]. Although CFTs can involve various organ systems, the gastrointestinal (GI) tract is rarely involved^[9]. Calcifying fibrous submucosal tumors (SMTs) are difficult to differentiate from other SMTs such as small lipomas, neuroendocrine and gastrointestinal stromal tumors (GISTs) cell tumors. Only a few case reports have described CFTs occurring in the stomach^[9-11]. The CFTs described in these reports were relatively large when discovered and required surgical resection. Here, we describe a gastric CFT that was completely removed by endoscopic submucosal dissection (ESD) after a thorough assessment by endoscopic ultrasonography (EUS).

CASE REPORT

A routine health screen using upper gastrointestinal endoscopy revealed a submucosal tumor in a 37-year-old apparently healthy woman with no known family history of gastrointestinal disorders or malignant diseases. She had no abdominal discomfort or stomach and intestinal symptoms. Physical findings were unremarkable and all initial biochemical and hematological parameters were within normal limits. Narrow-band imaging endoscopy (GIF-H260Z; Olympus, Tokyo, Japan) indicated a 10 mm

diameter SMT with normal overlying mucosa in the lesser curvature of the lower corpus of the stomach (Figure 1A and B). The mucosa of the whole stomach was normal without chronic gastritis. Mucosal biopsies of both the middle portion and antrum of stomach confirmed the absence of *Helicobacter pylori* infection. Computed tomography (CT) did not detect any submucosal tumors or abnormal findings in any other organs, and no swollen lymph nodes. EUS visualized the SMT mainly within the second and third layers of the gastric wall, and the first layer was preserved (Figure 1E). The homogeneous tumor was internally isoechoic (Figure 1E). Hyperechoic foci with acoustic shadowing within the mass were consistent with calcifications (Figure 1F). The fourth layer of the gastric wall was obvious (Figure 1E and F), and therefore, the SMT was considered not to have invaded the muscularis propria. The endoscopy and EUS findings indicated that the SMT was localized within the submucosal propria, but it was too small to perform fine needle aspiration biopsy (FNA) under EUS. A biopsy specimen obtained from SMT also did not include the tumor contents and a definitive pathological diagnosis of the tumor could not be achieved. However, a precise diagnosis was required to rule out malignancy. The patient refused to undergo surgery, but consented to undergo endoscopic treatment. To completely resect the SMT using only endoscopic mucosal resection (EMR) was considered very difficult. Therefore, SMT was removed by ESD and not EMR to avoid SMT retention and comprehensively diagnose the SMT (Figure 1C and D). Pathological as-

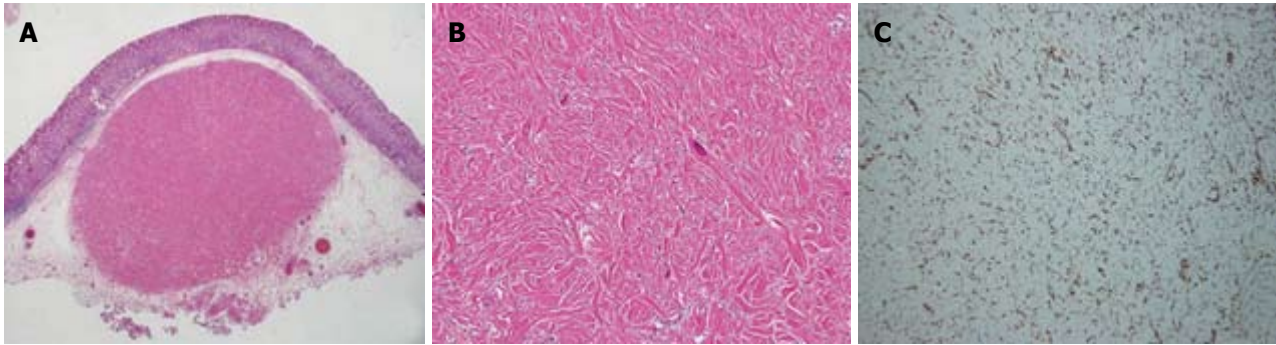


Figure 2 Pathological findings of resected small mucosal tumor. A: Complete submucosal tumor resection was confirmed; B: Hypocellular, spindle-cell tumor has densely hyalinized, collagenous matrix, scattered lymphoplasmacytic aggregates, some psammomatous foci and dystrophic calcification, Spindle-cells harbor no mitotic activity or atypia; C: Positive immunohistochemical staining for vimentin. Original magnification $\times 10$ (A), $\times 200$ (B), $\times 100$ (C).

assessment of the resected SMT (Figure 2A) revealed a hypocellular, spindle-cell mass with a densely hyalinized, collagenous matrix, scattered lymphoplasmacytic aggregates and a few foci comprising psammomatous and dystrophic calcifications (Figure 2B). The spindle cells in the tumor harbored no mitotic activity or atypia. Immunohistochemical staining was positive for vimentin (Figure 2C), but negative for CD117 (c-kit protein), CD34, desmin, smooth muscle actin (SMA) and S100. Therefore, the histopathological findings concurred with a diagnosis of a CFT.

DISCUSSION

Rosenthal originally described CFTs as benign, soft, fibrous masses with psammoma bodies in two girls aged 2 and 11 years^[1]. The histopathology of CFTs is that of a heavily collagenized paucicellular fibrous lesion composed of bland spindled cells, scattered psammomatous and/or dystrophic calcifications and variably prominent mononuclear inflammatory infiltrates. Because they were initially thought to represent a reactive process resulting from abnormally healing tissue, CFTs were originally described as calcifying fibrous pseudotumors^[12]. However, later studies indicated that they are true neoplasms with a tendency towards non-destructive local recurrence^[4]. Later reports described finding CFTs in ubiquitous anatomical sites including the pleura^[6], abdominal cavity and peritoneum^[3] and elsewhere^[4,12]. The etiology and pathogenesis of CFTs remain unknown, although location, immunohistochemical and pathological features suggest a mesenchymal sub-mesothelial origin^[3].

Small SMTs are usually asymptomatic and incidentally detected during endoscopic or radiological examinations. One retrospective study has suggested that the incidence of gastric submucosal lesions is 0.36%^[13]. Submucosal tumors are very difficult to accurately diagnose by endoscopic or radiological means. The most common SMTs of the alimentary tract are GISTs that originate from interstitial cells of Cajal^[14,15]. Other differential diagnoses of SMTs include fibromatosis, inflammatory myofibroblastic tumors, neuroendocrine cell tumors, schwannomas,

heterotopic pancreas, lipomas, cystic lesions, lymphomas and leiomyomas. Differentially diagnosing gastric mesenchymal tumors using only endoscopic imaging is also challenging. Gastric CFTs include SMTs that are endoscopically difficult to differentiate from other SMTs such as those described above, especially when they are very small. Although EUS and EUS-guided FNA are considered useful for diagnosing SMTs, these modalities cannot perfectly diagnose whole SMTs, when EUS findings are non-specific, or when SMTs are too small to be treated by FNA. The SMT was located in the second and third layers of the gastric wall in our patient and it had the same homogeneous, isoechoic features as the third layer. These findings excluded GIST, leiomyoma, cystic lesion, schwannoma, and lipoma from the differential diagnosis, but a more precise diagnosis by EUS remained impossible. The findings indicated that the mass was most likely a neuroendocrine cell tumor. However, the calcification detected by EUS in the SMT is uncommon among neuroendocrine cell tumors. Moreover, it was only 10 mm in diameter, which was too small to treat using EUS-guided FNA. Since endoscopy and EUS could not conclude a diagnosis, the SMT was resected by ESD.

Small mucosal tumors that are not diagnosed beforehand are always diagnosed by immunohistochemistry after surgical resection when FNA is not performed. Common SMTs are diagnosed as follows based on immunohistochemical positivity for CD117 (c-kit protein; GIST), CD34 (almost all mesenchymal neoplasms), smooth muscle actin (SMA), desmin (leiomyoma) and S100 (schwannoma derived from nerves)^[15]. The SMT in our patient did not express any of these immunohistochemical markers, which is a characteristic of CFT. Almost all reported CFTs were quite large when they were discovered, and thus to estimate the initial pathogenesis of CFTs difficult. The CFT in our patient was extremely small, and thus might represent the initial status of CFTs. Therefore, further examination was required to analyze this CFT in more detail.

A search of the Pub-Med database did not uncover any reports describing complete resection of a CFT using ESD. We completely resected an extremely small gastric

CFT by ESD after the patient had undergone a detailed examination using EUS. The calcification indicated by EUS is considered a useful feature for detecting CFTs and for narrowing down the differential diagnoses of SMTs. We believe that this manuscript is the first report to describe a calcified gastric CFT detected by EUS. The size of this CFT might indicate the initial status of such tumors, clarify one pathogenetic mechanism of development in the GI tract and provide an informative clue to the pathogenesis and development of CFTs in general.

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Uncomplicated spontaneous rupture of pancreatic pseudocyst into stomach: A case report

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Author contributions: Somani PO designed the report and wrote paper; Somani PO, Khot AA and Rath PM were attending doctors for the patient; Jain SS and Shah DK organized the report.

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Abstract

Pseudocysts of the pancreas are not rare, but spontaneous perforation and/or fistulization occurs in fewer than 3% of these pseudocysts. Perforation into the free peritoneal cavity, stomach, duodenum, colon, portal vein, pleural cavity and through the abdominal wall has been reported. Spontaneous rupture of the pancreatic pseudocyst into the surrounding hollow viscera is rare and, may be associated with life-threatening bleeding. Such cases require emergency surgical intervention. Uncomplicated rupture of pseudocyst is an even rarer occurrence. We present a case of spontaneous resolution of a pancreatic pseudocyst with gastric connection without bleeding. A 67-year-old woman with a large pancreatic pseudocyst resulting from a complication of chronic pancreatitis was referred to our institution. During hospital stay, there was sudden decrease in the size of epigastric lump. Repeat computed tomography (CT) revealed that the size of the pseudocyst had decreased significantly; however, gas was observed in stomach and pseudocyst along with rent between lesser curvature of stomach and pseudocyst suggestive of spontaneous cystogastric fistula. The

fistula tract occluded spontaneously and the patient recovered without any complication or need for surgical treatment. After 5 wk, follow up CT revealed complete resolution of pseudocyst. Esophagogastroduodenoscopy revealed that the orifice was completely occluded with ulcer at the site of previous fistulous opening.

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Key words: Chronic pancreatitis; Cystogastric fistula; Fistula; Pancreas; Pancreatitis; Pseudocyst

Core tip: Spontaneous rupture of the pancreatic pseudocyst into the surrounding hollow viscera is rare and, may be associated with life-threatening bleeding. Such cases require emergency surgical intervention. Uncomplicated rupture of pseudocyst is an even rarer occurrence. We present a case of spontaneous resolution of a pancreatic pseudocyst with gastric connection without bleeding. Only few cases had been reported in literature till date. We managed the case conservatively without surgical intervention.

Somani PO, Jain SS, Shah DK, Khot AA, Rath PM. Uncomplicated spontaneous rupture of pancreatic pseudocyst into stomach: A case report. *World J Gastrointest Endosc* 2013; 5(9): 461-464 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/461.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.461>

INTRODUCTION

Pseudocysts of the pancreas are not rare, but spontaneous perforation and/or fistulization occurs in fewer than 3% of these pseudocysts^[1]. Spontaneous rupture of the pancreatic pseudocysts is known to occur into the stomach, duodenum, biliary tract, renal collecting system, colon and bronchial tree^[2]. However, most of these spontaneous ruptures are associated with bleeding

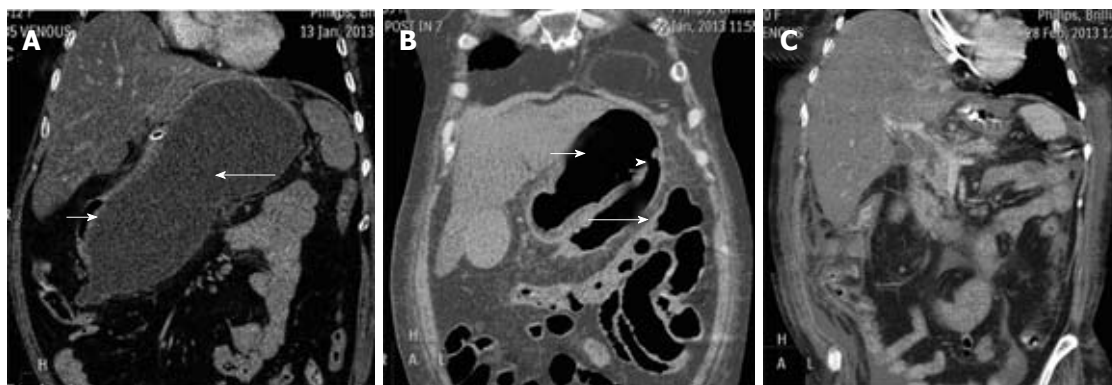


Figure 1 Computerized Tomography of abdomen showing pseudocyst of pancreas. A: Large pseudocyst (long arrow) causing extrinsic compression of stomach (short arrow); B: Ruptured pseudocyst of pancreas (long arrow) draining through a rent (arrowhead) into stomach (short arrow); C: Complete resolution of pseudocyst of pancreas.

complications needing emergency surgical intervention^[3]. Spontaneous rupture of the pancreatic pseudocyst into the surrounding hollow viscera is rare and, whenever it occurs, is associated with life-threatening bleeding. Uncomplicated rupture of pseudocyst is an even rarer occurrence^[4]. We present a case of spontaneous resolution of a pancreatic pseudocyst with gastric connection.

CASE REPORT

A 67-year-old female was admitted to hospital with one month history of abdominal pain and recurrent vomiting. She had history of recurrent episodes of similar abdominal pain in past. She also noticed fullness in upper abdomen. On admission, vitals were stable. On examination there was cystic lump in epigastrium around 8 cm × 6 cm with mild tenderness. Rest of the Physical examination was unremarkable. Haemoglobin was 12.7 g/dL (normal range, 12-16 g/dL), serum amylase level was 180 U/L (normal range, 28-160 U/L); lipase, 94 U/L (normal range, 0-60 U/L) and other laboratory parameters were within normal limits. On admission, computed tomography (CT) of abdomen (Figure 1A) revealed a pseudocyst measuring 20 cm × 12 cm arising from body and tail compressing the stomach along with atrophic pancreas suggestive of chronic pancreatitis. Patient was managed conservatively. After ten days we noticed sudden decrease in the size of epigastric lump. Repeat CT revealed that the size of the pseudocyst had decreased significantly; however, gas was observed in stomach and pseudocyst along with rent between lesser curvature of stomach and pseudocyst suggestive of spontaneous cystogastric fistula (Figure 1B). Esophago-gastroduodenoscopy (EGD) showed a 2.5-cm orifice of the fistula along the lesser curvature of stomach (Figure 2A and B). Patient was hemodynamically stable and without any complications, so was managed conservatively. After 5 wk, follow up CT revealed complete resolution of pseudocyst (Figure 1C). EGD revealed that the orifice was completely occluded with ulcer at the site of previous fistulous opening (Figure 2C).

DISCUSSION

Pseudocysts occur in about 25% of patients with chronic pancreatitis and are most common in alcoholic chronic pancreatitis. The natural history of pseudocysts in chronic pancreatitis is not fully defined. Overall, complications of pseudocysts occur in 20% to 40% of cases. Complications include compression of large peripancreatic vessels, stomach or duodenum; infection; hemorrhage; and development of a fistula. Treatment is not necessary in all patients. Patients who have mature pseudocysts smaller than 6 cm, minimal or no symptoms, no complications, and are reliable may be managed conservatively. Even larger pseudocysts that remain asymptomatic can be managed expectantly. Very large pseudocysts, an enlarging pseudocyst and symptomatic or complicated pseudocysts require therapy. Therapy for pseudocysts can be surgical, percutaneous or endoscopic. Surgical therapy has been used most extensively and usually involves cyst decompression into a loop of small bowel or stomach, often coupled with a pancreatic ductal drainage procedure. Surgical therapy has a long-term success rate of 90% and an operative mortality of less than 3%^[5].

There are many mechanisms that lead to resolution of a pseudocyst. At times, it regresses after the inflammatory reaction resolves or it can resolve spontaneously with natural drainage to the duodenum through the pancreatic duct. When erosion of a pseudocyst occurs near the gastrointestinal tract and a fistula is formed, the fistula can lead to resolution of the pseudocyst. In some cases, the pseudocyst can resolve as it leaks or ruptures into the abdominal cavity^[6]. It is expected that temporary or permanent resolution of the pseudocyst will occur with drainage through a fistula between the pseudocyst and the gastrointestinal tract^[7]. As high-density protein from the pseudocyst moves to the gastrointestinal tract through a fistula, patients manifest sudden clinical improvement with resolution of the pseudocyst after temporary symptoms of diarrhoea, vomiting, abscess and blood or hematochezia. When the pseudocyst resolves as

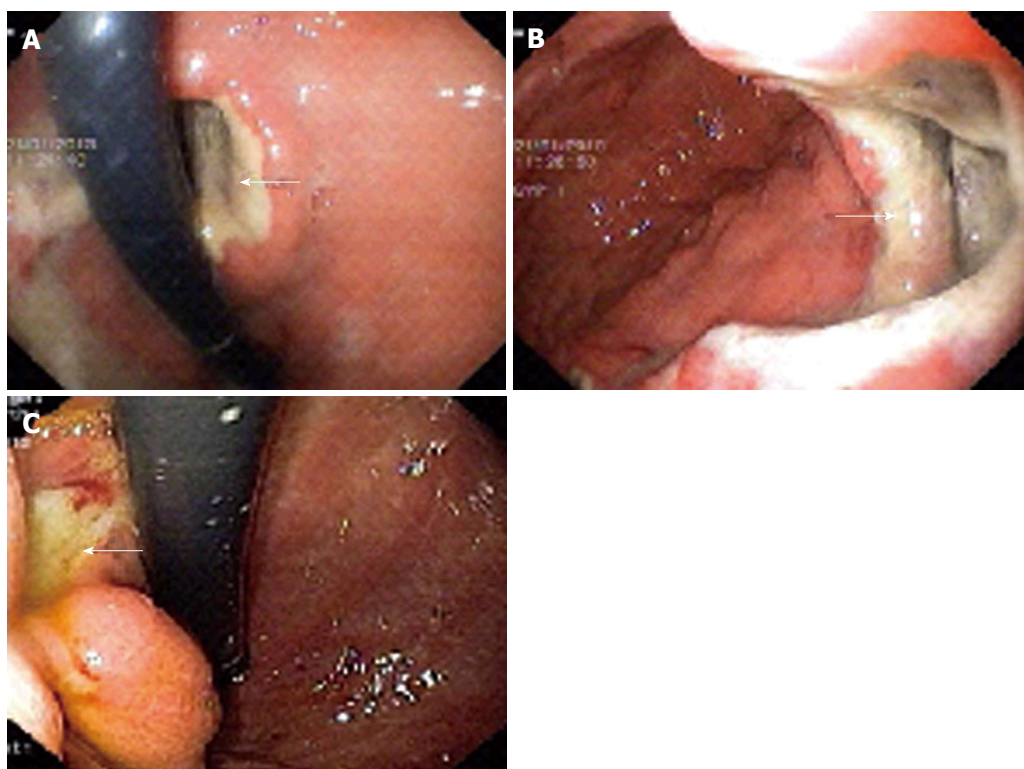


Figure 2 Oesophagogastroduodenoscopy showing pseudocyst of pancreas. A, B: Orifice (arrow) of the fistula between stomach and the pseudocyst of pancreas; C: Ulcer (arrow) at the site of healed fistulous communication between pancreatic pseudocyst and stomach.

a result of fistula formation, the patient does not require surgery. When a patient develops hematochezia, this may imply that the fistula exists near the large intestine, whereas hematemesis may imply that it exists near the stomach or duodenal wall. The locations in the gastrointestinal tract most vulnerable to fistula formation, in patients with pancreatitis, are the transverse colon and splenic flexure, followed by the duodenum; however, the small intestine, stomach and esophagus are uncommon locations^[8].

The rupture of pancreatic pseudocysts into surrounding viscera is a well-known phenomenon. Usually, spontaneous drainage and amelioration of symptoms result when the pseudocyst ruptures into the hollow gastrointestinal tract. Three pathogenetic mechanisms of bleeding and rupture of pancreatic pseudocysts have been suggested. First, uncontrolled severe inflammation and activated lytic enzymes, such as elastase and trypsin, might cause progressive digestion of the elastic component of the vessel wall, with consequent erosion and disruption. Second, pseudocysts might produce erosion of vessels as a consequence of persistent compression, ischemia and the elastolytic action of enzymatic contact. Third, the inflammatory process and the pseudocyst might cause compression or thrombosis in the portal or splenic vein, leading to localized portal hypertension^[3].

The patient presented here had epigastric mass on admission and was found to have pseudocyst on CT abdomen. After ten days patient had sudden decrease in the size of epigastric lump for which she underwent CT

abdomen which showed gas in stomach and pseudocyst along with rent between lesser curvature of stomach and pseudocyst suggestive of spontaneous cystogastric fistula. Patient was hemodynamically stable and without any complications like gastrointestinal bleeding or anemia. After 5 wk repeat CT abdomen showed resolution of pseudocyst and fistula.

Unlike the formation of a fistula between the large intestine and the pseudocyst, a fistula between the stomach and the pseudocyst does not require urgent surgery, unless it is accompanied by abscess formation or bleeding^[8].

Severe acute pancreatitis (SAP) is known to be complicated by fistulization into the neighboring organs. Pancreatocolonic fistulas are the most common, whereas pancreatogastric fistulas are the rarest. In a study from the Mayo Clinic, fistulization was reported in 25 (41%) of the 61 patients operated for SAP. Fourteen of them had cutaneous fistulas, whereas 19 had gastrointestinal (GI) tract fistulas (8 colonic, 5 duodenal, 4 enteric and 2 gastric). A majority of these fistulas are reported after necrosectomy, and rarely is the diagnosis made preoperatively^[9].

Rupture of a bleeding pseudocyst into the stomach is rare^[3]. Uncomplicated rupture of pseudocyst is an even rarer occurrence^[4]. There are only few case reports in literature of uncomplicated spontaneous rupture of pseudocyst into stomach^[4,6,8,10].

In conclusion, we have presented a case of patient with a pseudocyst, resulting from a complication of chronic pancreatitis, which resolved spontaneously

through the formation of a fistula between the pseudocyst and the stomach. The fistula occluded spontaneously and the patient recovered without complication or need for surgical treatment.

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Use of enhancement algorithm to suppress reflections in 3-D reconstructed capsule endoscopy images

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Key words: Capsule endoscopy; Three-dimensional reconstruction; Phantom; Experiment; PillCam; Software; Accuracy

Core tip: In an attempt to approximate a three-dimensional (3-D) reconstruction of the digestive tract surface, a software that recovers information-using gradual variation of shading - from monocular two-dimensional capsule endoscopy images has been proposed. Light reflections on the surface of the digestive tract are still a significant problem. Therefore, a phantom model and simulator has been constructed in an attempt to check the validity of a highlight suppression algorithm. Our results confirm that 3-D representation software performs better with simultaneous application of a highlight reduction algorithm. Furthermore, 3-D representation follows a good approximation of the real distance to the lumen surface.

Abstract

In capsule endoscopy (CE), there is research to develop hardware that enables "real" three-dimensional (3-D) video. However, it should not be forgotten that "true" 3-D requires dual video images. Inclusion of two cameras within the shell of a capsule endoscope though might be unwieldy at present. Therefore, in an attempt to approximate a 3-D reconstruction of the digestive tract surface, a software that recovers information-using gradual variation of shading-from monocular two-dimensional CE images has been proposed. Light reflections on the surface of the digestive tract are still a significant problem. Therefore, a phantom model and simulator has been constructed in an attempt to check the validity of a highlight suppression algorithm. Our results confirm that 3-D representation software performs better with simultaneous application of a highlight reduction algorithm. Furthermore, 3-D representation follows a good approximation of the real distance to the lumen surface.

Koulaouzidis A, Karargyris A. Use of enhancement algorithm to suppress reflections in 3-D reconstructed capsule endoscopy images. *World J Gastrointest Endosc* 2013; 5(9): 465-467 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/465.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.465>

TO THE EDITOR

In capsule endoscopy (CE), there is research to develop hardware that enables "real" three-dimensional (3-D) video by using an infrared projector and a CMOS camera^[1,2]. However, it should not be forgotten that "true" 3-D requires dual video-images; furthermore, the inclusion of two cameras within the shell of a capsule endoscope might be unwieldy at present^[3]. Therefore, major drawbacks at present are size, power consumption and packaging issues^[4]. In an attempt to approximate a 3-D reconstruc-

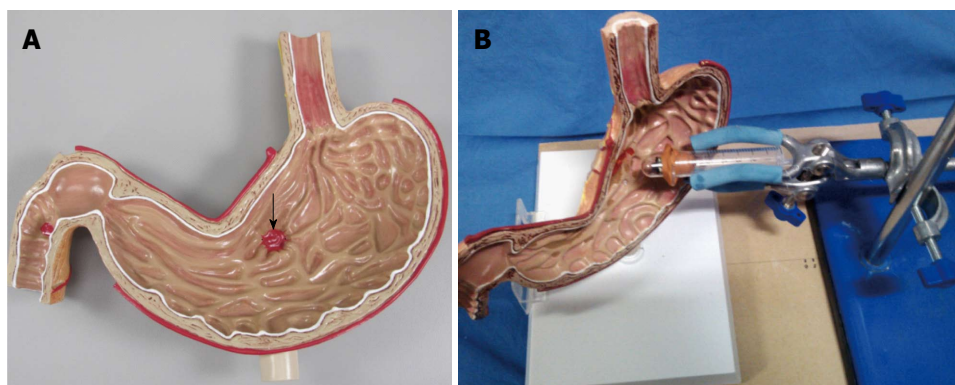


Figure 1 Phantom model (A) and task simulator setting (B). A: The arrow points to the gastric ulcer ("1/2 diameter and 3/16" depth).

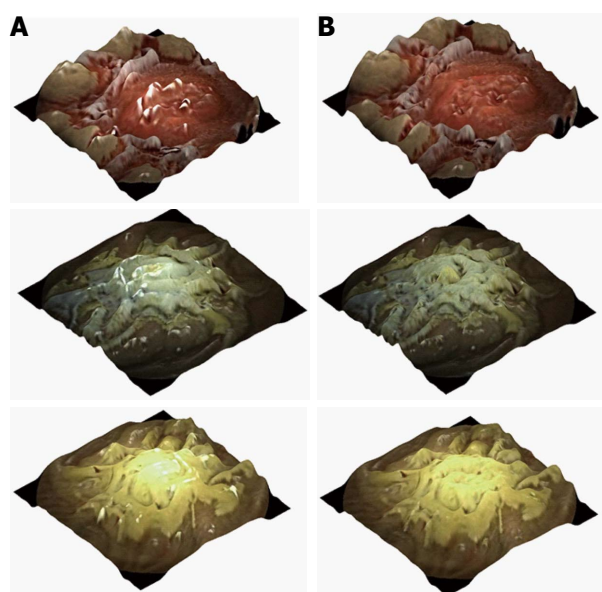


Figure 2 Three-dimensional representation of images captured for the 3 models: red, white and yellow. A: Original three-dimensional (3-D) represented images; B: The processed 3-D represented images using the highlight suppression algorithm.

tion of the digestive tract surface, Koulaouzidis *et al*^[4] and Karargyris *et al*^[5] proposed the use of a software [Shape-from-Shading (S/S)] that utilizes monocular CE frames. Essentially, S/S algorithms recover information -using gradual variation of shading^[6]- on the shape of objects given a single two-dimensional (2-D) image. 3-D representation may be helpful in conjunction with other image enhancement tools *e.g.*, virtual chromoendoscopy (FICE)^[7] and/or color (blue) mode analysis of CE videos^[8].

However, light reflections on the surface of the digestive tract are still a significant problem, not only for 3-D representation but also for traditional 2-D CE. When light falls on to a surface, some of the beams are reflected back straightaway -specular reflection- while the rest of the beams penetrate it before reflected (diffuse reflection). As most digestive tract structures/surfaces are di-electric and homogeneous, they display both types of reflections^[4]. To reduce reflections, a highlight suppress-

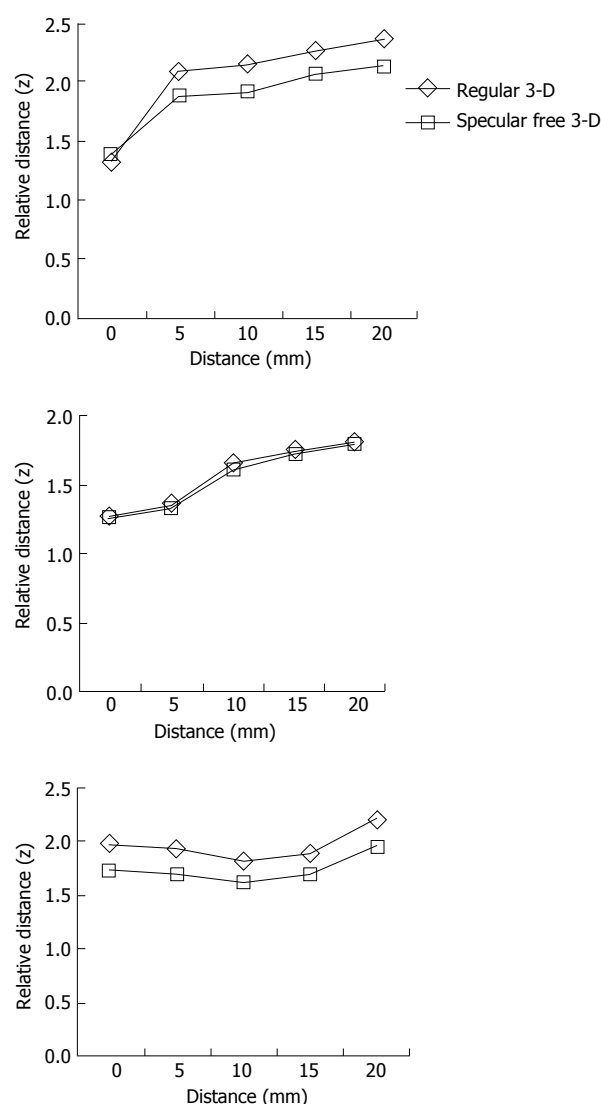


Figure 3 Relative distance of three-dimensional representation calculated over images taken from various distances of the capsule from the models.

sion algorithm^[9] has been applied onto CE images.

To test this algorithm, a phantom task simulator was created. A Stomach Ulcer Anatomical Model (manufacturer: Anatomical Chart Company G200) was used; the

stomach model has an red-colored base ulcer (1/2" diameter and 3/16" depth; Figure 1A); the latter was thereafter colored buttercup yellow using quick-drying spray paint (Tor Coatings[®] Ltd., United Kingdom) and white (using flat white spray from Plasti-Kote[®] Ltd.). A PillCam[®] SB2 (Given[®] Imaging Ltd., Yoqneam, Israel) was mounted on a plastic tube and held (with the use of regular lab stand) at 0, 5, 10, 15 and 20 mm from the ulcer base (usual working distance of the CE *in vivo*, Figure 1B). The images were uploaded to a workstation and they were categorized based on distance and ulcer base color (red, yellow and white). We aimed to check whether the ulcer models appear closer or further based on their 3-D representation.

Tsai's S/S^[9,10] algorithm was applied on each image in order to reconstruct its 3-D representation with (Figure 2A) or without (Figure 2B) software highlight suppression^[9]. Tsai's S/S algorithm cannot measure the real distance of the camera to the model's surface but it gives the relative distance (*z*) to the black frame background. For each image, we selected the region of interest (ROI) of the ulcer model on the 3-D representation and we calculated the average depth (*z*) for each ROI.

The results (charts, Figure 3) confirm that the distance of the camera from the model surface increases so does the relative distance (*z*) on the 3-D representation. This effect is more evident for the white and yellow ulcer models. However, relative distance does not follow a similar trend for the red-based ulcer model. This is likely due to the saturation of the red color creating variations to the shading: red color appears darker or lighter. Finally, from the charts we conclude that the highlight suppression algorithm improved the quality of the images.

In conclusion, 3-D representation software seems to perform better with simultaneous application of a highlight reduction algorithm. Furthermore, 3-D representation follows a good approximation of the real distance to

the lumen surface.

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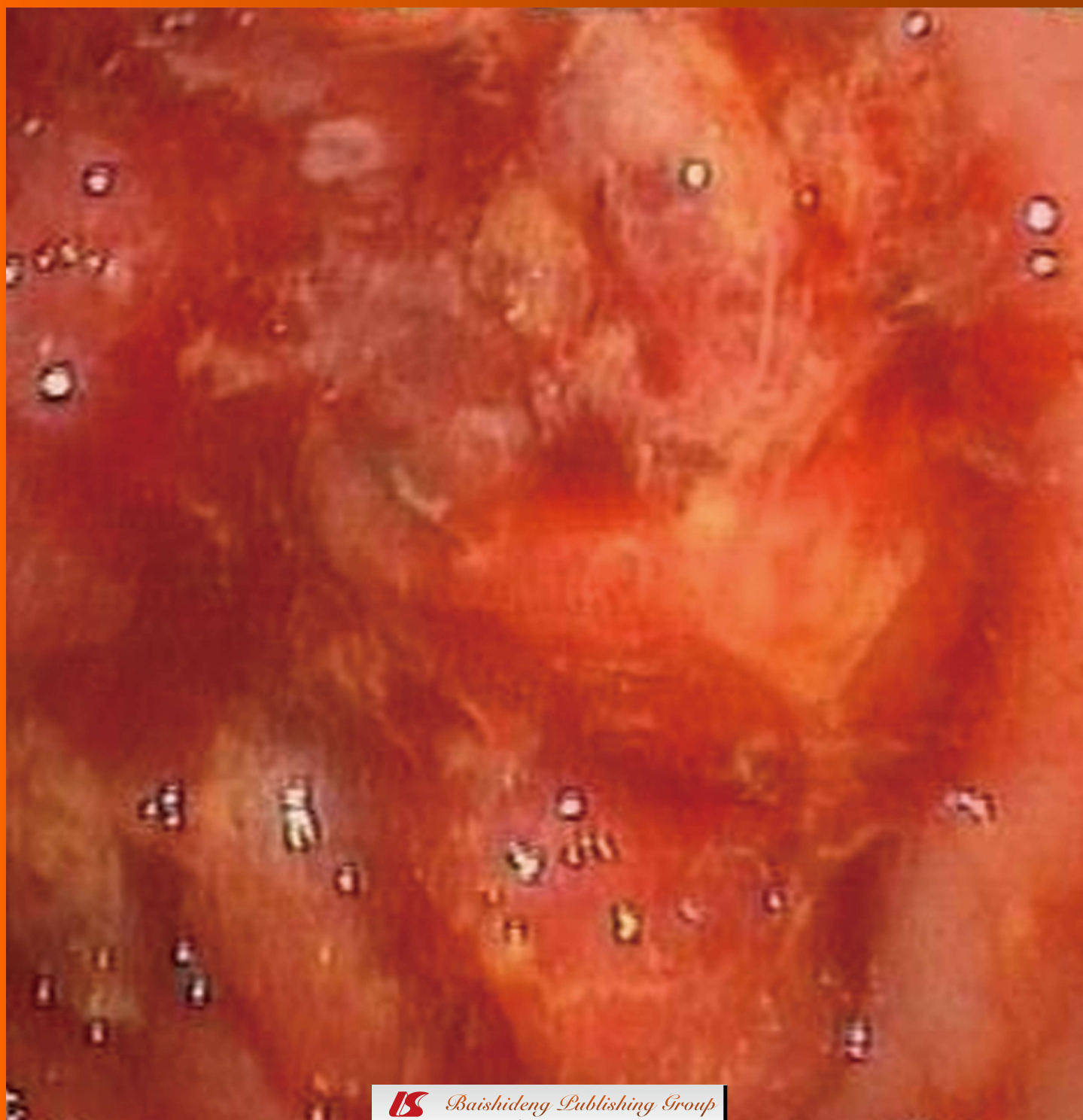
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How we can measure quality in colonoscopy?

Leonidas A Bourikas, Zacharias P Tsiamoulos, Adam Haycock, Siwan Thomas-Gibson, Brian P Saunders

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Abstract

Measuring quality is a current need of medical services either to assess their cost-effectiveness or to identify discrepancies requiring refinement. With the advent of bowel cancer screening and increasing patient awareness of bowel symptoms, there has been an unprecedented increase in demand for colonoscopy. Consequently, there is an expanding open-discussion on missed rates of cancer or precancerous polyps during diagnostic/screening colonoscopy and on the rate of adverse events related to therapeutic colonoscopy. Delivering a quality colonoscopy service is therefore a healthcare priority. Colonoscopy is a multi-step process and therefore assessment of all aspects of the procedure must be addressed. Quality in colonoscopy refers to a combination of many patient-centered technical and non-technical skills and knowledge aiming to patient's safety and satisfaction through a continuous effort for improvement. The benefits of this endless process are hiding behind small details which

can eventually make the difference in colonoscopy. Identifying specific quality metrics help to define and shape an optimal service and forms a secure basis of improvement. This paper does not aim to give technical details on how to perform colonoscopy but to summarize what to measure and when, in accordance with the current identified quality indicators and standards for colonoscopy.

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Key words: Colonoscopy; Quality assurance; Metrics; Standards; Outcome

Core tip: With the advent of bowel cancer screening and increasing patient awareness of bowel symptoms, there has been an unprecedented increase in demand for colonoscopy. Delivering a quality colonoscopy service is therefore a healthcare priority. Colonoscopy is a multi-step process and therefore assessment of all aspects of the procedure must be addressed. Quality in colonoscopy refers to a combination of many patient-centered technical and non-technical skills. Identifying specific quality metrics help to define and shape an optimal service.

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INTRODUCTION

Colonoscopy is the cornerstone in diagnosis and management of colorectal disease allowing direct optical diagnosis, tissue sampling for histological analysis and therapy of colonic lesions^[1]. Quality of colonoscopy practice is highly variable and there is increasing public awareness of missed cancers, incomplete procedures and

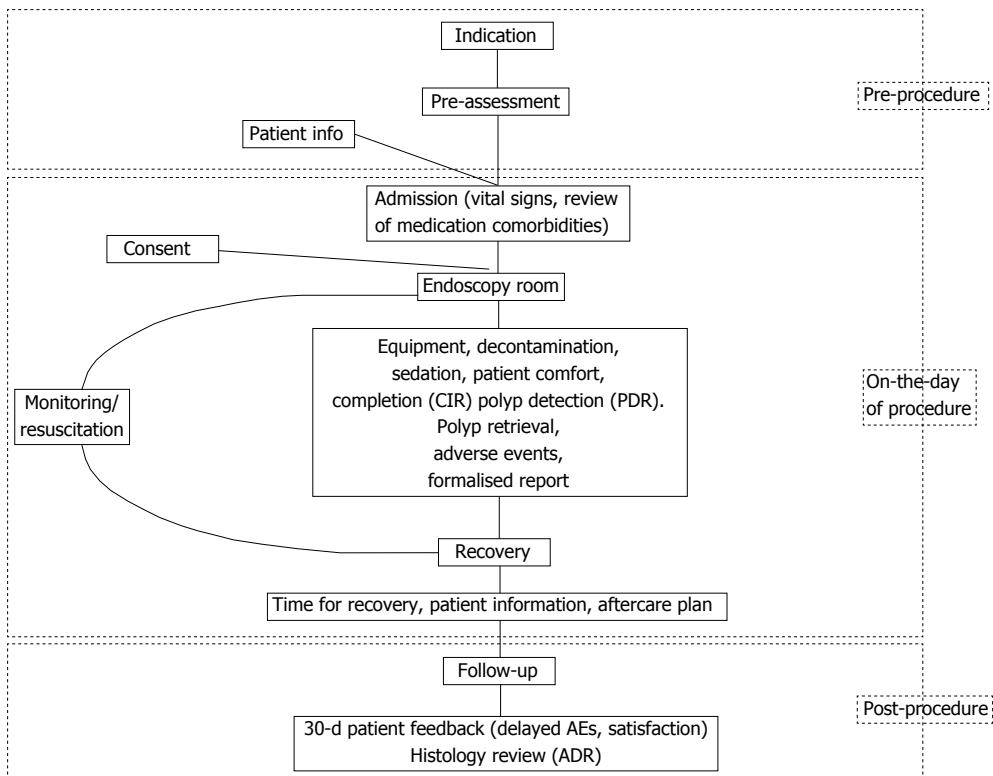


Figure 1 The cascade of colonoscopy. AE: Adverse event; ADR: Adenoma detection rate.

of adverse events related to colonoscopy which are potentially preventable^[2,3]. The establishment of important, measurable quality indicators (metrics) and minimum quality standards is essential to define and shape a quality colonoscopy service.

The current quality indicators and standards for colonoscopy are based on varying levels of evidence, ranging from local perceptions and expert consensus to evidence from randomized controlled trials. The terms “auditable outcome” (an important indicator for which no clear evidence base exists) and “quality standard” (an auditable outcome for which there is an evidence base that can support a minimum standard) have been introduced to help define quality in endoscopy^[4]. This paper does not aim to give technical details on how to perform colonoscopy but rather summarizes what to measure and when, in accordance with the current identified quality indicators and standards for colonoscopy.

HOW WE CAN MEASURE QUALITY

A colonoscopy service can be broken down into three main steps: pre-procedure, on the day of procedure and post-procedure (Figure 1). A high quality colonoscopy service should be patient-centered, evidence-based, cost-effective and adhering to best practice. Quality indicators and standards for each step of the colonoscopy service should be as simple and easy to audit as possible (Table 1).

Pre-procedure

An appropriate indication for colonoscopy should be

determined in 100% of cases. Guidelines for indications and contraindications for colonoscopy should be used as a filter to avoid unnecessary and potentially hazardous procedures^[5,6]. Time-scheduling should be based on priority (surveillance *vs* symptoms suggestive of CRC) and urgent referrals should be seen more rapidly. In our opinion a 6-wk time limit should be the maximum waiting time for a routine colonoscopy and $\geq 85\%$ of individuals initially offered a colonoscopy should finally undergo a colonoscopy^[4].

We recommend nurse-led patient pre-assessment either in a dedicated clinic or by telephone consultation especially when this has not been done by the vetting gastroenterologist. The endoscopist needs to have complete information of patient’s medical history prior to colonoscopy; comorbidities such as clotting disorders, use of anticoagulants or anti-platelet agents, diabetes, allergies, renal function impairment, glaucoma, heart failure and factors related to the risk of endocarditis should be recognised prior to colonoscopy and instructions given to each patient should be driven by current recommendations and local policy^[7-10]. The American Society of Anaesthesiologists (ASA) status and factors which could increase the risk and technical difficulty of colonoscopy, such as previous abdominal surgery (*i.e.*, hysterectomy) or diverticular disease should be recorded^[7,11].

Patient information leaflets should be available and sent out to patients as a routine, along with a copy of the consent form. Patients must be aware of why the procedure is being organised, what is involved and of the risks related to colonoscopy. They should be informed about

Table 1 Quality metrics for colonoscopy as proposed by ESGE's guidelines and BCSP in United Kingdom

When to measure	Outcome to measure	Standard
Pre-procedure	Appropriateness	100% indicated
	Pre-assessment-bowel prep to use	100% of cases
	Patient information	100% of cases
On the day of procedure	Awaiting time when positive test	< 4 wk (< 2 wk desirable)
	Review of comorbidities, check of vital signs	100% on admission
	Informed consent	100% signed
	Decontamination of endoscopes	100% agreement with local policy
	Appropriate function and availability of endoscopes/equipment	100% checked by competent staff
	Equipment for resuscitation and monitoring	100% regular checks
	CO ₂ insufflation	100% availability
	CIR	> 90% unadjusted
	Use of reversal agents	< 1/500 cases
	Bowel cleansing	good/excellent > 90%
	Patient comfort	NA
	Polyp detection rate	Dependent on case mix
	Polyp retrieval rate	> 90%
	Time of scope withdrawal	> 6 min
	Complication rates	Bleeding < 1/100
		Perforation < 1/1000 (diagnostic)
		< 1/500 (therapeutic)
Post-procedure	Electronically based endoscopy report	100% attached to histology request
	Aftercare plan	100% provided at recovery area
	Time for recovery	NA
	Annual number of procedures/endoscopist	> 150 (> 300 desirable)
	Adenoma detection rate	> 15% unadjusted to race or gender
	Time of histopathology report	< 15 d post-colonoscopy
	Patient feedback/delayed AEs	100% at 30 d
	Endoscopic Surveillance needed	100% agreement with guidelines

CIR: Caecal intubation rate; AEs: Adverse events; NA: Not available.

Table 2 Groups of patients in whom polyethylene glycol bowel-preparation is considered as safer and thus should be preferred

Candidates for polyethylene glycol bowel preparation for colonoscopy
¹ GFR < 60 mL/min per 1.73 m ²
Electrolyte imbalance
Cardiac failure
Liver cirrhosis
Hypertension with arteriosclerosis
Patients on diuretics
(when cannot be stopped 24 h prior to colonoscopy)
Patients on ACE inhibitors
(when cannot be stopped 72 h prior to colonoscopy)
Patients on NSAIDs
(when cannot be stopped 72 h prior to colonoscopy)

¹Estimated glomerular filtration rate (GFR) from serum creatinine concentration. NSAIDs: Nonsteroidal antiinflammatory drugs; ACE: Angiotensin-converting enzyme.

the options for sedation in advance and the associated restrictions on travelling home^[7].

A clean bowel is a prerequisite for a reliable and efficient examination^[12,13]. Clear patient information, reduced fiber diet, regardless of type of bowel preparation used, help to maximise bowel cleansing^[14]. PEG-electrolyte is the preparation of choice in patients with renal impairment although it does not eliminate the risk of acute renal failure and it is considered safer for patients with cardiac failure^[15,16]. Adequate hydration is vital to protect

against adverse events of bowel preparation while timing and in particular PM/AM splitting of administration of the recommended dose and assurance of patient's understanding of the process also appear to be important^[14,17]. Table 2 outlines patients at risk of electrolyte imbalance and documents those who of when should have an assessment of renal function prior to bowel preparation. Those with established renal disease, stage III or greater, should have PEG-electrolyte bowel preparation^[18-22]. In our institution we use a combination of 10 senna tablets and 2 doses of sodium picosulfate the day before colonoscopy for morning appointments, while the second dose of sodium picosulfate is taken in the morning of the same day for afternoon colonoscopies. The patient is encouraged to drink at least 2 L of clear fluids daily for 2 d before the procedure and to avoid fiber 2 d before scheduled colonoscopy. We usually use a 2lt PEG solution (MOVIPREP) when needed. Although hospitalisation has been related with poorer bowel cleansing and should be routinely avoided, hospital admission prior to colonoscopy may be required in some cases, especially for patients in whom reduced absorption of regular medications may prove problematic and may need intravenous administration. Fragile patients with multiple comorbidities which are at risk of cardiac or renal failure and should be monitored during bowel prep are often admitted to hospital prior to colonoscopy^[23]. Selection of these patients is a matter of careful clinical pre-assessment.

Colonoscopy in obese patients may prove technically demanding in some cases however, in our practice and according to previous reports, routine colonoscopy is the screening test of choice and can be performed adequately in obese patients when optimal standards are fulfilled^[23]. Patients with previous incomplete procedures, multiple comorbidities or on anticoagulant treatment in whom discontinuation can prove catastrophic should be offered a virtual colonoscopy (CT colonography) as an alternative. In these cases virtual colonoscopy may prove an important pre-assessment tool regarding the cost, tolerability and reduced time of the procedure compared with conventional colonoscopy^[24,25].

On the day of the procedure

A brief review of the cardiorespiratory function including blood pressure, pulse rate and oxygen saturation in addition to documentation of adverse events related to bowel preparation or any medication given prior to colonoscopy (*i.e.*, antibiotic prophylaxis) should be performed on the day of the procedure and before the patient's entrance into the endoscopy room.

A signed informed consent should be obtained by 100% of patients prior to colonoscopy, ideally in a separate area rather than the endoscopy room where a patient's privacy can be assured. Consent for colonoscopy must include a clear and realistic explanation of the procedure, possible attendant discomfort, the benefits and a clear discussion of risks and potential adverse events including sedation reactions, bleeding (immediate and delayed), perforation and missed pathology. Patient's right to withdraw consent at any stage of the colonoscopy process should be understood by all members of the team^[4,26]. Some institutions having the patient consented in clinic by the requesting consultant as well as giving the prescription for bowel preparation and patient leaflets and thus alleviating the need for postal issue for the same. This practice can prove beneficial acting as an indirect vetting as well of high risk patients.

Endoscopy room

The appropriateness, availability and functionality of the endoscopy room and equipment used during colonoscopy (including equipment used for patient monitoring) should be ensured through regular checks. Cleansing and decontamination of endoscopes should conform to current National or International guidelines^[27].

Monitoring of vital signs (blood pressure, pulse and oxygen saturation) and regular checks of patient's comfort and ability for verbal communication should be routinely used during colonoscopy. The use of CO₂ capnography is recommended to identify hypoventilation and hypoxia if heavy sedation required^[28].

Patient's comfort during colonoscopy is a critical quality outcome which refers to public acceptance rate of the procedure as a screening tool^[29]. Levels of patient discomfort (no or minimal, mild, moderate, severe) should be recorded during colonoscopy.

The use of CO₂ insufflation, instead of air, is currently a quality standard to maximize comfort during unsedated colonoscopy and flexible sigmoidoscopy and permits reliable radiologic examination at the same day following colonoscopy^[7,30]. Moreover, since carbon dioxide is an inert gas that cannot form a combustible mixture with hydrogen and methane, CO₂ insufflation avoids the very rare risk of explosion during colonoscopy with electrocautery and reduces post-polypectomy admissions after removal of large polyps^[31,32]. Insufflation of CO₂ should be avoided in patients with COPD, known CO₂ retention or severely reduced pulmonary function.

The use of sedation improves patient tolerance of colonoscopy. A "titrated" (administered gradually during procedure) low dose of an anxiolytic, such as midazolam (1.25-5 mg), given alone or combined with an opiate like pethidine (12.5-100 mg) or fentanyl (25-100 µg) are usually sufficient to achieve conscious sedation during colonoscopy^[33], however, thresholds of pain and over-sedation remain undistinguishable and variable between individuals. Dosage reduction should be considered for older patients (> 70)^[33-35]. Nitrous oxide/oxygen inhalation (Entonox) should be an alternative for people that cannot have intravenous sedation^[36]. The type and dose of medications used the level of sedation (minimal-anxiolysis, moderate-conscious, deep or general anaesthesia) and the use of reversal drugs should be recorded at every colonoscopy and should be an auditable safety outcome.

The adequacy of colonic cleansing is an important outcome related to the reliability and completion rates of colonoscopy and should be reported at each procedure. Valid scales for assessment of quality bowel preparation have been made according to the presence of solid or semisolid stool and the relative limitation to achieving adequate visualization^[37,38]. Excellent or adequate bowel preparation documented in > 90% of cases has been considered as a standard of bowel preparation efficacy^[4,7].

Intubation of the most proximal part of the colon is a prerequisite to achieving complete examination. Intubation of the terminal ileum (TI) is not required if there is not specific indication while obtaining biopsies from normal TI is discouraged secondary to the relative concern of variant Creutzfeldt - Jakob disease's transmission^[39]. Caecal intubation rate (CIR) is a key quality indicator that reflects the performance skills of each colonoscopist, but can be affected by a variety of factors that can make the insertion of the scope difficult or impossible^[40]. The main conflict in measuring the CIR of each colonoscopist is whether it should be adjusted for bowel preparation, obstructive lesions or for symptomatic patients. Overall, an unadjusted CIR > 90% can be used as the quality standard of colonoscopy, regardless of case^[7].

The routine use of photodocumentation or videorecording is an emerging necessity in relation to the medicolegal risks of missed pathology or adverse events

(AEs) following colonoscopy^[41]. Photographic evidence of the appendix orifice and/or the ileocaecal valve has been considered as a standard practice to achieve completion^[7]. Unarguably, additional pictures of the ileal mucosa provide strong evidence of completion^[42]. Rectal retroversion has been considered as an established diagnostic technique to improve detection of lesions abutting the dental line^[43,44] however an adequate examination can also be performed by tip manipulation in the forward view.

The incidence of colorectal cancer (CRC) can be significantly reduced through detection and appropriate removal of adenomatous polyps during colonoscopy^[1]. The polyp detection rate (PDR) is defined as the number of colonoscopies at which one or more polyps were found (regardless of histological type) divided by the total number of colonoscopies performed (in the same time period). Counting polyps or polypectomy rates is easy during colonoscopy but is not as important parameter as adenoma detection rate (see later). A high retrieval rate (> 90%) of polyps removed is a recognized quality standard in the United Kingdom BCS program and can be affected by polyp size and cold snare technique of polypectomy^[45]. The number and size of adenomatous polyps removed at colonoscopy should be recorded as this defines the risk of CRC and determines endoscopic surveillance^[4,46,47].

Time spent on withdrawal (WT) is an important quality outcome and should be recorded during colonoscopy. A time for scope withdrawal of more than 6 min has been well-correlated with increased detection of adenomas and thus is considered as an important quality standard to be followed by each endoscopist^[48]. Longer WT has been related with increased detection of proximal and serrated polyps^[49,50]. Probably adequate withdraw technique and high technical endoscopist's skills are more important to increase detection rate when appropriate WT (> 6 min) has been spent, but this is a matter of proper training and accreditation in colonoscopy that exceeds the purposes of this paper^[51,52].

AEs in colonoscopy are uncommon but can be life threatening. Appropriate documentation of AEs related to colonoscopy is a substantial outcome of safety of the procedure. A Lexicon has been previously developed to provide clear definitions for AEs and levels of severity, including the minimum threshold at which an AE should be documented and reported^[53]. Early AEs (bleeding, perforation, oversedation, vasovagal attacks), whether they have been adequately resolved during the procedure (*i.e.*, use of haemostatic equipment or reversal drugs, hydration) or whether further actions are required, have to be clearly documented.

The endoscopist should be competent with the function of all supplementary equipment used during the procedure. Therapeutic colonoscopists should be technically competent to identify and safely remove high-risk lesions and be comfortable with techniques of endoscopic haemostasis^[54,55]. Around 90% of post-pol-

ypectomy bleeding should be amenable to conservative management without the need for surgical intervention. According to current recommendations based on data from retrospective studies, the incidence of bleeding for colonoscopies where polypectomy is performed should not exceed 1/100^[4]. However, this is a cut-off point that needs to be adjusted according to the time (immediate or delayed) and severity of bleeding, patients' comorbidities and complexity of the procedure (*i.e.*, EMR or simple polypectomy). Future analysis of risk factors for delayed bleeding should be possible and would optimally permit individualization of the risk of bleeding between patients. Risk of perforation should not exceed 1/1000 procedures, but may have to be adjusted to 1/500 for therapeutic colonoscopies with polypectomy^[4]. In cases of therapeutic colonoscopy, the final report should include a clear description of "alarm post procedural symptoms" symptoms such as rectal bleeding, fever or abdominal pain that can be associated with delayed AEs requiring immediate medical support^[4,56,57].

An increased number of AEs (*ie* bleeding or perforation) during therapeutic procedures always raise issues about the adequacy of therapeutic skills of each endoscopist. The European guidelines for quality assurance in colorectal cancer screening and diagnosis have proposed 5 levels of competency in colonoscopy related to the interventional armamentarium of each colonoscopist. According to this consensus colonoscopists should be able at least to remove lesions < 10 mm in order to avoid additional endoscopic procedures. We recommend that basic EMR technique for sessile polyps 1-2 cm in size, or for small flat adenomas smaller than 1 cm, should be within the armamentarium of all colonoscopists.

Recovery area

Standard protocols for monitoring and for emergencies should be available in the recovery area. Checks of availability and proper function of resuscitation and monitoring equipment should be regularly updated. Time of recovery is an important auditable outcome and should be recorded. After recovering from sedation and before leaving the endoscopy unit, patients need to be told about the outcome of their procedure in a simple and comprehensive way. Breaking bad news regarding suspicion of cancer should be done according to the established local policy. The average waiting time for the histopathology report and the aftercare plan should be provided and supported by a detailed written report of the procedure that includes a contact telephone number (24 h/d, 7 d/wk) in case of a procedure-related complication. An electronically based and formalized endoscopy report is essential for further interpretation of outcomes.

A copy of the endoscopy report should be attached to any histology request and should be as detailed as possible to provide accurate description of suspicious lesions including their location, their estimated size, their nature according to accredited classification systems (*i.e.*,

Paris or Lateral Spreading Tumors - LST - classification)^[58], whether they are ulcerated and in case of excision whether this was completed or not.

Post-procedure

Adenoma detection rate (ADR) is currently the benchmark of quality in colonoscopy and represents the number of colonoscopies at which one or more histologically confirmed adenomas were found divided by the total number of colonoscopies performed in the same time period^[59]. ADR reflects a colonoscopist's technical skills and care to achieve visualization of the entire colon during the procedure. High ADRs reduce the probability of interval cancer by correctly identify surveillance intervals^[60]. The overall prevalence of CRC, polyps and adenomas may differ between patient populations according to gender, race, diet or environmental factors and subsequently ADRs may vary^[61]. Measurement of ADR is greatly assisted by a direct link between the databases of the endoscopy and pathology departments, but this is not available everywhere^[62]. Polypectomy rates can potentially provide an ADR estimate based on previous ADRs but polyp detection rate (PDR) should be used cautiously for polyps of the left colon^[63-66]. Previous reports argue that reliability of ADR is much higher when refers to a sufficient volume of colonoscopies (> 150/year in our BCSP) while the number and features (size, histology or grade of dysplasia) of adenomas detected per procedure is not included when counting ADR^[67,68]. The mean number of adenomas per procedure (MAP) (defined as the total number of adenomas detected divided by the number of procedures) and the mean number of adenomas per positive procedure (MAP+) (defined as the total number of adenomas detected divided by the number of procedures in which one or more adenomas were detected) can provide additional information for endoscopist's performance^[44,69,70]. We recommend an ADR > 15% as the minimum outcome unadjusted for gender or race.

The reliability of a colonoscopy service is dependent on a well-organized aftercare system. This should provide patients with easy-access to further care pathways deemed necessary by colonoscopy such as appropriate time for follow-up colonoscopy (indicated by current guidelines) need for radiological or surgical examination or referral to local Multi-Disciplinary-Team (MDT) meeting. This network should ensure that no patient is lost to follow-up and it requires good communication between relevant departments (Gastroenterology, Radiology, Histopathology and Surgery).

A routine policy of contacting patients within a defined period of time (30 d) following colonoscopy is recommended to check for delayed adverse events related to the procedure and to obtain the overall patient's feedback for the service. A simple quality questionnaire for each part of colonoscopy service is useful to detect problems with the service. We recommend a routine 30-d check for every patient having a colonoscopy while patients should also be encouraged to report any AE

in the meantime. Regular reviews of complications and 30-d mortality is an essential part of quality assurance. Records of adverse events should be kept active. Clusters of AEs should instigate a formal review of individual cases.

CONCLUSION

Quality in colonoscopy encompasses optimal collaboration of various professionals with clearly defined processes. Quality assurance in colonoscopy should be based on measurement of simple and reproducible outcomes which permit regular checks on each step of the colonoscopy service. CIR and ADR are the key elements of personal endoscopic performance and their value is maximized when standards of patient's safety, comfort and satisfaction are adequately monitored and reviewed.

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Enteroscopy in small bowel Crohn's disease: A review

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Abstract

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract resulting in inflammation, stricturing and fistulae secondary to transmural inflammation. Diagnosis relies on clinical history, abnormal laboratory parameters, characteristic radiologic and endoscopic changes within the gastrointestinal tract and most importantly a supportive histology. The article is intended mainly for the general gastroenterologist and for other interested physicians. Management of small bowel CD has been suboptimal and limited due to the inaccessibility of the small bowel. Enteroscopy has had a significant renaissance recently, thereby extending the reach of the endoscopist, aiding diagnosis and enabling therapeutic interventions in the small bowel. Radiologic imaging is used as the first line modality to visualise the small bowel. If the clinical suspicion is high, wireless capsule endoscopy (WCE) is used to rule out superficial and early disease, despite the above investigations being normal. This is followed by push enteroscopy or device assisted enteroscopy (DAE) as is appropriate. This approach has been found to be the most cost effective

and least invasive. DAE includes balloon-assisted enteroscopy, [double balloon enteroscopy (DBE), single balloon enteroscopy (SBE) and more recently spiral enteroscopy (SE)]. This review is not going to cover the various other indications of enteroscopy, radiological small bowel investigations nor WCE and limited only to enteroscopy in small bowel Crohn's. These excluded topics already have comprehensive reviews. Evidence available from randomized controlled trials comparing the various modalities is limited and at best regarded as Grade C or D (based on expert opinion). The evidence suggests that all three DAE modalities have comparable insertion depths, diagnostic and therapeutic efficacies and complication rates, though most favour DBE due to higher rates of total enteroscopy. SE is quicker than DBE, but lower complete enteroscopy rates. SBE has quicker procedural times and is evolving but the least available DAE today. Larger prospective randomised controlled trial's in the future could help us understand some unanswered areas including the role of BAE in small bowel screening and comparative studies between the main types of enteroscopy in small bowel CD.

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Key words: Crohn's disease; Enteroscopy; Ileoscopy; Balloon-assisted; Device-assisted; Spiral device; Over-tube; Stricture; Dilatation

Core tip: Management of small bowel Crohn's disease has reached new frontiers with the recent renaissance of enteroscopy, that has improved diagnosis and enabled therapeutic interventions. The use of magnetic resonance enteroclysis or wireless capsule endoscopy as the first line modality followed by enteroscopy is the most cost effective. Enteroscopy could be achieved using either a push enteroscope or device-assisted enteroscope (DAE). The latter includes double balloon enteroscopy (DBE), single balloon enteroscopy and more recently spiral enteroscopy. All three DAE modalities are comparable, though most favour DBE due to higher rates of total enteroscopy. The article

is intended for the general gastroenterologists, non-gastroenterologists and general practitioners

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INTRODUCTION

Crohn's disease (CD) is a chronic inflammatory condition of the gastrointestinal tract resulting in inflammation, stricturing and fistulae secondary to transmural inflammation^[1,2]. Diagnosis relies on clinical history, abnormal laboratory parameters characteristic radiologic and endoscopic changes within the gastrointestinal tract and most importantly histology for confirmation and grading of severity^[2]. CD can affect the entire gastrointestinal tract from mouth to anus, in addition to being a multisystem disease. It affects only the small intestine in 30%, ileo-colonic in 50%, colonic disease alone in 30% and upper GI tract in approximately in 5%^[3,4]. CD may have characteristic endoscopic features like aphthous ulcers, longitudinal erosions, cobble stone appearance and fissures^[4,5] (Figure 1).

The detection of small bowel CD and its management presents its own challenges, especially when the disease is present beyond the reach of the gastroscope and colonoscope. This is mainly due to length of the small bowel but also the tortuous anatomy and the floppy mesentery that leads to looping when a scope is advanced beyond the duodenum^[6-13]. The distal 10-20 cm of the ileum can often be accessible with ileo-colonoscopy but more proximal visualisation is often limited by looping. In addition, disease of the ileo-caecal valve can prevent intubation of the ileum. Enteroscopy helps in assessing mucosal disease while cross sectional imaging is better for transmural involvement including fistulae. Small bowel radiological investigations include barium follow through, computed tomography (CT) enteroclysis or enterography, magnetic resonance enteroclysis or enterography and small bowel ultrasound (USS)^[7,9-13]. The latter is not widely used since the ultrasound waves have limited penetration through air. However it is useful in assessing thickness of the small bowel and vascularity with Doppler and correlates with active disease. Wireless capsule endoscopy (WCE) is a sensitive test for small bowel disease and is often used to investigate small bowel CD, prior to any invasive deep bowel enteroscopy, once small bowel strictures have been excluded^[1,14-19]. Di-onissio *et al*^[20] had shown in their meta-analysis comparing 18 prospective studies that WCE was best in evaluation of non-stricturing small bowel CD and magnetic resonance enteroclysis (MRE) had the highest diagnostic yield in known CD. This review is not going to cover the various radiological investigations or WCE^[20,21].

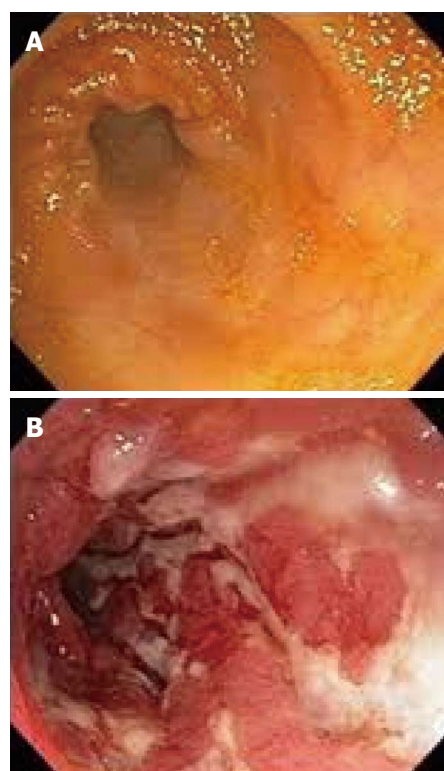


Figure 1 Normal (A) vs small bowel Crohn's (B).

Technological advances have extended the reach of the gastroenterologist, enabling access to the entire gut using flexible fibre optic scopes, with a combination of pushing, pulling and torquing to pleat the long and tortuous small bowel. Enteroscopy has improved the field of small bowel CD, in which radiological investigations previously predominated. Despite all these tools to empower the gastroenterologist and radiologist, the assessment of small bowel damage in CD is still far from sufficient. Evidence available from randomised controlled trials comparing the various modalities is limited and at best regarded as Grade C or D (based on expert opinion). Most of the studies performed to date are single centre experiences (retrospective studies) or multicentre trials involving small numbers. Thus a main limitation of this article is lack of comparative data specifically on CD.

The advantages of enteroscopy include the ability for real-time viewing of the small bowel, to biopsy abnormal mucosa and to undertake therapy such as pneumatic dilatation using the through-the-scope (TTS) balloons, achieving hemostasis, polypectomy, local injection of triamcinolone and immunomodulatory drugs and more recently metallic and biodegradable stent insertion^[18,22-25]. Endoscopic dilatation (ED), the commonest therapeutic use of deep enteroscopy in CD, has been used when medical therapy fails to relieve obstruction. These are often done using centre based and regional guidelines, which are often tailored depending on the availability of local expertise, financial constraints and patient preference. The scope of an enteroscope is much wider, including comple-

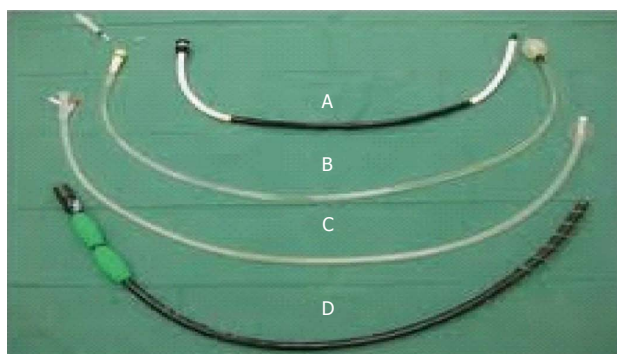


Figure 2 Device assisted enteroscopes. A: Conventional semi-rigid overtube (Olympus); B: Double-balloon overtube (Fujinon); C: Single-balloon overtube (Olympus); D: Spiral overtube (Spirus Medical). Available from: URL: www.analgastro.gr.

tion colonoscopy and for endoscopic retrograde cholangiopancreatography in surgically altered anatomy^[24,25]. The various methods currently available worldwide can be either a push enteroscopy (PE) or device-assisted enteroscopy (DAE) using overtubes (Figure 2). The latter includes balloon-assisted enteroscopes (BAE) [double balloon enteroscopy (DBE) and single balloon enteroscopy (SBE)] and more recently spiral enteroscopy (SE). The complimentary use of cross sectional imaging and endoscopy is invaluable in the diagnosis and management of small bowel CD (Table 1).

PUSH ENTEROSCOPY

Traditional push enteroscope was developed in the 1980's. PE has a working length between 220 and 250 cm and is inserted per orally directly into the proximal jejunum^[26]. The alternative is to use an adult or paediatric colonoscope for the same purpose. It can be used for both diagnostic and therapeutic purposes^[26-29]. The push enteroscope may be used with or without an overtube (Figure 3). There have been several studies comparing the use of an overtube in push enteroscopy but not specifically in CD. Taylor and colleagues studied a small group of 38 patients (19 with an overtube and 19 without) and compared the depth of insertion as measured by the distance of insertion with the scope in a shortened position^[29]. The median total straightened scope length of insertion just reached significance (125 cm *vs* 110 cm). From the pylorus the depth of insertion was also significant (70 cm *vs* 50 cm). However, there was no significant difference in the detection of small bowel pathology^[29]. Overall complication rate of this widely available procedure in this study was 1%.

This technique is still commonly used to assess and treat proximal small bowel pathology due to its ease of use. Benz and colleagues studied enteroscopy in a group of 80 patients randomly assigned to enteroscopy with an overtube *vs* enteroscopy without an overtube^[27]. The authors found that depth of insertion as measured by distance in a straightened position from the pylorus and

Table 1 Ranking of enteroscopic techniques for small bowel Crohn's disease

Modality tested	PE	DBE	SBE	SE
Availability	1	2	3	4
Ease of use	1	4	3	2
Platform used	Any	Fujinon	Olympus	Any
No of operators	1	1 ²	1	2 ¹
Depth achieved	4	1	2	3
Speed	1	4	3	2
Therapeutic	4	2	2	1 ¹
Safety	1	2	2	2
Cost	1	3	3	2

The numbers 1 to 4 refer to the authors ranking, with 1 being the highest and 4 being the lowest. ¹Once motorised might need only one operator. Best for stent insertion due to the stability achieved due to the overtube stabilization, though completion rates better for DBE/SBE; ²Needs two operators in the early phase of the learning curve. PE: Push enteroscopy; DBE: Double balloon enteroscopy; SBE: Single balloon enteroscopy; SE: Spiral enteroscopy.

number of counted folds was significantly increased by using an overtube. A further study by the same author compared 2 working lengths of endoscope (250 cm *vs* 220 cm) to compare the depth of insertion in 28 patients^[28]. An overtube was used in all cases. The median insertion from the pylorus was 72.5 cm *vs* 70.0 cm but no significant difference was demonstrated in depth of small bowel insertion using a longer endoscope^[28].

Another method of improving depth of insertion into the small bowel is by using a variable stiffness scope in an attempt to reduce excess looping of the scope within the stomach^[30]. Harewood and colleagues prospectively studied enteroscopy in 3 groups of patients (one with standard enteroscope with overtube, one without overtube and a third one with variable stiffness)^[31]. Depth of insertion beyond the ligament of Treitz was significantly greater using a variable stiffness enteroscope (89 cm) compared to a standard enteroscope (68 cm) and was over twice that without an overtube (41 cm) ($P = 0.03$). In this study, patients in the overtube group required significantly more sedation than the other groups, although the overall patient tolerance and procedure duration showed no significant difference. Again, no additional yield of pathological findings was observed with the greater depth of insertion^[32]. In a small study by Perez-Cuadrado *et al*^[33], 50% (4 of 8) of this patient group with suspected CD had detectable macroscopic and/or microscopic evidence of small bowel CD not detected by other endoscopic or radiological methods. The same author demonstrated the therapeutic role of PE in small bowel Crohn's for jejunal stricture dilatation^[32]. In a recent study by Darbari *et al*^[34], it was shown that PE was useful and safe in proximal small bowel disease, predominantly CD, leading on to definite change in management. In this study, proximal small bowel CD was detected in 23 out of 44 suspected cases. ED is often considered successful if the scope could be passed through the stricture once dilated. ED should ideally be limited to accessible linear fibrotic strictures under 4 cm

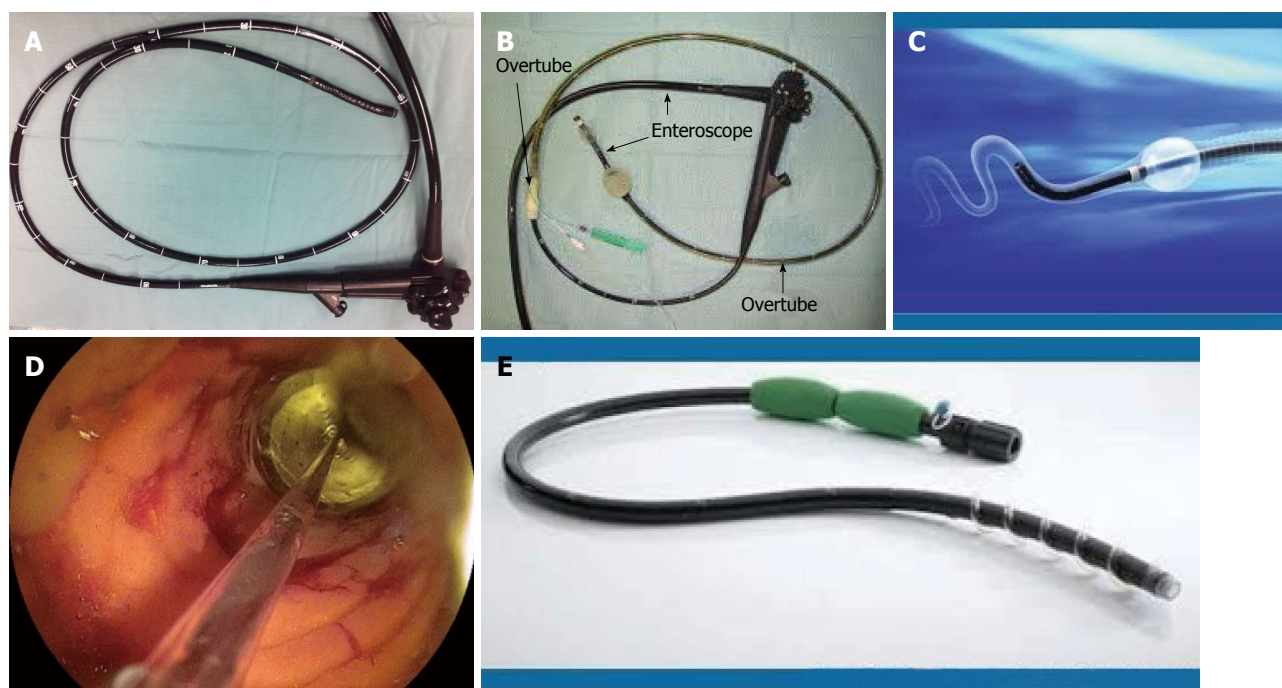


Figure 3 Enteroscope. A: Push enteroscope; B: Double balloon enteroscope (www.sciencedirect.com); C: Single balloon enteroscope (www.medscape.com); D: Balloon dilatation of jejunal stricture (www.kcvi.cz); E: Spiral enteroscope (www.medscape.com).

length to minimise risk of perforation^[35,36].

DBE

DBE, originally developed in 2001 by Prof Hironori Yamamoto, is useful in the diagnosis of small bowel diseases including (CD)^[9,23,37-39] (Figure 3B). DBE is often used following WCE due to potential miss rate of the latter and to guide the approach of insertion of DBE (antegrade or retrograde). The standard system has an endoscope with an outer diameter of 8.5 mm and a working length of 200 cm^[38-40]. It is also provided with a 145 cm soft overtube with 12.2 mm outer diameter and a dedicated pump. One balloon is attached to the tip of the scope, after back loading the overtube (which has an additional balloon attached to the tip of the overtube)^[6,25,32,39,41,42]. DBE can be performed with an antegrade (oral) followed by a retrograde (anal) approach or vice versa, with conscious sedation, deep sedation or general anaesthesia. Either air or carbon dioxide can be used, the latter recommended due to better patient tolerance, especially for therapeutic procedures and less post procedural discomfort, when a prolonged procedure is anticipated. Fluoroscopic guidance could be used till competence is achieved, but is not essential^[39-41,43].

The overall yield of DBE was better than push enteroscopy and similar to capsule. Oshitani *et al*^[6] showed that, in their study of 30 patients with CD, small bowel ulcers and aphthae were picked up in 9 patients who underwent DBE who had normal small bowel follow through. WCE done in 8 of these patients without symptoms of strictures showed additional finding of small bowel scarring in only one of the patients, though

one of the eight developed capsule retention, that was retrieved using DBE. Nine ileal strictures were picked up with barium compared to only 6 with DBE^[6].

The scope is inserted as far as possible into the bowel. Then the overtube balloon is inflated to anchor the tip in place and the scope is gently pulled backward to pleat the small bowel behind the balloon. The scope is further advanced into the lumen, followed by inflation of the scope balloon to anchor its tip. Thus by repetitive cycles of balloon inflation/deflation, the scope is advanced. In the early stages of training, this needs two operators, though once experienced one would be sufficient (Figure 4)^[39]. A practical tip that is often advocated by Professor Yamamoto to advance an enteroscope is, slight “jiggling” of the scope, with alternating small “in-out” and “right-left” movements, that enables the tip to move forward. The distal most point is tattooed with India ink in the antegrade approach, to be visualised *via* the retrograde approach for total enteroscopy^[24,37,44,45]. The procedure time can vary between 70 to 120 min for the ante-grade procedure and about 15-20 min longer for the retrograde approach, with ileal intubation rates in the latter being over 90% in high volume centre^[43]. DBE has a steep learning curve^[39,46]. Zhang *et al*^[47] rightly commented that the combined analysis of imaging and gastro endoscopic findings in addition to a diligent clinical history and examination is essential to enhance the diagnostic efficiency of DBE.

In a study of 37 patients with CD who underwent DBE diagnostic yield was 60%. Yield levels increased if direction of insertion (ante-grade or retrograde) was aided by prior investigations^[9]. The retrograde approach is useful for lesions noted in the distal 40% of

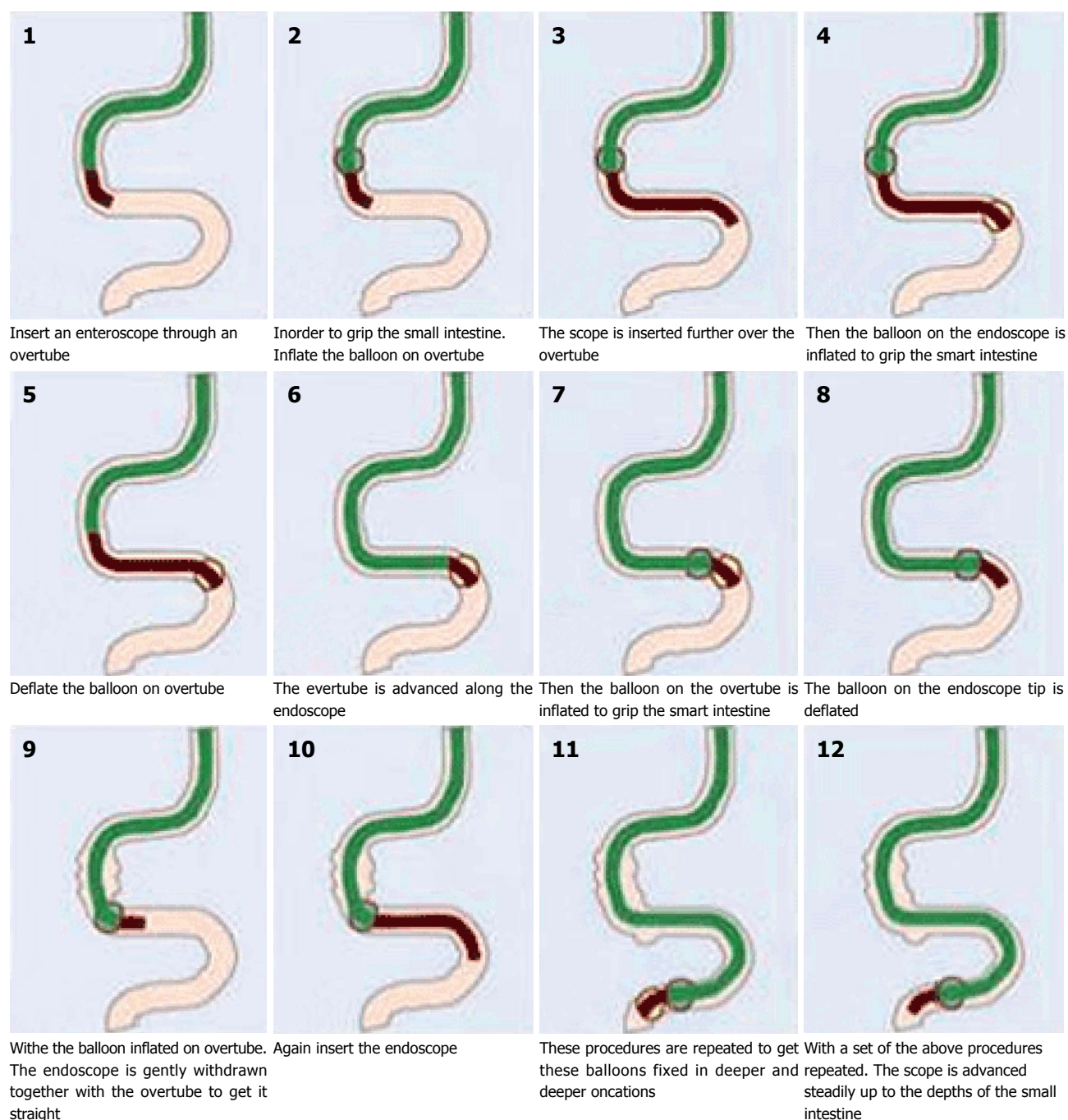


Figure 4 Push and pull technique with double balloon enteroscopy. Available from: URL: www.wjsvitagarten.com.

the WCE^[48]. In an early retrospective study, the role of DBE in evaluation of 40 patients with CD was found to be superior to radiological studies in detecting mucosal ulcers and strictures^[6]. Moreover endoscopic findings often precede radiologic findings that often delay the diagnosis by 1 to 7 years, and hence earlier diagnosis with DBE may lead on to earlier mucosal healing that is the corner stone in management of CD^[8,45,49,50]. The ability of therapeutic potential of DBE remains a significant advantage over capsule endoscopy. In a study of 19 patients (10 amenable to endoscopic therapy), Pohl *et al*^[51] demonstrated that dilatation under fluoroscopy yielded a clinical improvement in 80% and avoidance of

surgery in 60% albeit over a mean short term follow up period of 10 mo, with no reported complications. The technique is also useful for retrieval of retained capsules^[2,38,43,52].

In a similar study, 8 of 9 patients with Crohn's strictures underwent successful endoscopic dilatation (1 patient had a perforation). Clinical improvement occurred in these 8 patients with no surgical requirement over a follow up of 20 mo. Twenty five percent of patients did require a second dilatation^[53]. DBE has been shown to alter medical management in patients with established and suspected CD. Mensink and colleagues identified 24 patients with active CD (60% of study population)

resulting in a change in management in 75% through a step up approach in these patients medical management. Over 80% of these patients had a clinical improvement with a reduction in CDAI^[54,55]. In a further study by the same author a small population of Crohn's patients with suspected proximal small intestinal Crohn's underwent DBE. Approximately three quarters of patients had proximal small bowel Crohn's features, and approximately 50% were beyond reach of standard enteroscopy. There was a change in management in three quarters of those patients with detectable disease by DBE^[55]. DBE can also help in assessment of radiologic abnormalities and thus to avoid unnecessary exploratory surgery^[8,49,54,56].

The procedure hence is very valuable with a high success rate, but not preferred for those with difficult anatomy due to previous surgery, pathology or acute angle at the stoma due to higher perforation rate (0.4% of procedures and up to 3% when dilated)^[43,57-59]. It should also be avoided in those with latex allergy since the balloons are made of latex^[8]. The other complications include small risk of pancreatitis (0.3% of procedures), bleeding (0.2% of procedures) and aspiration pneumonia^[60-62]. ED should be postponed till the ulcer heals due to higher risk of perforation and is discouraged if over 6 cm long^[63].

SBE

SBE was introduced in 2007. It uses an enteroscope with 200 cm working length and 2.8 mm channel diameter, an overtube with a silicone balloon that has an outer diameter of 13.2 mm and a balloon controller pump^[57,64,65]. The technique is similar to DBE, with the only difference being that the tip of the flexible scope is used to anchor the endoscope, avoiding need of a second balloon^[65] (Figure 3C). The depth of insertion ranges from 133 to 270 cm and 73 to 199 cm for the retrograde examination, with a therapeutic yield between 7% to 50%. Total enteroscopy rate is lower than DBE, but is a safe, effective and useful technique for deep small bowel endoscopy^[64,66-68]. The main advantage of SBE is the ease of assembling the apparatus taking 5 min compared to 15 min for DBE and overall shorter procedure duration of 55 min compared to 95 for DBE. Secondly it has variable stiffness, thus eliminating the need for a stiffening wire^[67,69-73]. Thirdly SBE can be used in patients with latex allergy unlike DBE. Dr. Reddy's group from Hyderabad, initially described use of "power suction" during straightening of the scope, that can be used instead of inversion of the tip, to minimise the perforation rate that is around 2%^[74].

In a small study in children between 8 and 18 years old by de Ridder *et al.*^[68], it was shown that SBE is a safe technique and picks up active small bowel Crohn's that has been missed by magnetic resonance imaging and USS. Similarly, Di Nardo *et al.*^[69], showed the safety, yield and therapeutic efficacy of SBE in their study of 16

children with suspected and 14 with known Crohn's with atypical presentation, who had negative radiologic and conventional upper and lower gastrointestinal endoscopy. In a recent randomised multicenter trial, Domagk *et al.*^[66] showed the non-inferiority of SBE over DBE in evaluation of small bowel pathology^[71]. Takano *et al.*^[70] showed in their randomised controlled trial that, total enteroscopy was much better accomplished with DBE than SBE, though it was a single centre study involving only small numbers. Bortlik *et al.*^[75] showed that in their experience of SBE in 35 patients, it provided an evaluation of mucosal healing after treatment and revealed severe inflammatory changes in one third. Therapeutic procedures especially dilation using TTS balloon were done in approximately a third (Figure 3D). SBE is cheaper, easier to perform, has a shorter learning curve than DBE and is a less complex method of balloon assisted enteroscopy^[65,66,68,71,73,76]. Current results are conflicting if the SBE and DBE have comparable performance and diagnostic yield. However, more studies favour use of DBE for total small bowel enteroscopy^[70].

SE

This is the latest of the armamentarium, available since 2008 to gastroenterologists, to examine the small bowel and is simpler and faster than the predecessors^[71,77,78]. The current second generation device uses an FDA approved 118 cm Endo-Ease DiscoveryTM SB overtube with a soft raised helix, a coupling device to fix the lubricated overtube to the enteroscope 25 cm from its tip, two handles for manual rotation and an injection port for lubrication (C 8)^[74,79-82]. The distal end of the device has an external diameter of 16 mm and the internal diameter of the overtube is 9.8 mm. Clockwise rotation pleats the small bowel onto the scope, once engaged and advances the same thus transforming the torquing force into a linear one, the concept developed by Spirus Medical, Inc. and proposed for use in enteroscopy by Dr. Akerman *et al.*^[77,81,82] in 2006. Push and rotation technique is used until the scope gets beyond the Ligament of Trietz, followed by only rotation. The small bowel does not get twisted as it is held by the mesentery. It can be performed under conscious sedation or general anaesthetic, preferably the latter. In an intubated patient, the cuff on the endotracheal tube has to be deflated before introducing the spiral enteroscope to prevent oesophageal trauma, until it enters the stomach^[77,83,84] (Figure 3E).

The major advantage of SE is the rapid advancement and stable controlled withdrawal enabling therapeutics to be delivered effectively^[42,71,77,84]. The overtube can be disengaged from the coupler enabling complete withdrawal of the endoscope and reintroduction (often needed for removal of multiple polyps), without losing the position in the small bowel^[42,71,84-86]. The other major advantage is that no dedicated enteroscopy system needs to be purchased and the Endo-Ease spiral overtube could transform an ordinary enteroscope or a paediatric colono-

scope to a SE device^[40,77,78,81]. Spiral enteroscopy is very useful for proximal small bowel pathology, especially for therapeutic interventions, due to the stability achieved with the overtube.

This procedure requires two operators, one operator handling the scope and the other rotating the overtube. The enteroscope is unlocked from the overtube, advanced and then withdrawn using the hook and suction technique. Anticlockwise rotation of the handle of the overtube is used to withdraw the system allowing visualisation of the mucosa in a controlled fashion. The depth of insertion of SE is usually calculated on the way out. It has not yet been safely demonstrated for retrograde approach, unlike DBE. A promising motorised overtube is in its early stages of development, which could make it single operator dependent. Sore throat and transient difficulty in swallowing are described by around a quarter of the patients, though tiny asymptomatic mucosal disruptions are similar to the balloon assisted devices.

In a study by Buscaglia *et al*^[83] the mean procedure length was around 34 min with a mean insertion depth of 262 cm. One of the early studies by Frieling *et al*^[87] showed that the diagnostic yield of DBE was superior to that of SE. But as the authors commented, one of the main drawbacks was that it involved only small numbers of 17 and 18 subjects respectively. In yet another small cross over study involving 10 patients, May *et al*^[42] showed that SE had a shorter procedure duration by a mean of 22 min, though the depth of insertion was greater by about 60 cm with DBE. Khashab *et al*^[86] in their first comparative study on SE *vs* SBE, showed greater depth of maximal insertion with the former, although the yield and procedure length were comparable. Akerman *et al*^[77,81] showed an overall severe complication rate less than 0.3% in their review of 2950 patients treated with SE, with perforation occurring in 0.4% of the first 1750 patients and no reported cases of pancreatitis. However Teshima *et al*^[88] showed that asymptomatic hyperamylasaemia occurred in up to 20% of patients undergoing SE. Data is limited especially with regards to comparative studies specifically related to use of SE in CD. But overall it is considered to be a safe and quick procedure and compares favourably with other DAE for assessing the small bowel and for delivering therapies in the midgut^[71,77,79,80,83-86,89,90].

OTHER METHODS OF DEEP SMALL BOWEL ENTEROSCOPY

Intraoperative enteroscopy (IOE) developed over 35 years ago enables the entire gut to be viewed without making an incision on the intestine, by the cooperation of the operating surgeon and the endoscopist^[91]. It was done using rigid sigmoidoscopes in the 50's, until fibre optic scopes became available in the 70's^[92]. Once the surgeon has completed exploring the small bowel laparoscopically and freed the bowel from any adhesions, small bowel loops can be pleated over the orally

inserted PE. The current role of IOE is in difficult mid gut pathology, in guiding the surgeon intraoperatively and in marking the lesion with a suture to be dealt with on removing the scope^[92-96]. There have not been many studies evaluating role of IOE in CD^[94,97]. Complications include standard ones associated with laparoscopy and endoscopy, prolonged post operative ileus, air embolism and multiorgan failure. IOE once regarded as the gold standard for small bowel evaluation has been relegated a "last resort" in the era of less invasive therapeutic total enteroscopy with DAE^[91,95-98].

CONCLUSION

Novel biologic agents and progress in our assessment and management of small bowel CD, which is currently far from sufficient, might help alter the natural history and predict outcomes in Crohn's disease. However enteroscopy, which is a rapidly evolving field, has had a significant renaissance recently and the small bowel is no longer the black box for the endoscopist or the final frontier. The lack of randomised controlled trial's (RCT's) and meta-analysis on enteroscopy in small bowel Crohn's limits more detailed comparative data between various techniques. PE is still a useful tool in centres that do not have WCE, BAE or SE. An algorithm that we suggest for investigation of small bowel CD would be gastroscopy and colonoscopy (with terminal ileal assessment). This might be followed by either a barium small bowel follow through or CT enteroclysis and increasingly by using MRE, considering the lack of radiation and possibility of repeated studies, considering the fact that the age group affected is often young or middle aged people of child bearing age, to limit radiation exposure. If MRE is normal one could consider WCE, if there is a high index of suspicion of early mucosal disease or malabsorption, which may not show up in MRE. If there is evidence of active small bowel Crohn's especially strictures or fistulae, then ideally aggressive treatment with anti tumour necrosis factor from the outset. If any complications of CD are seen, such as strictures or bleeding, then DBE/SBE or SE, depending on availability of local expertise, to assess the pathology and consider local treatment-biopsy, diathermy, balloon dilatation or injection of various drugs as might be appropriate to the setting. If initial small bowel imaging at time of first diagnosis is normal, then currently no recommendations are available regarding surveillance intervals or its clinical relevance. There may be multi centre studies in the future can look into appropriate screening intervals and on a more tailored approach for enteroscopy in CD.

A comparison of the various enteroscopy techniques is summarised in the table below. The evidence suggests that all three DAE modalities have comparable insertion depths, diagnostic and therapeutic efficacies and complication rates and can be used as complementary tools. However, most gastroenterologists including the authors, favour DBE due to higher rates of total enter-

oscopy. Larger prospective RCT's in the future could help us understand some unanswered areas including the role of BAE in small bowel screening, comparative studies between the main types of BAE in the field of small bowel CD and strengthen the available evidence, especially with regards to their potential roles and clinical impact. Further studies are needed for device refinement and development to make them more cost effective.

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Which endoscopic treatment is the best for small rectal carcinoid tumors?

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endoscopic microsurgery. It is necessary to carefully choose an effective and safe primary resection method for complete histological resection.

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Key words: Carcinoid tumor; Rectum; Polypectomy; Endoscopic mucosal resection; Endoscopic submucosal dissection

Core tip: Rectal carcinoids less than 10 mm in diameter can be resected by various endoscopic techniques, such as conventional polypectomy, endoscopic mucosal resection (EMR), cap-assisted EMR (EMR-C), endoscopic submucosal dissection (ESD), or transanal endoscopic microsurgery (TEM). There are currently limited comparative data to recommend a specific endoscopic treatment. Therefore, the choice of treatment modalities for small rectal carcinoids depends on the degree of endoscopic or surgical expertise at a given facility. Furthermore, any one of the above treatment methods could have a favorable clinical outcome if performed by gastroenterologists or surgeons with special techniques. EMR-C and TEM can be used as a salvage treatment after incomplete resection by endoscopic polypectomy. The efficacy of endoscopic submucosal resection with ligating device and ESD for salvage treatment requires further investigation.

Abstract

The incidence of rectal carcinoids is rising because of the widespread use of screening colonoscopy. Rectal carcinoids detected incidentally are usually in earlier stages at diagnosis. Rectal carcinoids estimated endoscopically as < 10 mm in diameter without atypical features and confined to the submucosal layer can be removed endoscopically. Here, we review the efficacy and safety of various endoscopic treatments for small rectal carcinoid tumors, including conventional polypectomy, endoscopic mucosal resection (EMR), cap-assisted EMR (or aspiration lumpectomy), endoscopic submucosal resection with ligating device, endoscopic submucosal dissection, and transanal

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INTRODUCTION

Carcinoids, also termed well-differentiated neuroendocrine tumors (NETs), are the most common neu-

roendocrine tumor of the gastrointestinal tract^[1]. The incidence and prevalence of carcinoid tumors have increased quickly and steadily worldwide over the past few decades^[2]. Rectal carcinoids are typically small, localized, nonfunctioning tumors that rarely metastasize^[2]. The Surveillance, Epidemiology, and End Results registry database of the National Cancer Institute showed that the age-adjusted incidence of rectal carcinoids has increased from approximately 0.2 per 100000 in 1973 to 0.86 per 100000 in 2004^[2,3]. The increased incidence can be partially explained by widespread colorectal cancer screening, heightened awareness, and improved diagnostic modalities. Rectal carcinoids comprise 12.6% of all carcinoid tumors and represent the third largest group of the gastrointestinal carcinoids in Western countries^[1]. The frequency of rectal carcinoids is higher in studies from South Korea (48%) and Taiwan (25%) compared to Western countries^[4,5]. The causes of racial/ethnic differences in NETs by site are unclear and require further investigation.

The treatment of rectal carcinoids depends on the tumor size (Figure 1). Recent consensus guidelines on the management of rectal carcinoids suggests that small tumors (< 1-2 cm) confined to the mucosa or submucosa can be managed with endoscopic resection due to their low risk of metastatic spread^[6]. Rectal carcinoids estimated endoscopically as < 10 mm in diameter without atypical features and confined to the submucosal layer without lymphovascular invasion rarely metastasize. Therefore, these tumors are considered good candidates for local excision, including endoscopic resection. A variety of endoscopic techniques are used to treat rectal carcinoids. Those techniques include conventional polypectomy, endoscopic mucosal resection (EMR), cap-assisted EMR (EMR-C or aspiration lumpectomy), endoscopic submucosal resection with ligating device (ESMR-L), endoscopic submucosal dissection (ESD), and transanal endoscopic microsurgery (TEM). Due to a lack of controlled prospective studies, the management of small rectal carcinoid tumors has been a matter of debate. In this Technical Advances article, we review the efficacy and safety of various endoscopic treatments for small rectal carcinoid tumors.

CONVENTIONAL POLYPECTOMY OR EMR

Endoscopic resection of rectal carcinoids with conventional polypectomy or EMR is a simple procedure (Figure 2)^[7-9]. However, it is difficult to achieve histologically complete resection with these techniques because 76% of rectal carcinoids extend into the submucosal layer^[9,10]. In addition, crush injury of resected specimens could lead to difficulty in pathologic evaluation^[7]. The histologically complete resection rate of conventional polypectomy varies from 28.6% to 100% according to previous studies^[11]. Incomplete resection of the tumors often requires additional surgical intervention.

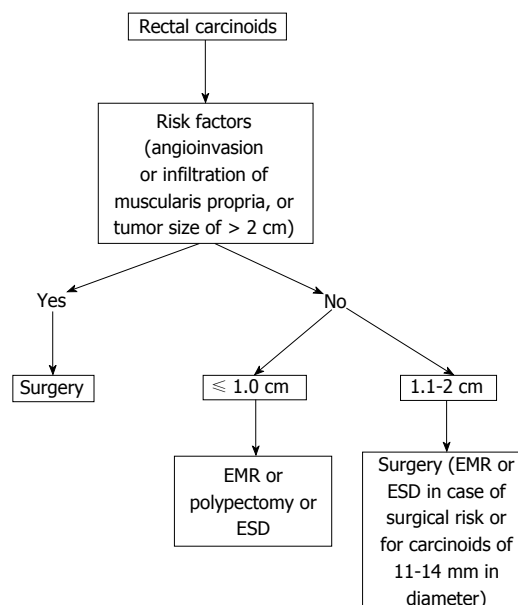


Figure 1 Treatment of rectal carcinoids. EMR: Endoscopic mucosal resection; ESD: Endoscopic submucosal dissection.

POLYPECTOMY OR EMR USING TWO-CHANNEL COLONOSCOPY

Using a two-channel colonoscope, both grasping forceps and a polypectomy snare can be inserted into the gastrointestinal lumen simultaneously. Therefore, rectal carcinoids can be pulled toward the center of the lumen and resected by electrocoagulation (Figure 3). Iishi *et al*^[12] demonstrated that the complete resection rate of rectal carcinoids with a two-channel colonoscopy (9 of 10 tumors, 90%) was significantly higher than with a one-channel colonoscopy (2 of 7 tumors, 29%). In addition, there were no complications during or after endoscopic treatment. Polypectomy or EMR using the two-channel method are expected to have a deeper vertical resection margin and lead to a curative resection. However, a recent study showed a positive resection margin in 11 (26%) of 58 EMR samples collected using the two-channel method. Furthermore, the complete resection rate of this method was not different from conventional EMR^[13]. Another limitation is that the mucosa can be torn before the tumor is adequately elevated with the grasping forceps^[14].

EMR-C OR ASPIRATION LUMPECTOMY

Aspiration lumpectomy is an endoscopic approach for a tumor that can be easily resected by lifting the mucosa away from the submucosa with saline injection, followed by aspirating the lesion into a transparent cap or cylinder^[15]. In 1996, Imada-Shirakat *et al*^[16] reported that histologically complete resection was achieved in eight patients with rectal carcinoids less than 10 mm and located within the submucosal layer using this technique. There were no recurrences or distant metastasis found during the mean observation period of 13.3 mo. Nagai

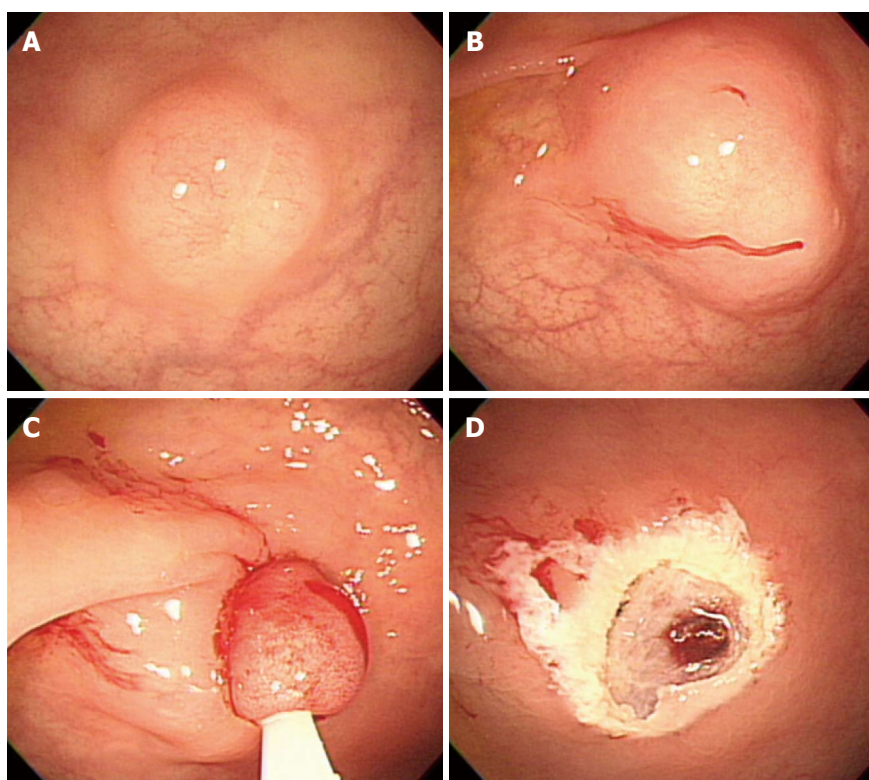


Figure 2 Endoscopic mucosal resection. A: An approximately 6 mm rectal carcinoid tumor; B: Injection of submucosal saline solution; C: Endoscopic mucosal resection (EMR) procedure; D: A clear, post-EMR ulcer.

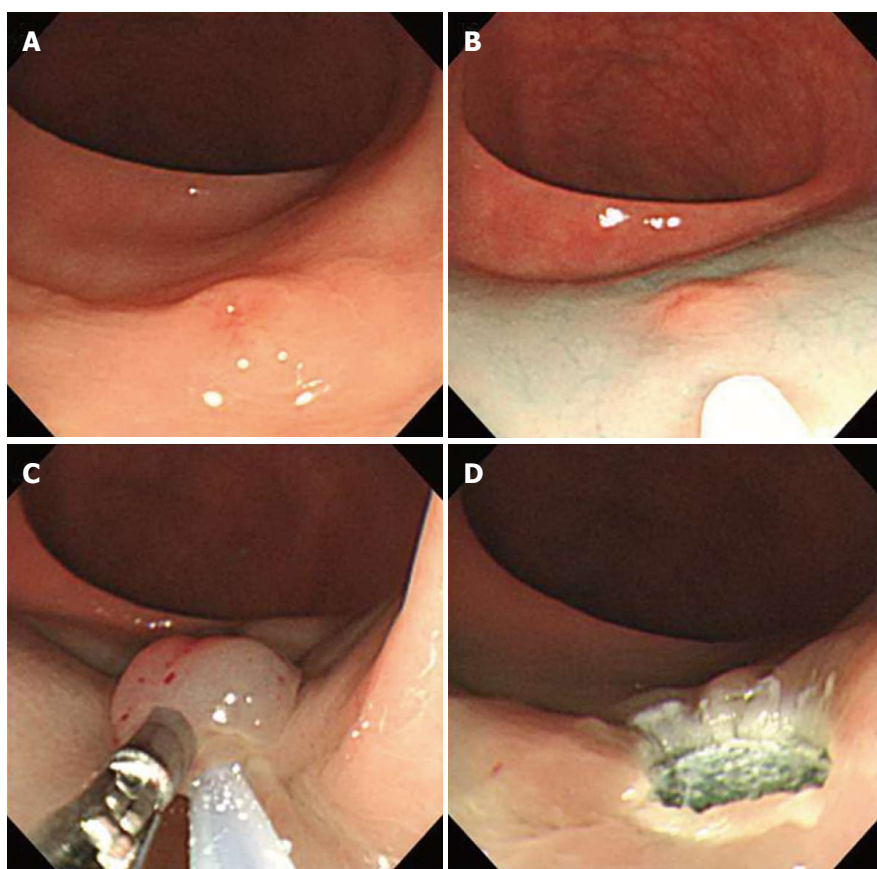


Figure 3 Endoscopic mucosal resection using two-channel colonoscopy. A: An approximately 5 mm rectal carcinoid tumor; B: Injection of submucosal saline solution into the base of the lesion using needle forceps; C: Pulling the lesion with grasping forceps and snare resection; D: A clear, post-endoscopic mucosal resection ulcer.

et al^[14] demonstrated that the rate of complete resection with aspiration lumpectomy (100%) was significantly higher ($P < 0.05$) than with saline assisted snare resection (termed ‘strip biopsy’) in a small series of consecutive

patients with rectal carcinoids. Jeon *et al*^[17] used this technique for secondary endoscopic treatment to remove the remnant tumor after primary EMR or polypectomy, which is technically difficult due to submucosal fibrosis

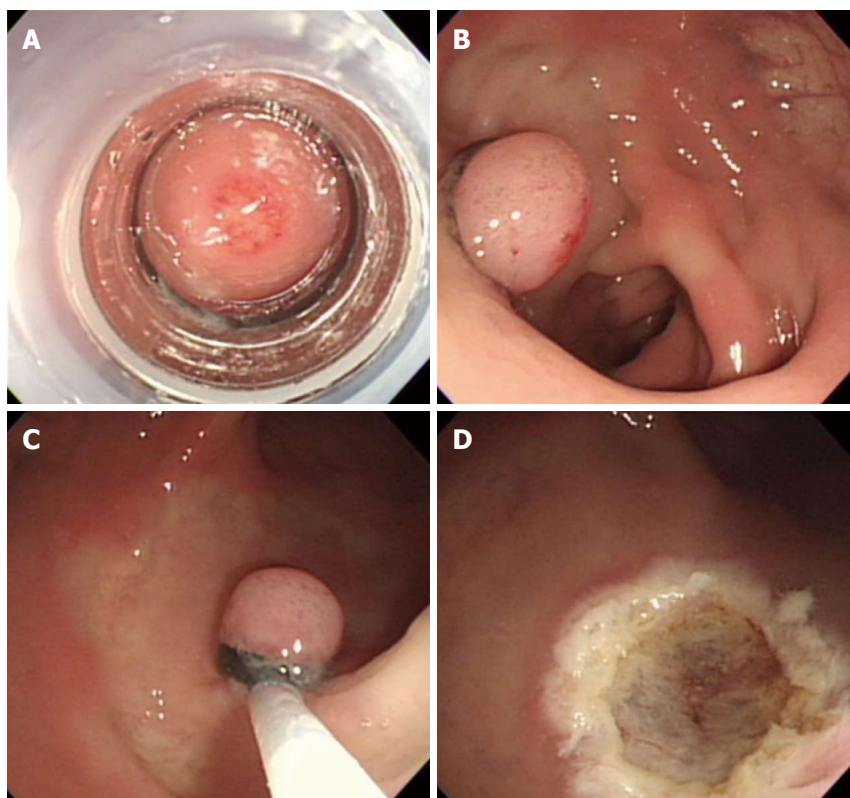


Figure 4 Endoscopic submucosal resection with ligating device. A: Aspiration of a carcinoid tumor into the ligating device; B: Deployed elastic band; C: Snare resection performed below the band; D: A clear, post-endoscopic submucosal resection with ligating device ulcer.

of residual tissue. This study demonstrated that EMR-C is a useful method for salvage treatment of a failed *en bloc* resection of rectal carcinoids after primary EMR or polypectomy. One of the interesting findings of this study is that all 7 patients had positive microscopic margins after primary EMR but negative endoscopic and histological findings based on a biopsy of the scarred tissue. The pathologic findings from all tissue obtained by salvage resection showed the existence of remnant tumor. This result suggests that a negative biopsy in a surveillance examination does not prove the absence of a remnant tumor and that false negative results might be due to embedding or the residual remnant tumor during tissue healing after the primary resection.

ENDOSCOPIC SUBMUCOSAL RESECTION WITH LIGATING DEVICE

In 1999, Berkelhammer *et al.*^[18] first introduced the band-snare resection as a method of EMR for small rectal carcinoids. This method may provide a more appropriate resection margin compared to standard polypectomy (Figure 4). A randomized controlled study comparing ESMR-L to EMR showed that the complete resection rate of ESMR-L (100%, 8/8) was significantly higher than EMR (57.1%, 4/7), and all patients were followed-up for 3 years without any recurrence^[19]. In a large case series including 61 patients, the complete resection rate of ESMR-L was 95.2% (60 out of 63 lesions)^[20]. The complete resection rate for lesions located in the lower rectum was 98.3%, which was significantly higher than lesions in the upper rectum and rectosigmoid colon

(50%). In a large-scale study comparing ESMR-L (45 lesions) and EMR (55 lesions) including 100 cases, the overall ESMR-L complete resection rate was higher than EMR (93.3% *vs* 65.5%, respectively, $P = 0.001$)^[21]. In addition, this study demonstrated that the location of the tumors had no influence on the complete resection rate when ESMR-L was performed, in contrast to the results of EMR. Recently, Moon *et al.*^[22] introduced EMR using a double ligation technique (ESMR-DL) to treat 11 patients with small rectal carcinoids. The lesion was aspirated into the ligating device, and an elastic band was placed around the base. Then, a detachable snare was used to perform a ligation below the elastic band, and the lesion was removed with snare resection above the band. After ESMR-DL, there were no immediate or delayed complications such as bleeding or perforation.

ESD

Endoscopic submucosal dissection is considered a valuable endoscopic treatment for early gastric cancer and large superficial gastric neoplasms. This technique provides a higher *en bloc* and histologically complete resection rate than EMR, enables accurate pathologic diagnoses, and is less invasive than surgery (Figure 5)^[23]. Recently, ESD has been applied to the treatment of large colorectal neoplasms and has been reported to be more effective than either EMR or EMR-precutting^[24]. However, ESD has the disadvantage of a considerably higher risk for perforation because the technique involves dissection of the submucosal tissue beneath the lesion. In addition, highly trained endoscopists are required. Thus,

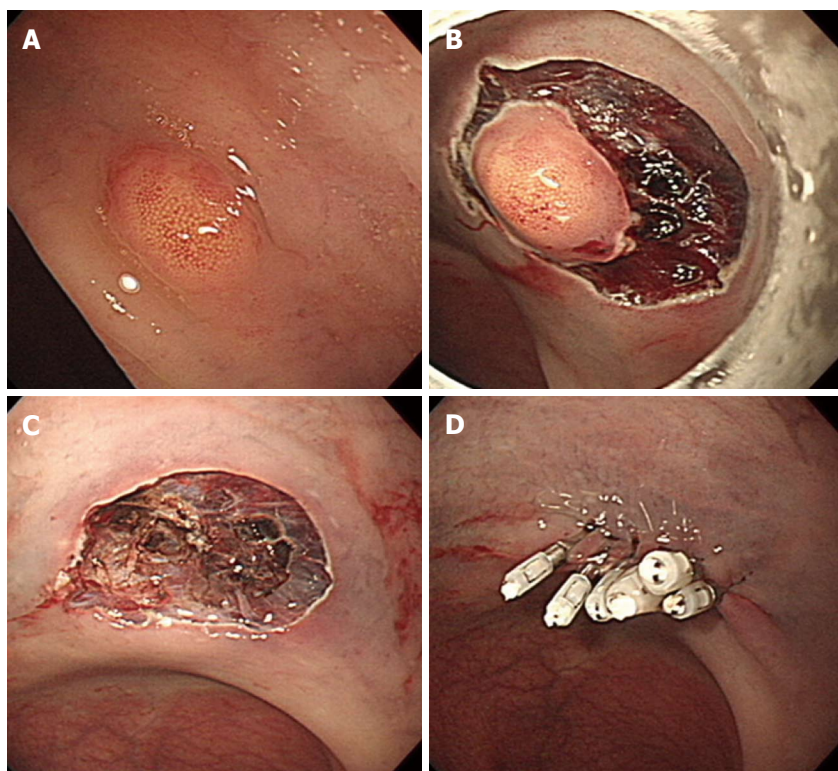


Figure 5 Endoscopic submucosal dissection.
A: An approximately 5 mm rectal carcinoid tumor;
B: Mucosal incision and submucosal dissection; C:
A clear, post-endoscopic submucosal dissection
ulcer; D: Endoscopic closure of the ulcer floor with
endoclips.

the safety issues associated with this technique must be solved. As a result, ESD is not yet widely accepted for the treatment of colorectal neoplasms^[25].

There have been few studies reporting the efficacy and safety of ESD for the resection of rectal carcinoids. Recently, Onozato *et al*^[26] reported that ESD was technically feasible in five cases with rectal carcinoids less than 10 mm. In addition, no complications were observed, and all lesions were completely resected histologically. In a meta-analysis including four studies^[27-30], ESD was a more effective procedure for the treatment of rectal carcinoids and had a higher complete resection rate than EMR^[31]. ESD was more effective than EMR in complete histological resection [odds ratio, 0.29; 95%CI: 0.14-0.58; $P = 0.000$]. Additionally, ESD was as safe as EMR (rate difference, -0.01; 95%CI: -0.07 - 0.05; $P = 0.675$). The recurrence rate did not differ significantly between the EMR and ESD groups. The duration of ESD was longer than EMR. Because the rectum is fixed in the retroperitoneum, the risk of peritonitis following perforation is lower than in other parts of the colon. One of limitations of ESD with a knife is the inability to fix the knife to the target lesion, which leads to high complications such as bleeding and perforation. New grasping type scissor forceps, which can grasp and incise the targeted tissue using an electro-surgical current, may reduce these complications^[32]. More recently, there have been a few studies comparing ESD to other endoscopic treatment modalities besides EMR. Kim *et al*^[33] reported a large retrospective analysis including 115 patients, which were classified into an EMR group ($n = 33$), ESMR-L group ($n = 40$), and ESD group ($n = 44$). The curative resection rate in the EMR group was 77.4%, which was

significantly lower than that of the ESMR-L (95%) and ESD groups (97.7%). This result suggests that ESMR-L and ESD may be superior to conventional EMR. A recent study by Choi *et al*^[25] comparing ESMR-L ($n = 29$) with ESD ($n = 31$) for the endoscopic treatment of rectal carcinoids showed that the complete resection rate was 80.6% in the ESD group and 82.8% in the ESMR-L group ($P = 0.833$). The resection time was significantly longer in the ESD group than in the ESMR-L group. The authors concluded that ESMR-L might be considered the treatment of choice for small rectal carcinoid tumors because of reduced procedure time. A small comparative study by a Japanese group^[34] also showed a similar result to the above study. A retrospective analysis of 3 types of endoscopic resection technique by Zhao *et al*^[35] demonstrated that complete resection rates using the EMR, EMR-C, and ESD were 80%, 100%, and 100%, respectively. The average procedure time was the shortest in the EMR-C group. This study concluded that EMR-C might be the best endoscopic excision method, considering the clinical efficacy, surgical time, and complication rate.

TEM

Transanal endoscopic microsurgery was originally designed by Buess *et al*^[36] in the 1980s. The procedure allows full thickness excisions as high as 20 cm from the anal verge to be performed using a 40-mm operating rectoscope. Although TEM is not superior to conventional transanal excision (TAE) for resecting lesions in the lower rectum, it has distinct advantages for removing lesions in the mid and upper rectum^[37]. In addition to improved

access to more proximal lesions, TEM provides several advantages over TAE, including improved visualization with better exposure, higher likelihood of achieving clear resection margins, and lower recurrence rates^[38]. The application of TEM for rectal carcinoids has been described in several small case series^[6]. Kinoshita *et al.*^[39] reported clinical experience including 27 patients with rectal carcinoids treated by TEM. In this study, TEM was performed as a primary excision ($n = 14$) or as completion surgery after incomplete resection by endoscopic polypectomy ($n = 13$). Negative margins were obtained in all cases. There was no additional radical surgery performed, and patients were followed-up for 70 mo without recurrence. The largest series in the United States included 24 patients over a 12-year period^[40]. There were 6 (25%) primary surgical resections, and 18 (75%) resections were performed after incomplete snare excisions during colonoscopy. This study showed all negative margins, a similar zero rate of recurrence and a similarly low morbidity rate. In addition to its usefulness in primary surgical resection of rectal carcinoids especially in the mid and upper rectum, TEM can be used as a salvage treatment after incomplete resection by endoscopic polypectomy. The possible complications of TEM include bleeding and perforation. In addition, transient soiling can occur due to the large width of the rectoscope tube^[37].

FUTURE PERSPECTIVES AND CONCLUSIONS

In rectal carcinoids estimated endoscopically as < 10 mm in diameter, endoscopic treatment is a feasible option. Although endoscopic resection of rectal carcinoids with conventional polypectomy or EMR is a simple procedure, it is difficult to achieve histologically complete resection. EMR-C, ESMR-L, and ESD showed similar efficacy and safety. However, there are currently limited comparative data to recommend a specific endoscopic treatment. Therefore, the choice of treatment modalities for small rectal carcinoids depends on the degree of endoscopic or surgical expertise at a given facility. Furthermore, any one of the above treatment methods could have a favorable clinical outcome if performed by gastroenterologists or surgeons with special techniques.

Endoscopic treatment for rectal carcinoid requires special techniques for a deeper resection to achieve clear margins. For this purpose, lesions are usually lifted using submucosal injection with saline solution with or without epinephrine. In addition, adequate submucosal injection is important for the reduction of thermal damage to tissue as well as the prevention of complication such as bleeding or perforation. Although electrocauterization during endoscopic resection could destroy remnant tumor, its burning or coagulation artifact may make the pathologic examination of resection margin difficult. Therefore, to separate the margin of carcinoid tumor from the underlying muscle layer adequately could pro-

vide better pathological assessment of radial margins and the depth of invasion^[41].

EMR-C and TEM can be used as a salvage treatment after incomplete resection by conventional polypectomy or EMR. However, the efficacy of ESMR-L and ESD for salvage treatment requires further investigation. Endoscopic tattooing of colonic lesions helps to localize polypectomy sites that may difficult to identify with repeat endoscopy^[42]. In cases with positive resection margin after endoscopic treatment of rectal carcinoids, tattooing the area of resection will help facilitate the lesion site location for further resection.

Newly developed over-the-scope clip (OTSC) has a higher compression force and the capacity to capture a larger volume of tissue than the through-the-scope clip^[43]. Recent prospective study has shown that perforations occurring after full-thickness resection of gastric subepithelial tumors less than 3 cm could be managed by OTSC closure^[44]. Although further prospective clinical trial is required, this study suggests that endoscopic full-thickness resection with OTSC closure can be applied to selected patients with colonic subepithelial lesions to have malignant potential. Finally, a prospective large-scale study is warranted for the assessment of therapeutic efficacy of various endoscopic treatments and long-term outcome.

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Colorectal stenting as first-line treatment in acute colonic obstruction

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Abstract

Tumoral obstructions in almost the entire gastrointestinal tract can be resolved with interventional digestive endoscopy techniques. Self-expanding metal stent (SEMS) insertion in the obstructed colon is a minimally invasive and relatively simple procedure providing an effective first-line treatment for relief of acute malignant obstruction symptoms and serving either as a pre-operative or "bridge to surgery" procedure or as palliative definitive care. This technique was introduced in the early 1990s. Although there is still debate about its real value, a lot of reports have been published since then and the procedure is advocated by many surgical groups as the method of choice for the initial treatment of left-sided tumoral colonic obstruction. Before the procedure, colonic obstruction has to be diagnosed by abdominal radiographs, water contrast enema and/or a computed tomography scan. The greatest information is provided by the latter and it is perhaps the method of choice prior to stenting. Skills and training are mandatory, as in all interventional procedures. The key step for success is to cross the malignant stricture with a guidewire. Care must be taken not to over insufflate an obstructed colon during the procedure. SEMS slide over the guidewire through the endoscope working channel or in parallel, outside the endoscope. An average 7% perforation rate has been reported during the procedure and other minor complications can appear in the

follow up. However, as a whole, this technique seems to compare favorably with surgery.

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Key words: Self-expanding metal stent; Malignant colorectal obstruction; Emergency surgery; Interventional endoscopy

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INTRODUCTION

Patients with malignant colorectal obstruction (MCRO) usually present at the emergency room (ER) because of abdominal pain, vomiting and distension. After a physical examination, abdominal radiographs show typical signs of large bowel obstruction with air-fluid levels. First therapeutic measures include fluid resuscitation with electrolyte correction. Further diagnostic procedures have to be undertaken to confirm both the colonic obstruction and the exact anatomical location. According to individual hospital policies, the colon can be cleansed with enemas and a colonoscopy can be performed. Care has to be taken not to over insufflate in order to avoid perforation. Water instead of air should be employed to allow colonoscopy advancement.

However, in patients with acute abdominal pain in whom perforation is suspected, a computed tomography (CT) scan is a preferable diagnostic modality after clinical and plain abdominal radiograph evaluation. If a tumoral obstruction in the left-side colon is diagnosed, insertion of a self-expanding metal stent (SEMS) as first treatment can be considered^[1].

COLONIC OBSTRUCTION RELIEF WITH SEMS

As in the esophagus, duodenum or biliary tree, MCRO can be also treated in the large bowel by means of SEMS.

Dohmoto *et al*^[2] reported the treatment of a rectal tumoral obstruction by means of a SEMS for the first time in 1990. From that time, a large number of works dealing with this topic have been annually published. Initially, they were single or a few case reports^[3]. Afterwards, large series were reported^[4], in addition to review articles^[5] and randomized studies comparing this new modality with the classical surgical approach^[6].

Figure 1 shows the increase of publications on SEMS for MCRO when the words “colon AND stent” are searched for in PubMed.

The most valuable benefit provided by this relatively new interventional technique is to relieve obstruction by means of a minimally invasive procedure, avoiding an operation in an unstable patient. The colon can be cleansed properly and patients can undergo a scheduled surgical procedure. This kind of MCRO decompression is also called a bridge to surgery (BTS). The classical surgical approach involved a primary colostomy and a second or third operation for tumor removal and colostomy closure.

Right colon obstructions do not necessarily need bowel cleansing before surgery; therefore, the major impact of SEMS in MCRO are in the left colon^[7]. In addition, non-operable patients (*i.e.*, multiple metastases) can have the stent as a palliative measure to avoid a colostomy.

Bowel perforation is the main contraindication for stenting. In addition, in cases of multiple strictures or short life expectancy (hours or few days), other options instead of stent insertion must be undertaken.

NONFLUOROSCOPIC INSERTION OF AN “OVER-THE-WIRE” STENT IN A RECTOSIGMOID MCRO

Once MCRO has been diagnosed and surgical consultation made, if the obstruction is below 25 cm from the anus (up to mid-sigmoid), a possibility is to bridge the stricture in the endoscopy office without fluoroscopy. The majority of such strictures can be traversed by means of ultrathin endoscopes (six or less millimeters in diameter). The endoscope is negotiated through the narrowed tumoral lumen until healthy colon is found. The endoscope is advanced as far as possible. A metallic Savary or a similar stiff guidewire is inserted through the working channel of the endoscope and placed beyond the malignant stenosis. The endoscope is withdrawn, leaving the guidewire in place. Important figures to record are tumoral length and the distance from the anus.

Afterwards, the endoscope is reinserted beside the guidewire and placed at the level of the stricture. A

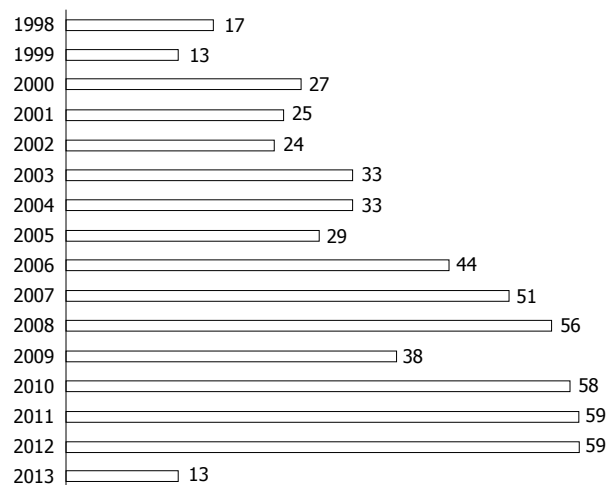


Figure 1 Number of scientific papers published in the last years about stents in tumoral colonic obstructions. Search was done with the terms “colon and stent” in PubMed. Year 2013 ends in the month of March.

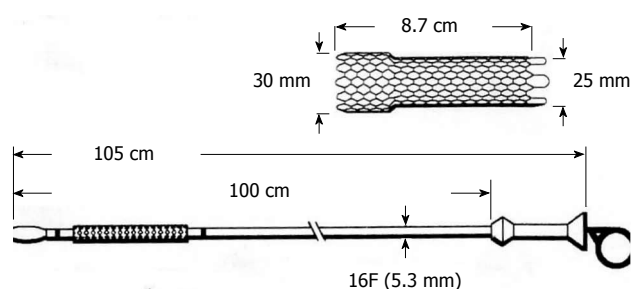


Figure 2 Ultraflex Precision stent from Boston Scientific. This self-expanding metal stent is called over the wire because it cannot be inserted through the working channel of a therapeutic endoscope. Many other stent manufacturers have similar stents.

folded stent that cannot be inserted through the working channel of the endoscope because it is greater than 3.7-4.2 mm, as shown in Figure 2, is slid over the guidewire. These SEMS are called over-the-wire (OTW) to differentiate from through-the-scope (TTS) stents that have a folded diameter that allows it to be inserted undeployed through the working channel of a therapeutic endoscope (Figure 3A).

The endoscope gives stiffness to the system stent guidewire and prevents it from bending. The advancement of the stent through the stricture is also monitored with the endoscope. The stent is released under endoscopic vision.

This insertion technique has been used for a long time^[8,9] and it has been successful in the majority of occasions, allowing the MCRO to be resolved in the endoscopy suite. Nevertheless, several points have to be underlined.

First of all, the procedure tends to always be more difficult than anticipated. Despite bowel cleansing, there are always liquid or semisolid feces in the colon that impedes good vision. The placing of a hemostatic clip in the lowest stricture margin is helpful to clearly mark

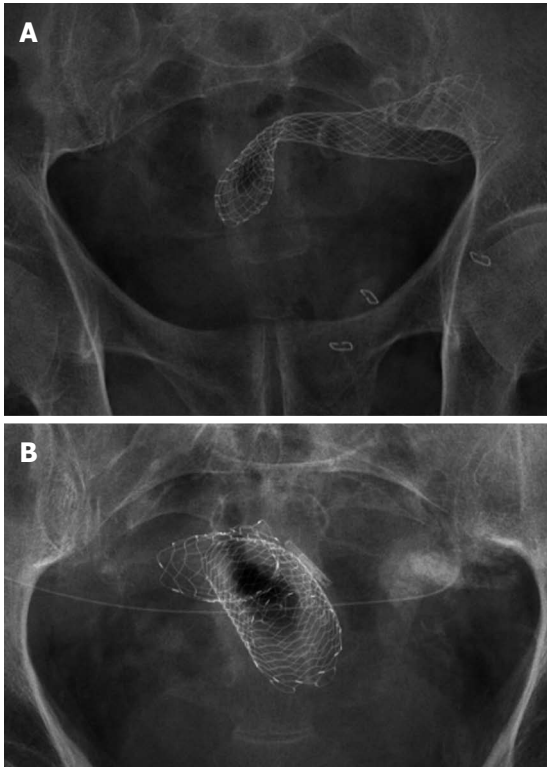


Figure 3 Wallflex (A) and Ultraflex (B) stents from Boston Scientific. A: This self-expanding metal stent (SEMS) is called a through the scope (TTS) stent because it can be inserted in the folded way through the working channel of a therapeutic endoscope. Many other stent manufacturers have similar stents; B: Ultraflex Precision inserted in a tumoral stricture in the sigmoid, a hemostatic clip was placed to mark the lower part of the stricture. Despite the strange configuration due to sigmoid bends, the stent was in correct position; the patient had an abdominal catheter for hydrocephaly decompression.

where the stent has to be placed in the endoscopic view.

The endoscopist has to have skills in interventional endoscopy. A recent paper^[10] pointed out that at least 30 procedures of SEMS insertion in left MCRO are the initial learning curve for mastering the technique.

With the nonfluoroscopic technique, stent deployment events beyond the stricture are not seen so they have to be “supposed”. In some OTW SEMS, like the Ultraflex Precision (Figure 2), deployment begins in the closest part to the endoscopic view, that is, in the distal tumoral end or downstream. Once the stent has been partially opened, it can be pushed if it is far from the stricture but it cannot be pulled because the open mesh can damage the colon.

After the procedure, pelvic or abdominal radiographs have to be taken to confirm proper stent deployment. When the stricture has been completely bridged, the SEMS takes an hourglass-like configuration with both ends open. Nevertheless, due to sigmoid bends, sometimes Rx images are not clear. As can be seen in Figure 3B, foreshortening occurs in the image but the SEMS was in correct position and the obstruction was resolved. In this figure, a hemostatic clip marking the lowest tumor margin is also seen. In addition, the patient had an abdominal catheter for hydrocephaly decompression.

NONFLUOROSCOPIC INSERTION OF A “TTS” STENT IN A LEFT COLON MCRO

Insertion of OTW stents far from the mid-sigmoid (around 25 cm from the anus) is difficult because the assembly stent guidewire tends to bend, despite the endoscope being placed side-to-side. If the MCRO has been traversed with the ultrathin endoscope, a 0.035 inch guidewire can be inserted through the working channel of the endoscope and placed as far as possible beyond the tumor (in upstream position). The ultrathin endoscope is removed, leaving the guidewire in place. This guidewire is back loaded in a therapeutic channel endoscope which is carefully advanced until the tumor. A TTS stent can be easily inserted. The endoscope gives enough stiffness to the system to advance the undeployed stent through the tumor.

Extreme care should be taken not to dislodge the guidewire placed beyond the stricture in the maneuvers of ultrathin endoscope withdrawal or therapeutic endoscope advancement.

MCRO must be never dilated before stenting because there is a great risk of tumor perforation.

ENDOSCOPIC INSERTION OF SEMS IN MCRO WITH FLUOROSCOPIC GUIDANCE

This method is considered as the ideal for many endoscopists^[11]. Fluoroscopic facilities are necessary. C-arms fluoroscopic devices used sometimes for Endoscopic Retrograde Cholangiopancreatography (ERCP) are not good if they have no capacity to image the entire abdomen and if the patient table cannot be easily moved (Figure 4).

A therapeutic endoscope is advanced until the tumoral stricture is found. Using a gastroscope or short colonoscope with large working channel is very useful to facilitate devices exchange during the procedure.

With the endoscope in front of the stricture, an ERCP catheter loaded with a hydrophilic tip guidewire is passed through the working channel. The most important step is “cannulation” of the stricture with the guidewire. Almost all the strictures have an orifice, although sometimes it can be very difficult to find. As shown in Figure 5, gentle probing of the tumor with the guidewire leads to finally finding the path. The correct position of the guidewire beyond the stricture is given by the fluoroscopic view. If the patient is in the supine position (lying on his/her back), anatomical orientation is improved.

After traversing the tumor with the guidewire, the catheter is slid over it and contrast medium is injected to delineate the stricture. The catheter is removed, always leaving the guidewire tip as far as possible in the colon. A TTS stent is passed over the guidewire and deployed inside the tumor with fluoroscopic guidance of upstream maneuvers and endoscopic monitoring of downstream (in the endoscopic view) events.



Figure 4 C-arms fluoroscopic devices used sometimes for endoscopic retrograde cholangiopancreatography are not good for colonic stenting unless they have capacity to image the entire abdomen and if the patient table cannot be easily moved.

SCIENTIFIC EVALUATION OF SEMS FOR MCRO

As previously said and as shown in Figure 1, a lot of papers have been published on this topic (Table 1). Nevertheless, few are randomized studies comparing the traditional surgical approach of MCRO with SEMS treatment.

In a recent review from a surgical standpoint^[31], it appears that technical and clinical success rates for stenting are lower than expected. SEMS is sometimes associated with a high incidence of clinical and silent perforation. Stenting instead of loop colostomy can be recommended only if the appropriate expertise is available in the hospital. The goal of stenting, a decrease of the stoma rate, can be advocated only if the complication rates of stenting are lower than those of stoma creation in the emergency situation. Until now, this has been not demonstrated in a prospective randomized trial.

Furthermore, when pathology surgical specimens are compared, tumors resected after stenting differed significantly in terms of ulceration at or near the tumor, perineural invasion and lymph node invasion. These findings are found less in tumors operated on without previous stenting^[32].

On the contrary, many studies in clinical practice favor stenting as first-line treatment for left MCRO. Randomized trials in this setting appear to be difficult and perhaps randomization is not the only answer for structured objective evaluation of endoscopic therapy^[33].

In one of the largest retrospective endoscopic series published in 2010^[20], there were reported outcomes on 168 patients who underwent SEMS placement for definitive palliation and 65 patients with SEMS inserted as a BTS. Technical and immediate clinical success rates were 96% and 99% in the palliative group and 95% and 98% in the preoperative group 41/168 (24%). Patients in the palliative group had complications, including perforation (9%), occlusion (9%), migration (5%) and erosion/ulcer (2%). Mean stent patency was 145 d. The majority of

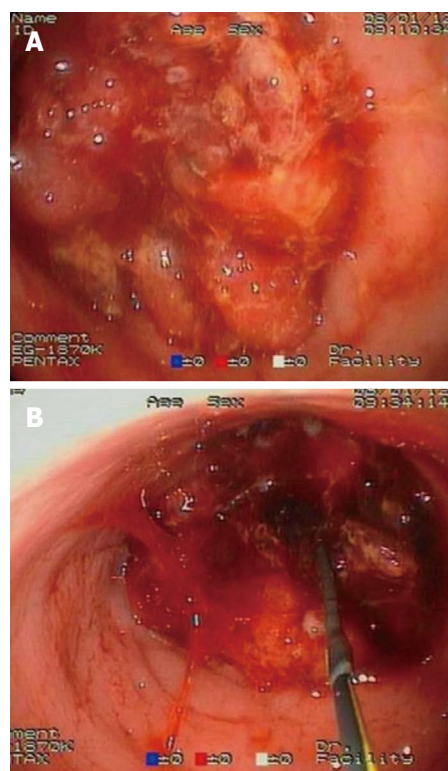


Figure 5 Endoscopic retrograde cholangiopancreatography catheter loaded with a hydrophilic tip guidewire. A: the obstructive tumor appears not to have any orifice that enabled stenting; B: gentle probing of the tumor with the guidewire leads to finally finding the path.

patients were free of obstruction from implantation until death. Therefore, this large group of patients had their normal intestinal transit restored without having undergone an operation and without a stoma. Unfortunately, patients on oncological bevacizumab treatment triple the perforation rate.

Preoperatively placed stents remained *in situ* for a mean of 25.4 d and remained patent until surgery in 73.8% of patients. Complications were present in 23.1% of patients and 94% of them underwent elective colectomy. Conclusions drawn from this large cohort of patient are that colorectal SEMS placement is relatively safe and effective but has a complication rate of nearly 25%. However, only perforation (less than 10%) is a life-threatening complication. Other complications such as stent occlusion can be managed endoscopically.

Some surgical groups found SEMS treatment for MCRO in operable patients (BTS) very useful to carry on a laparoscopic procedure. Law *et al*^[34] evaluated surgical outcomes after stent insertion for obstructing colorectal malignancy and these patients were compared with a laparoscopic and open approach. Their experience showed that after successful SEMS insertion for MCRO, elective surgical resection could be performed safely. The combined endoscopic and laparoscopic procedure provided a less invasive alternative to the multistage open operations and it was found feasible for patients with obstructing colon cancer.

Table 1 Some series about self-expanding metal stents in malignant colorectal obstruction published in the last years *n* (%)

Ref.	Publication year	No. of patients	Technical success	Clinical success	Perforation rate
García-Cano <i>et al</i> ^[4]	2006	175	162 (92.6)	138 (78.8)	7 (4)
Ptok <i>et al</i> ^[12]	2006	48	44 (92)	44 (92)	0
Soto <i>et al</i> ^[13]	2006	62	58 (93.54)	56 (90.3)	3 (4.8)
Karoui <i>et al</i> ^[14]	2007	31	30 (97)	27 (87)	0
Lee <i>et al</i> ^[15]	2007	80	78 (97.5)	77 (96.2)	0
¹ Repici <i>et al</i> ^[16]	2007	44	42 (95.4)	41 (93.1)	0
Repici <i>et al</i> ^[17]	2008	42	40 (95.2)	40 (95.2)	1 (2.38)
Im <i>et al</i> ^[18]	2008	51	51 (100)	43 (84.3)	1 (1.9)
Fernández-Esparrach <i>et al</i> ^[19]	2010	47	44 (94)	44 (94)	3 (7)
Small <i>et al</i> ^[20]	2010	233	224 (96.1)	222 (95.2)	18 (7.7)
Park <i>et al</i> ^[21]	2010	151	149 (98.6)	140 (92.7)	0
Branger <i>et al</i> ^[22]	2010	93	86 (92.5)	80 (86)	3 (3.2)
Donnellan <i>et al</i> ^[23]	2010	43	40 (93)	40 (93)	2 (4.6)
Lee JH <i>et al</i> ^[24]	2010	46	46 (100)	39 (84.8)	2 (4.3)
Lee HJ <i>et al</i> ^[25]	2011	71	68 (95.8)	68 (94)	4 (5.6)
Luigiano <i>et al</i> ^[26]	2011	39	36 (92.3)	35 (89.7)	2 (5.1)
Jiménez-Pérez <i>et al</i> ^[27]	2011	182	177 (98)	141 (94)	5 (3)
Tominaga <i>et al</i> ^[28]	2012	24	24 (100)	20 (83)	0
Yoshida <i>et al</i> ^[29]	2013	33	33 (100)	32 (97)	0
Bonfante <i>et al</i> ^[30]	2013	48	46 (96)	46 (96)	1 (2)

¹In 2007, there are two articles published by Repici *et al*. One about the Ultraflex Precision stent in the left colon and the other on right colon stenting.

SEMS in MCRO are also inserted by interventional radiologists. In one of the first reports comparing this new method with the surgical approach^[35], Martínez-Santos *et al*^[35] found that placement of a preoperative stent in patients with left-sided malignant colon and rectal obstruction prevented 94% of unnecessary operations and a large number of colostomies after elective surgery. These results were obtained with a lower rate of severe complications as well as a shorter hospital stay. This work cannot be considered a true randomized trial because patients with MCRO received a SEMS if they presented in the ER from Monday to Friday when an interventional radiologist was present in the hospital, whereas patients were operated on if they presented on week-ends. Besides, if patients with MCRO presented out of working hours (*i.e.*, during the night), they were stabilized with intravenous fluids, put on *nil per os* with a nasogastric tube and received a stent early the next morning.

Kim *et al*^[36] found that when the colorectal obstruction had a tortuous, curved angulation of the colon or was located at or proximal to the descending colon, the endoscopic method of SEMS placement appears to be more useful than the radiological method. However, once SEMS placement was technically successful, the clinical success rate, complication rate and stent patency did not differ with the method of insertion.

In the midst of the debate between pros and cons of SEMS as the initial treatment for MCRO, a surgical group^[37] reports on its experience stating that in case of colorectal obstruction, endoscopic colon stenting as a bridge to elective operation should be considered as the treatment of choice for resectable patients given the significant advantages for short and long-term outcomes. Palliative stenting is effective but associated with a high rate of long-term complications.

However, when surgery and stents are compared as a palliative measure^[25], SEMS were found not only an effective and acceptable therapy for initial palliation of MCRO, but they also showed long-term efficacy comparable to that with surgery, reducing costs (*i.e.*, hospital stay).

Some plastic tubes (such as the Dennis colorectal tube) are less expensive alternatives to clean the obstructed colon before operation. But in a recent report^[38], a 4.5% perforation rate with a 1.5% mortality was reported.

Finally, the distal part of the stent should be placed at least 6 cm from the anus on the contrary patients can suffer an unpleasant tenesmus.

CONCLUSION

Despite the still ongoing scientific debate^[39-43], SEMS for MCRO appears to be the modern treatment for colonic obstruction^[39,44,45]. Comparison between colonic SEMS manufactured by major stent companies show no important differences between them^[40]. In addition, manufacturers are continuously working on stent improvement to allow a proper obstruction decompression^[46]. It is better to use bare (uncovered) stents for MCRO rather than covered ones that are more prone to have complications^[41].

Endoscopically, obstructions in the entire colon can be bridged with stents^[42], however, the major impact of SEMS for MCRO are left-sided tumoral strictures. In this setting, colonic stents represent the best option when skills are available^[7].

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Post-Anaesthetic Discharge Scoring System to assess patient recovery and discharge after colonoscopy

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Abstract

AIM: To investigate whether discharge scoring criteria are as safe as clinical criteria for discharge decision and allow for earlier discharge.

METHODS: About 220 consecutive outpatients undergoing colonoscopy under sedation with Meperidine plus Midazolam were enrolled and assigned to 2 groups: in Control-group (110 subjects) discharge decision was based on the clinical assessment; in PADSS-group (110 subjects) discharge decision was based on the modified Post-Anaesthetic Discharge Scoring System (PADSS). Measurements of the PADSS score were taken every 20 min after colonoscopy, and patients were discharged after two consecutive PADSS scores ≥ 9 . The investigator called each patient 24-48 h after discharge to administer a standardized questionnaire, to detect any delayed complications. Patients in which cecal intubation was not performed and those who were not found at follow-up phone call were excluded from the study.

RESULTS: Thirteen patients (7 in Control-group and 6 in PADSS-group) were excluded from the study. Recovery from sedation was faster in PADSS-group than in Control-group (58.75 ± 18.67 min vs 95.14 ± 10.85 min, respectively; $P < 0.001$). Recovery time resulted shorter than 60 min in 39 patients of PADSS-group (37.5%), and in no patient of Control-group ($P < 0.001$). At follow-up phone call, no patient declared any hospital re-admission because of problems related to colonoscopy and/or sedation. Mild delayed post-discharge symptoms occurred in 57 patients in Control-group (55.3%) and in 32 in PADSS-group (30.7%). The most common symptoms were drowsiness, weakness, abdominal distension, and headache. Only 3 subjects needed to take some drugs because of post-discharge symptoms.

CONCLUSION: The Post-Anaesthetic Discharge Scoring System is as safe as the clinical assessment and allows for an earlier patient discharge after colonoscopy performed under sedation.

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Key words: Colonoscopy; Conscious sedation; Patient discharge; Recovery room; Complications

Core tip: About 220 consecutive outpatients undergoing colonoscopy under sedation were enrolled to investigate whether the Post-Anaesthetic Discharge Scoring System (PADSS) is a safe clinical assessment for earlier patient discharge after colonoscopy. The patients were assigned to two groups: in Control-group (110 subjects) discharge decision was based on the clinical assessment; in PADSS-group (110 subjects) discharge decision was based on the modified PADSS. Recovery from sedation was faster in PADSS-group than in Control-group (58.75 min vs 95.14 min, $P < 0.001$). Recovery time resulted shorter than 60 min in 39 patients in PADSS-group (37.5%), and in no patient in Control-group ($P < 0.001$).

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INTRODUCTION

Colonoscopy frequently causes considerable discomfort or pain to patients, and analgesia and sedation are often necessary for a successful colonoscopy. The decision to use premedication and the kind of premedication are influenced by national and cultural differences among countries^[1], and by the rules regulating the drugs use. Propofol Deep Sedation is frequently used in some countries such as United States, whereas conscious sedation induced by means of a combination of a benzodiazepine and an opiate is more frequently used in other countries such as Italy^[2-5], because of its excellent analgesic and sedative effects^[6]. Moreover, Propofol can only be administered by anesthetists in Italy.

The annual number of colonoscopies performed on an outpatient basis is increasing, and the increase is expected to continue, because of the screening programs for the colon cancer prevention that are ongoing in many countries. Likewise, the number of examinations performed under sedation is also increasing, and this fact can cause some problems to digestive endoscopy centers, as they are often not provided with sufficiently spacious observation rooms. At the time of discharge from the digestive endoscopy center, patients should be home-ready: they should be clinically stable and able to rest at home. Although the discharge after ambulatory surgery and anesthesia can involve legal implications^[7,8], there is very little information and documentation about the recovery pattern and home-readiness of the ambulatory gastrointestinal endoscopy. The Guidelines for Sedation in Digestive Endoscopy of the Italian Society of Digestive Endoscopy (SIED) do not recommend the use of discharge scoring systems to assess the home-readiness, and generically state that "the patient must be awake and well-oriented, and vital parameters must be acceptable and stable"^[9,10].

Based on these observations and considering the aging population, it becomes even more important to have clear, evidence-based discharge criteria in clinical use, as patient safety must be our first priority. Several scoring systems have been devised to guide the process of discharge and home-readiness, to ensure patient safety^[11]. This prospective study was planned to evaluate whether the discharge scoring criteria are as safe as clinical criteria for discharge decision and allow for earlier discharge.

MATERIALS AND METHODS

Study population

This prospective, non-randomized study was conducted

on a population of 220 consecutive outpatients undergoing ambulatory elective colonoscopy in our Digestive Endoscopy Centre. Inclusion criteria were: age range 18 to 75 years, patients scheduled for elective sedated colonoscopy, and capability (evaluated by the endoscopist) of fully understanding the questionnaire. Exclusion criteria were: American Society of Anesthesiology (ASA) risk class 3 or higher^[12], previous colonic surgical procedure, willingness to undergo unsedated colonoscopy, inpatient status, planned endoscopic therapy, psychiatric diseases or long-term psychiatric drug addiction, concomitant neoplastic diseases, pregnancy or lactation. The first 110 subjects formed the control group (Co-group), in which discharge decision was based on clinical evaluation; the other 110 subjects formed the study group in which the discharge was based on the modified Post Anaesthetic Discharge Scoring System (PADSS-group)^[13].

Oral 4-L polyethylene glycol solution was used in all patients as a preparation for colonoscopy. Conscious sedation was induced by means of an *iv* combination of Meperidine 40-60 mg plus Midazolam 2-5 mg according to our routine practice, in order to obtain a degree of sedation ranging from 2 to 4 of the Ramsay's scale^[14].

The study protocol was approved by the Ethical Committee of our hospital, and all patients enrolled gave their written informed consent to participate in the study.

Outcome measurement

Pre-colonoscopy and during-colonoscopy assessment:

For each patient, age, gender, blood pressure (BP), blood oxygen saturation (SaO₂), and heart rate (HR) were recorded. Associated medical illnesses were graded according to the American Society of Anesthesiologists' Physical Status Classification (ASA grade)^[12]. Before colonoscopy the anxiety level of the patient was evaluated on a four-point verbal scale, where 1 = no anxiety, 4 = very anxious. Pre-colonoscopy abdominal pain was assessed with the Numerical Analogue Scale (0 = no pain; 10 = unbearable pain)^[15]. Heart rate, blood oxygen saturation, and blood pressure were monitored, and oxygen supplement (2 L/min) was provided throughout the duration of colonoscopy.

Post-colonoscopy assessment: Patients in which cecal intubation was not performed were excluded from the study. After colonoscopy, the patients were followed up in the recovery room, and 20 min after the end of colonoscopy they were scored using the Modified PADSS (Table 1)^[13]. Afterwards, they were re-scored every 20 min, until two consecutive PADSS scores ≥ 9 were achieved.

Using a 9-item questionnaire, the investigator documented each patient's postoperative course in a follow-up phone call 24-48 h after discharge, to assess any delayed complication. Patients who were not found at follow-up phone call were excluded from the study.

Discharge criteria: (1) Co-group: After colonoscopy, the endoscopist settled the observation time on the basis

Table 1 Modified Post-Anaesthetic Discharge Scoring System

Categories	Points
Vital signs	
BP and HR \pm 20% of pre-endoscopy value	2
BP and HR \pm 20%-40% of pre-endoscopy value	1
BP and HR \pm 40% of pre-endoscopy value	0
Activity	
Steady gait, no dizziness or meets pre-endoscopy level	2
Requires assistance	1
Unable to ambulate	0
Nausea and vomiting	
No or minimal/treated with p.o. medication	2
Moderate/treated with parenteral medication	1
Severe/continues despite treatment	0
Pain	
Minimal or no pain (Numerical Analogue Scale = 0-3)	2
Moderate (Numerical Analogue Scale = 4-6)	1
Severe (Numerical Analogue Scale = 7-10)	0
Surgical bleeding	
None or Minimal (not requiring intervention)	2
Moderate (1 episode of hematemesis or rectal bleeding)	1
Severe (\geq 2 episodes of hematemesis or rectal bleeding)	0
Total score	...
(Patients' scoring \geq 9 for two consecutive measurements are considered fit for discharge home)	

BP: Blood pressure; HR: Heart rate.

Table 2 Patients characteristics and main results

	Co-group (<i>n</i> = 103)	PADSS-group (<i>n</i> = 104)
Age, mean \pm SD, yr	58.45 \pm 11.65	57.21 \pm 11.6
Gender, M/F	46/57	46/58
ASA class I / II	40/63	41/63
Anxiety level, <i>n</i>		
1: none	16	9
2: mild	75	88
3: moderate	10	6
4: severe	2	1
Pain before colonoscopy, mean \pm SD	1.9 \pm 1.4	1.9 \pm 0.6
Recovery time, mean \pm SD, min ^b	95.14 \pm 10.85	58.75 \pm 18.67
Recovery time < 60 min, <i>n</i> (%) ^b	0 (0)	39 (37.5)
Early or late severe complications, <i>n</i>	0	0

^b*P* < 0.001, Post-Anaesthetic Discharge Scoring System (PADSS)-group *vs* Co-group. ASA: American Society of Anesthesiology.

of patient's age and clinical conditions, dosage of the administered drugs, and sedation degree. At the end of the observation time, the patient was discharged if BP, HR, and SaO₂ were stable; and (2) PADSS-group: Recovery-room nurse discharged the patient after a PADSS score \geq 9 was achieved in two consecutive measurements. The time from the end of colonoscopy to the patient discharge was recorded.

Estimation of sample size: The test power was exclusively based on the presence of two groups (Co-group and PADSS-group) resulting to be higher than 95% and suitable to reveal differences between discharges times of at least 10 min preserving a *P* value < 0.05.

Table 3 Results of post-endoscopy evaluation phone call

	Co-group (<i>n</i>)	PADSS-group (<i>n</i>)
Go back to the hospital	0	0
Problems since discharge	57	32
Abdominal distension (with or without pain)	21	7
Fever	1	2
Pain at the injection site	4	4
Headache	15	4
Nausea and/or vomiting	3	2
Drowsiness or difficult to wake-up	31	22
Weakness	20	19
Did you take drugs for these problems?	2	1

PADSS: Post-Anaesthetic Discharge Scoring System.

Statistical analysis

Interval variables were analyzed using the non parametric Kruskal-Wallis test, and nominal variables were analyzed using the χ^2 test, or, if necessary, the Fisher's exact test. Results were considered statistically significant if *P* values were < 0.05.

RESULTS

Thirteen patients (7 in Co-group and 6 in PADSS-group) were excluded from the study, as cecal intubation was not performed or the patients were not found at follow-up phone call. Two hundred and seven patients (92 males and 115 females) could be evaluated. Their characteristics are summarized in Table 2. The two groups did not differ for age, gender, pre-colonoscopy anxiety level and ASA classification. No patient needed reversal agents.

Recovery from sedation was faster in PADSS-group than in Co-group (58.75 \pm 18.67 min and 95.14 \pm 10.85 min, respectively; *P* < 0.001) (Table 2 and Figure 1). Recovery time resulted shorter than 60 min in 39 patients of PADSS-group (37.5%), and in no patient of Co-group (*P* < 0.001).

No early complication occurred in both groups. At follow-up phone call, no patient declared any need of hospital re-admission because of problems related to colonoscopy and/or sedation. Fifty-seven patients in Co-group (55.3%) and 32 in PADSS-group (30.7%) complained of mild post-colonoscopy symptoms (Table 3), but only three of them (2 in Co-group e 1 in PADSS-group) needed to take some drugs for these symptoms. The most common symptoms were drowsiness, weakness, abdominal distension, and headache.

DISCUSSION

The increasing number of digestive endoscopic examinations performed under sedation has highlighted the problem of the space and personnel required to recover the patients, and the need to identify criteria that can be used to determine when they can safely go home under

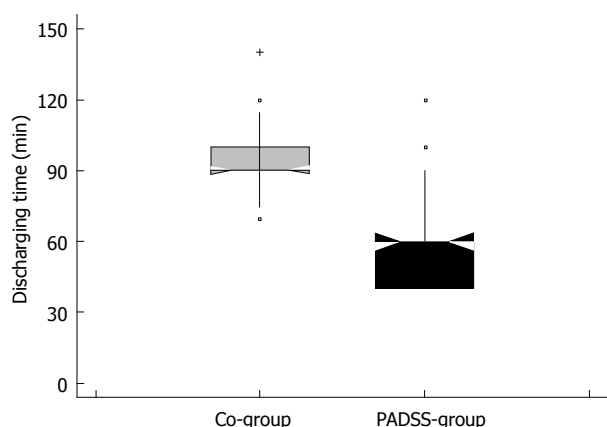


Figure 1 Comparison of recovery time for the two groups. PADSS: Post-Anaesthetic Discharge Scoring System.

the care of a friend or relative. Most centers still rely on clinical criteria for practical discharge decision after colonoscopy. Efforts to shorten recovery time by using sedative agents with shorter half life are gaining increasing popularity. The European Guidelines concerning Non-Anaesthesiologist Administered Propofol (NAAP) for Gastrointestinal Endoscopy was published in 2010^[16], but 21 national societies of anaesthesiology in Europe signed a Consensus Statement to declare their disagreement with the NAAP guidelines^[17]. Moreover, because of the well-known risks of Propofol administration, the manufacturers of the drug have added the following restriction: “For general anesthesia or monitored anesthesia care (MAC) sedation, DIPRIVAN Injectable Emulsion should be administered only by persons trained in the administration of general anesthesia and not involved in the conduct of the surgical/diagnostic procedure”. For these reasons, drugs with a very short duration of action, such as Propofol and Remifentanyl, are only administered by anesthetists in Italy, and their use under the direction of a gastroenterologist can have medico-legal implications^[18]. Therefore, sedation is generally obtained by means of Meperidine and Midazolam. However, Meperidine is an opioid analgesic with long duration of action (2-4 h)^[19], and the duration of the impairment after sedation and post-colonoscopy observation time are unavoidably long.

Several cognitive and psychomotor tests are available to assess the impairment after sedation, but most of them are toilsome and poorly suitable for clinical practice^[20-22]. The clinical scoring systems are based on clear, concise and standardized discharge criteria that can be used to determine when patients can safely go home under the care of a relative. The Aldrete scoring system and the PADSS have received widespread acceptance in assessing postanesthetic recovery^[23], and are currently used to assess home-readiness after ambulatory surgery. Conversely, to date there is very little information about their use in ambulatory gastrointestinal endoscopy.

In our study, the PADSS resulted as safe as clinical assessment and allowed for earlier patient discharge after colonoscopy performed under sedation. No patient had to be re-admitted because of complications, and just three patients (2 in Co-group and 1 in PADSS-group) taken some drugs for mild and transient symptoms (Table 3). Our data are comparable to those reported by a previous prospective study, in which the patients undergoing endoscopic procedures under sedation were assessed with the PADSS and were discharged within two hours^[24]. Furthermore, in our study 37.5% of patients in PADSS-group could be discharged within 60 min from the end of colonoscopy. This observation is quite interesting, as the patients were only discharged after two consecutive measurements achieving a PADSS score ≥ 9 . Since the measurements were taken every 20 min, the theoretical shortest time for patient discharge would be 40 min. We prudentially planned to discharge the patients after two measurements of PADSS score, as there are very few studies dealing with its use in digestive endoscopy, and no specific information is provided in literature on potential discharge problems. However, the discharge time could probably be even shorter, as prior reports suggested that patients can be discharged without problems after just one PADSS score ≥ 9 ^[23].

The patient's readiness for discharge needs to be addressed in a simple, clear and reproducible manner, to replace subjective clinical impression by assigning numeric values to parameters. Our trial was conducted in a large busy hospital, and its results show that well-defined discharge scoring criteria offer measurable advantage in decreasing total procedure time by shortening recovery time, and can represent a useful tool for all digestive endoscopy centers in which Meperidine is routinely used for sedation. The use of a standardized discharge scoring system can increase the flow of patients through the recovery process and allows for safe discharge without increasing post-discharge complications and without using any additional resources. The shorter mean recovery time achieved in the PADSS-group in comparison with the Co-group (about 37 min) entails a shorter time spent by the nurse in the recovery room. However, it would be quite hard to quantify such a time saving in terms of cost saving, as several patients are contemporaneously followed up by the recovery-room nurse. Nonetheless, the use of a standardized discharge scoring system represents a more cost-efficient manner while still maintaining quality of care, and becomes essential if discharge decision is entrusted to the nursing staff, which needs to evaluate the post-endoscopy course of the patient in a systematic way, applying to physician for consultation only when necessary.

Our study has some limits. First, it is a single centre study. Second, it is not a randomized trial. Moreover, although the scoring criterion is a reliable tool, it can not replace the critical thinking or professional judgment, as it does not allow to identify all the possible problems

(for instance, a hypoglycemic crisis). Calculating scores of PADSS entails that post-endoscopy vital sign parameters should be compared with pre-endoscopy values, to ensure the patient's return to homeostasis. However, if some pre-endoscopy values were abnormally elevated because of anxiety or pain, expecting the post-endoscopy values to be within $\pm 20\%$ range may not be appropriate.

In conclusion, having well-defined discharge scoring criteria is imperative in order to ensure a quick and safe discharge. Our study suggests that almost all patients undergoing sedation with Meperidine and Midazolam can be discharged within 2 h of colonoscopy, using the modified PADSS score. However, further and wider randomized trials are needed to confirm our observation.

COMMENTS

Background

The number of colonoscopies performed under sedation on an outpatient basis is increasing as the screening programs for the colon cancer prevention are ongoing in many countries. This fact can cause some problem to digestive endoscopy centres, as they are often not provided with sufficiently spacious recovery rooms.

Research frontiers

At the time of discharge after colonoscopy, patients should be home-ready, and this issue can involve legal implications. Nevertheless, there is very little information and documentation about the recovery patterns and home-readiness after colonoscopy, and many guidelines do not include the use of any standardized discharge scoring system.

Innovations and breakthroughs

In this prospective study, recovery from sedation resulted faster in Post-Anaesthetic Discharge Scoring System (PADSS)-group than in Control-group (58.75 min vs 95.14 min, $P < 0.001$), and no patient had to be re-admitted because of complications.

Applications

This study demonstrated that the use of PADSS is safe and allows for an earlier patient discharge after colonoscopy performed under sedation.

Terminology

PADSS is a clinical scoring system based on clear, concise and standardized discharge criteria, and is currently used to assess home-readiness after ambulatory surgery.

Peer review

This is an interesting study, which has important clinical applications.

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Usefulness of continuous suction mouthpiece during esophagogastroduodenoscopy: A single-center, prospective, randomized study

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Abstract

AIM: To develop a new continuous suction mouthpiece (CSM) and evaluate its usefulness for screening esophagogastroduodenoscopy (EGD).

METHODS: A total of 196 patients who were scheduled to undergo screening EGD were assigned to one of two groups: a group using the CSM and a group using a conventional mouthpiece. Extent of salivary flow, frequency of saliva suction, number of choking episodes

during the examination, and incidence of aspiration pneumonia after the examination were evaluated and compared between the two groups. Adverse events during and after EGD were also examined. In addition, the oral cavity was meticulously examined after the EGD.

RESULTS: The same number of patients was randomly allocated to each group. There were no significant differences between the two groups in sex, age, biopsy procedure, duration of procedure and depth of sedation. Aspiration pneumonia and other significant adverse events were not observed in either group. The grade of extent of salivary flow was significantly lower in patients with the CSM than in patients with the conventional mouthpiece ($P < 0.001$). Although there was no significant difference, less frequent suctioning and fewer choking episodes were observed in patients with the CSM than in patients with the conventional mouthpiece ($P = 0.082$ and $P = 0.084$, respectively). In addition, there were no patients in the CSM group who required saliva suctioning during the procedure.

CONCLUSION: Use of the CSM during screening EGD can reduce the extent of salivary flow. The device is expected to reduce complications and contamination with saliva.

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Key words: Mouthpiece; Esophagogastroduodenoscopy; Aspiration; Saliva; Suction

Core tip: Control of salivary flow during endoscopic examination is important. We focused on a mouthpiece designed for control of saliva in this study. First, we produced a new continuous suction mouthpiece (CSM). Then, we evaluated its usefulness for esophagogas-

troduodenoscopy (EGD). This study indicates that the CSM can reduce the extent of salivary flow during EGD. Moreover, it tended to reduce the frequencies of suction and choking episodes during EGD.

Maekita T, Kato J, Nakatani Y, Enomoto S, Takano E, Tsuji M, Nakaya T, Moribata K, Muraki Y, Shingaki N, Niwa T, Deguchi H, Ueda K, Inoue I, Iguchi M, Tamai H, Ichinose M. Usefulness of continuous suction mouthpiece during esophagogastroduodenoscopy: A single-center, prospective, randomized study. *World J Gastrointest Endosc* 2013; 5(10): 508-513 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i10/508.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i10.508>

INTRODUCTION

Screening esophagogastroduodenoscopy (EGD) is a common examination that is useful in detecting upper gastrointestinal disease. Hence, it is increasingly performed for patients. However, performance of EGD is associated with the risk of certain adverse events, including aspiration, because EGD is often performed with sedation. A study reported that the rate of aspiration during EGD with sedation was as high as 3.94%^[1] when subclinical cases were included. More attention should be paid to this risk.

One of the most important factors correlating with aspiration is the salivary flow induced by introduction/extraction of the endoscope into the oral cavity. Therefore, control of salivary flow during EGD is important for prevention of aspiration. However, few attempts have been made to control salivary flow, perhaps due to its difficulty. Currently, the endoscopist or an assistant must watch for the accumulation of saliva and suction it using a catheter, in case the patient undergoing EGD cannot discharge saliva from the mouth. In this context, control of salivary flow during EGD, if possible, might reduce the endoscopist's or nurse's suctioning efforts, resulting in prevention of complications associated with aspiration. Moreover, contamination of the patient's face or clothes with saliva could also be minimized.

During EGD, a hard plastic mouthpiece is used to protect the endoscope from being bitten and to enable its smooth insertion. A mouthpiece that can also suction saliva might be useful for preventing aspiration and contamination with saliva during EGD. Accordingly, we recently developed a new continuous suction mouthpiece (CSM), and reported its usefulness for prevention of complications associated with salivary flow during percutaneous endoscopic gastrostomy (PEG) procedures^[2]. The background of the study patients in this study differed from that of the patients in the PEG study. PEG is performed with the patient in the supine position, is a lengthy process, and is indicated for elderly patients with dysphagia. In contrast, EGD is performed with the patient in the left lateral position, is a shorter process, and is indicated for patients without dysphagia and severe

complications.

The aim of this study was to evaluate the usefulness and ability of the CSM for prevention of complications and contamination associated with saliva, including aspiration, during screening EGD.

MATERIALS AND METHODS

Equipment

The details of production of the CSM were reported previously^[2]. In summary, after cutting the junction part of a non-toxic polyvinyl chloride (PVC) suction tube (Nipro Suction Catheter® 14-Fr, Nipro, Osaka, Japan), the tube was bent double and the two sides were connected with two movable short bands made of non-toxic PVC suction tubing (Nipro Suction Catheter® 16-Fr, Nipro). The three parts divided by the short bands were made into: a 2- to 5-cm-diameter, adjustable intraoral loop part with 6 smooth 2.7-mm-diameter holes for suction; a binding loop part to fit mouthpieces of various sizes; and an extraoral part having two ends, both of which were linked to the Y-shaped connector (ARAM, Osaka, Japan). Finally, the MB-142 mouthpiece (Olympus, Tokyo, Japan) was inserted into the binding loop part (Figure 1).

For screening EGD in the CSM group, patients were placed on their left side and asked to bite down on the mouthpiece, with the intraoral loop with holes placed inside the left cheek. During EGD, continuous low pressure (10 kPa) suctioning with a suction unit (Shin-Ei Industries, Tokyo, Japan) was performed through the unification tube attached to the Y-shaped connector (Figure 2). In control subjects, the MB-142 mouthpiece was used in the usual way.

Patients and study design

This was a single-center, prospective, randomized, controlled study. Patients who underwent screening EGD in Nakaya Hospital (Wakayama, Japan) from February 2011 to December 2011 were recruited. Patients were excluded if they had a history of respiratory problems that could increase the risk of complications associated with aspiration pneumonia and salivary flow. Eligible patients were randomly assigned to one of the following groups: the group using the CSM, or the group using the conventional mouthpiece for EGD. During the EGD, salivary flow and complications associated with aspiration were evaluated and compared between the two groups. However, due to its nature, this study could not be blinded.

This study was approved by the ethics committee of Nakaya Hospital. Written, informed consent was obtained from each patient. This study was registered with the University Hospital Medical Information Network (UMIN) (registration number UMIN000009294). The CSM was developed solely by our institute without any financial or equipment support from companies.

EGD

A conventional gastrointestinal videoscope (GIF-XP260N;

Table 1 Patients' characteristics

	CSM	MB-142	P value
Sex, male/female	56/42	59/39	0.125
Age, yr, median (range)	66 (33-99)	56 (35-96)	0.269
Biopsy (yes/no)	30:68	24:74	0.344
Duration of procedure, min, median (range)	8 (4-21)	7 (3-21)	0.194
Sedation, none/mild/moderate/deep	11/7/17/63	17/3/8/70	0.090

CSM: Continuous suction mouthpiece.

Olympus) was orally inserted into the stomach to observe the upper gastrointestinal tract. During the examination, patients were placed on their left side. EGD for all patients was performed by one endoscopist and one assistant nurse.

Premedication with anticholinergic agents or glucagon was not used. Lidocaine (8%) was sprayed into the posterior pharynx of all patients before insertion of the endoscope to reduce the gag reflex. Then, midazolam (1-5 mg) was administered intravenously for sedation. Adequate monitoring of vital signs and oxygen saturation was performed throughout the examination.

Outcome assessment and evaluations

The primary outcome was occurrence of aspiration pneumonia. Secondary outcomes were extent of salivary flow, frequency of saliva suction, and the number of choking episodes during the procedure. Adverse events during and after EGD were also examined. In addition, the oral cavity was meticulously examined after the EGD to determine whether blood blisters or any suction tube fragments were present.

The duration of EGD using the CSM included the time required to bite down on the mouthpiece with the intraoral loop placed inside the left cheek. The level of sedation was defined as follows: mild, conscious sedation; moderate, between conscious and deep sedation; and deep, deep sedation. None means no use of sedatives. The extent of salivary flow was defined as follows: grade 1, no flow of saliva from mouth; grade 2, flow to the cheek; grade 3, flow to the ear; and grade 4, flow to hair or clothing. When a gurgling sound was heard in the oropharyngeal region, the assistant nurse promptly suctioned the saliva using the suction catheter (Nipro Suction Catheter® 14-Fr, Nipro). Choking episodes were counted each time they occurred during the examination, while consecutive coughs or chokes were counted as one choking episode.

Statistical analysis

The data are expressed as medians with ranges. Data were analyzed using the unpaired Mann-Whitney *U* test and Fisher's exact test. The level of statistical significance was $P < 0.05$. All analyses were performed using the SPSS 21.0 software package (SPSS Inc., Chicago, IL, United States).

RESULTS

A total of 196 subjects (115 men and 81 women, median age 62 years (range, 33-99 years) were recruited during the study period; all were considered eligible. Patients were divided equally into the CSM group and conventional mouthpiece groups (both $n = 98$). The patients' characteristics are summarized in Table 1. There were no significant differences between the two groups in sex, age, biopsy procedure, duration of the examination and depth of sedation.

Obvious aspiration pneumonia was not observed in any of the participating patients. The extent of salivary flow was significantly less in patients with the CSM than in patients with the conventional mouthpiece ($P < 0.001$) (Figure 3A). Although there was no statistical significance, less frequent suctioning and choking episodes were observed in patients with the CSM than in patients with the conventional mouthpiece ($P = 0.082$, and $P = 0.084$, respectively) (Figure 3B, C). In addition, no patients in the CSM group required saliva suctioning during the procedure. Complete failure of suctioning function did not occur in any patients with the CSM. In addition, neither blood blisters nor fragments of the PVC suction tubes were observed in the mouths of patients who used the CSM. No other significant adverse events were observed in any of the patients.

DISCUSSION

This is the first attempt to control salivary flow by continuous suctioning during screening EGD examination. Previously, little attention has been paid to the troubles and complications associated with endoscopy-related salivary flow. This study showed that, during EGD, salivary flow did not extend as far out of the mouth in patients with the CSM as in patients with the conventional mouthpiece. Moreover, fewer suctioning and choking episodes were observed in patients with the CSM, although the difference was not statistically significant.

The most relevant finding of this study is that the CSM could reduce the extent of salivary flow during screening EGD. As shown in the results, the grade of extent of salivary flow was higher in patients with the conventional mouthpiece, despite relatively short examination times. In contrast, patients with the CSM discharged less saliva during the procedure. This advantage implies that use of the CSM during EGD could prevent exposure of the patient's body or clothing and operating bed to saliva, resulting in relief for the patient from the discomfort associated with drooling of saliva. Moreover, reduced contamination of the operating bed with saliva could decrease the effort, time and cost required for cleanup.

In the present study, use of the CSM tended to reduce the frequencies of saliva suction and choking episodes during screening EGD, although statistical differences were not observed. The fact that there were no episodes

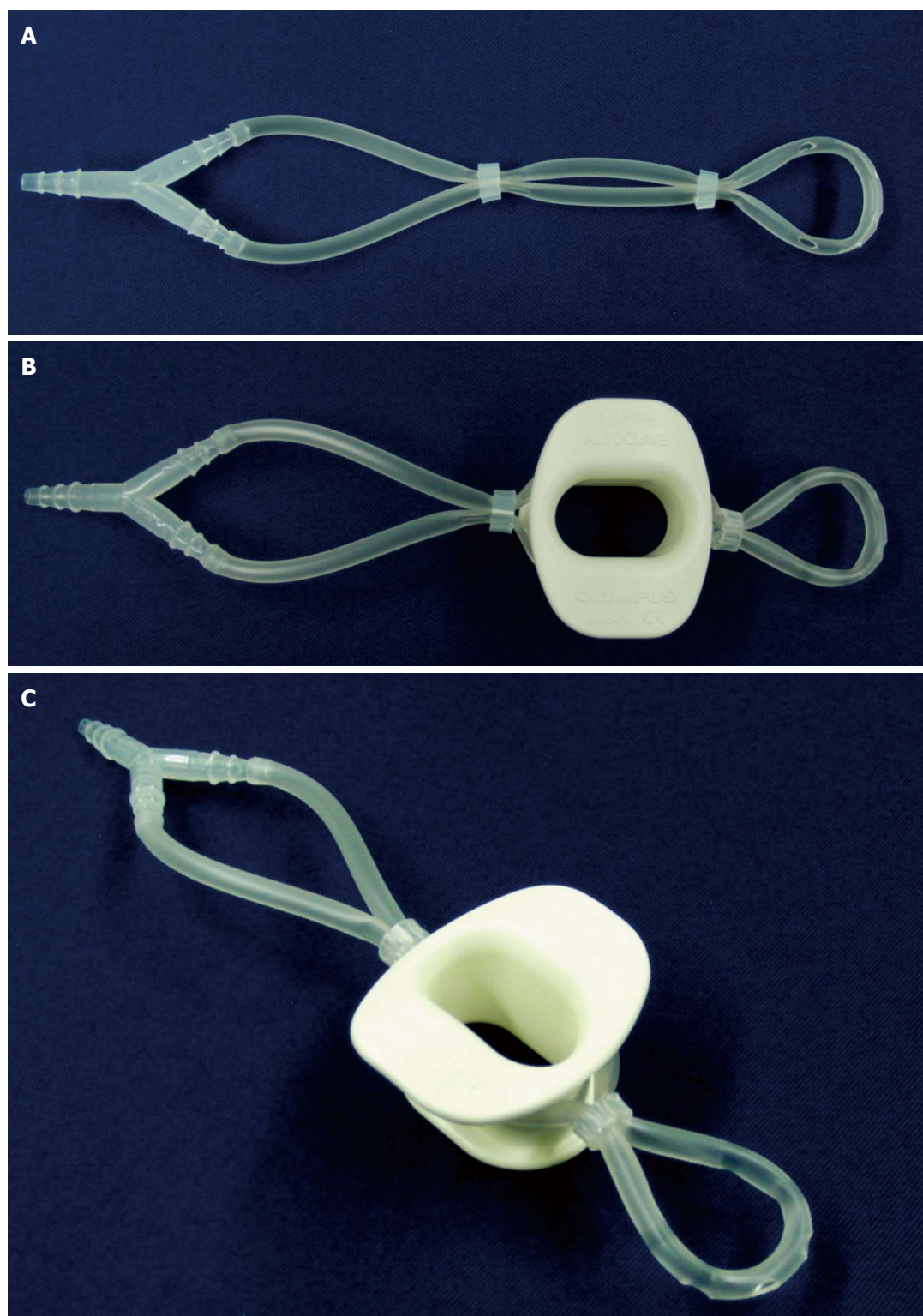


Figure 1 The continuous suction mouthpiece. A: The continuous suction mouthpiece (CSM) without the mouthpiece; B, C: The CSM with the mouthpiece.

of suctioning in the CSM group could imply that the assistant nurse's time and effort can be directed towards other, more important tasks during EGD. Reduced choking episodes from use of the CSM may decrease the complication of aspiration during EGD, although no aspiration pneumonia was observed in patients in both groups, perhaps due to the small number of patients in this study. Thus, use of this equipment, which can be

easily prepared with no special materials and at a low cost, is recommended during screening EGD.

Moreover, the CSM's continuous suction creates airflow in the oral cavity, which may reduce the discomfort in the oral cavity caused by endoscopy. In the questionnaire administered after EGD, 3 of 11 patients in the CSM group who did not use sedation answered that continuous suction during the procedure was comfortable. In this study, most

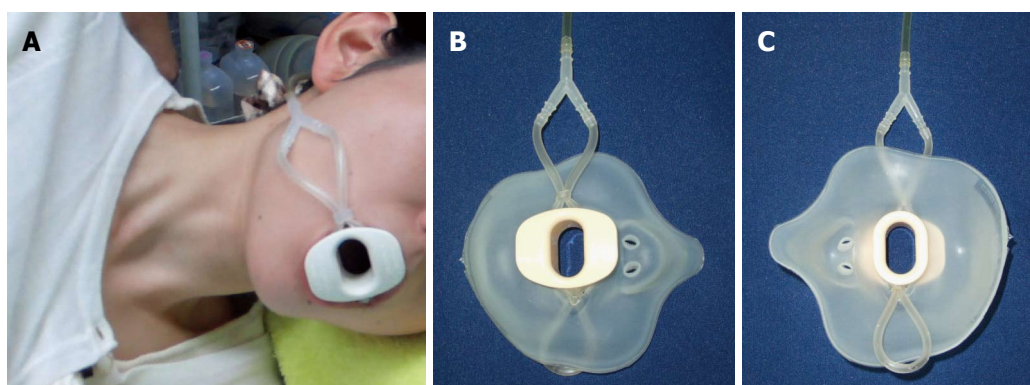


Figure 2 Use of the continuous suction mouthpiece. A: Image showing actual use of the continuous suction mouthpiece (CSM); B: Endoscopist's view of the CSM during its use; C: Patient's view of the CSM during its use.

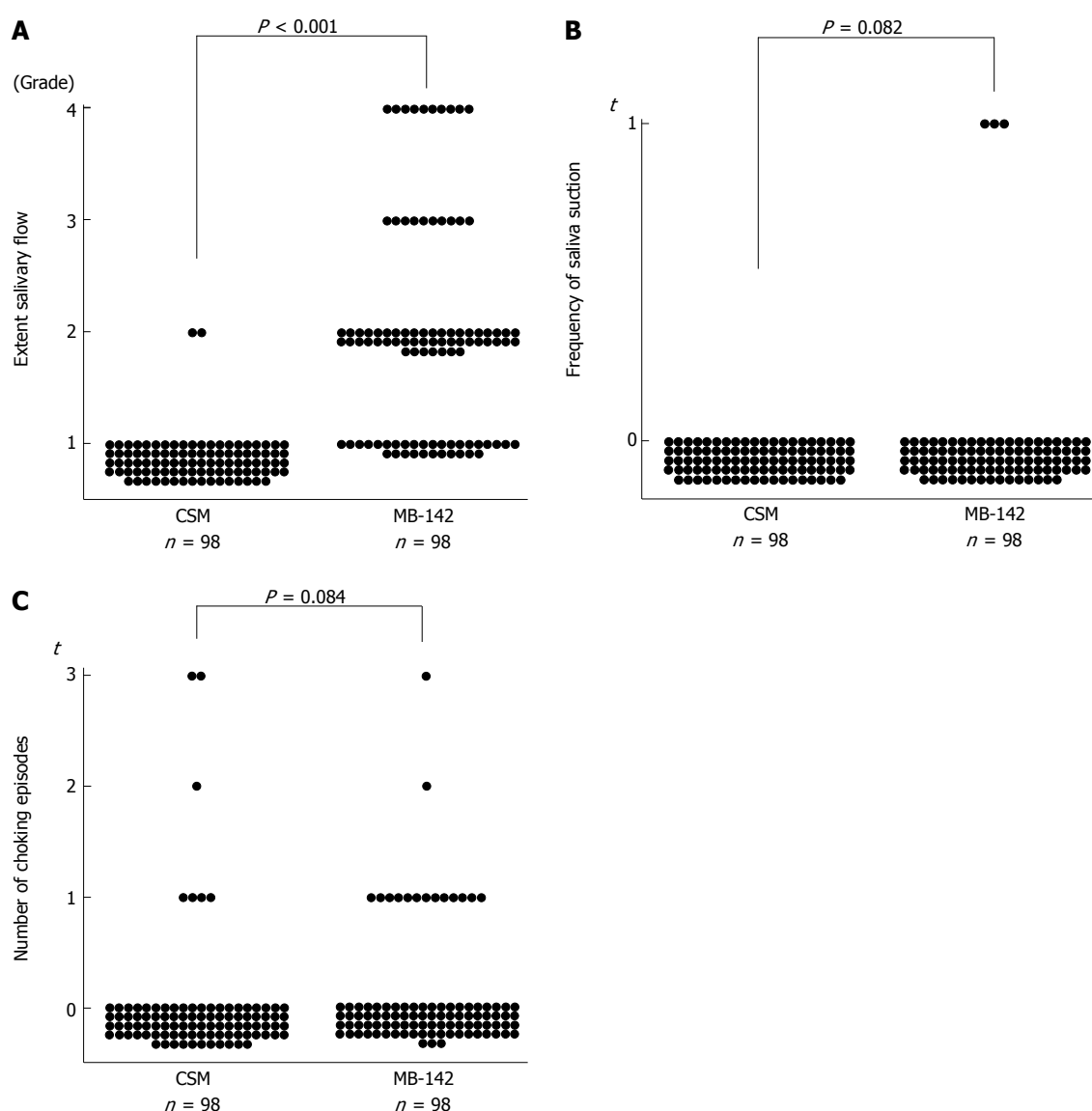


Figure 3 Obvious aspiration pneumonia was not observed in any of the participating patients. A: Extent of salivary flow. The grade of extent of salivary flow was significantly lower in patients with the continuous suction mouthpiece (CSM) than in patients with the conventional mouthpiece ($P < 0.001$); B: Frequency of saliva suction. No suction events were observed in patients with the CSM, while 3/98 (3.1%) of the patients with the conventional mouthpiece required suctioning during esophagogastroduodenoscopy (EGD) ($P = 0.082$); C: Number of choking episodes. Although not statistically significant, less frequent choking episodes were observed in patients with the CSM than in patients with the conventional mouthpiece ($P = 0.084$).

of the patients were sedated with midazolam and could not

comment about the CSM after the procedure. Future stud-

ies should confirm the level of comfort associated with use of the CSM during EGD performed without sedation.

Administration of anticholinergic agents is an alternative strategy to reduce salivary secretion and peristaltic activity of the gut during EGD. However, these agents cannot be used in patients with heart disease, glaucoma or prostate enlargement. In contrast, the CSM can be used in all patients because its use is not associated with any serious adverse effects. Thus, the improved mouthpiece would be superior to anticholinergics in terms of controlling salivary secretion during EGD.

The CSM may also be effective in endoscopic procedures other than EGD. Recently, we reported that the CSM is effective during PEG^[2]. Besides EGD and PEG, many other kinds of time-consuming upper endoscopic procedures have become commonplace, such as endoscopic submucosal dissection and peroral double-balloon enteroscopy. Since these procedures are also associated with an increased risk of aspiration^[3,4], use of the CSM may be recommended in all patients who undergo these procedures. Hence, the usefulness of this item in various procedures should be evaluated in the future.

This study had several limitations. First, neither the endoscopist nor the assistant nurse was blind as to which mouthpiece was used. Since the shape of the mouthpiece was different from conventional mouthpieces, blinding was not possible. Second, the number of patients was too small to evaluate some endoscopy-related complications, such as the frequency of aspiration pneumonia, the primary outcome of this study. This could be partly attributed to the study design, since the diagnosis of aspiration pneumonia was based on patients' symptoms alone. The reported rate of aspiration pneumonia with conventional EGD methods is 3.94%, as assessed by ¹⁸F-FDG PET scan^[1]. Therefore, the advantage of the CSM in terms of aspiration needs to be confirmed in studies that are designed for evaluating subclinical aspiration pneumonia and in older patients who have difficulty swallowing. Third, several factors may have influenced the outcome of this study. In particular, the amount of midazolam administered (1-5 mg) for sedation varied widely. The sedative agent might have influenced the extent of salivary flow. To overcome this limitation, it would have been preferable if we had defined the amount of sedative agent to be administered in mg/kg. Finally, use of the CSM involves a certain amount of time and cost. However, construction of a single CSM costs no more than \$1 (1 US dollar), in addition to the cost of the MB-142 mouthpiece.

The CSM reduced the extent of salivary flow during EGD. Moreover, it tended to reduce the frequencies of suction and choking episodes during EGD. This type of simple and inexpensive device is expected to reduce not only patient discomfort, but also the burden on medical staff during EGD. Therefore, use of the device in routine clinical practice is highly recommended.

COMMENTS

Background

Screening esophagogastroduodenoscopy (EGD) is a common examination that is useful in detecting upper gastrointestinal disease. Hence, it is increasingly performed for patients. However, more attention should be paid to the risk of aspiration during the procedure. One of the most important factors correlating with aspiration is salivary flow. No mouthpiece has previously been designed to control salivary flow during endoscopic examination.

Research frontiers

A new continuous suction mouthpiece (CSM) was developed and its usefulness during percutaneous endoscopic gastrostomy (PEG) was recently reported.

Innovations and breakthroughs

This is the first attempt to control salivary flow by continuous suctioning during screening EGD examination. Previously, little attention had been paid to the troubles and complications associated with endoscopy-related salivary flow. This study showed that, during EGD, salivary flow did not extend as far out of the mouth in patients with the CSM as in patients with the conventional mouthpiece. Moreover, fewer suctioning and choking episodes were observed in patients with the CSM, although the difference was not statistically significant.

Applications

The CSM may also be effective in endoscopic procedures other than EGD and PEG.

Terminology

A mouthpiece is used to protect the endoscope from being bitten and for smooth insertion of the endoscope, without hindrance from the tongue, during EGD.

Peer review

This is an interesting original article introducing a new continuous suction mouthpiece during EGD. The idea is very good. There was no statistical difference between choking episodes and the incidence of aspiration pneumonia in this article. However, it could reduce the extent of salivary flow during EGD. This is advantageous from a hygienic point of view. Use of this device is a good option during screening EGD and other endoscopic procedures. This device has the potential to make a significant contribution to the practice procedures of readers in the field.

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Duodenal subepithelial hyperechoic lesions of the third layer: Not always a lipoma

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Author contributions: Figueiredo PC and Pinto-Marques P performed the echoendoscopic examinations; Mendonça E, Oliveira P and Brito M performed, reviewed the pathology examinations; Serra D performed the endoscopic therapeutic procedures; Figueiredo PC and Pinto-Marques P organized the report; Figueiredo PC wrote the paper; all authors read and approved the final manuscript.

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Key words: Endoscopic ultrasonography; Endoscopic ultrasound-guided fine needle aspiration; Duodenum; Subepithelial tumor; Lipoma

Core tip: This case series reports four different and relevant pathologies with an echoendoscopic pattern usually suggestive of lipoma.

Figueiredo PC, Pinto-Marques P, Mendonça E, Oliveira P, Brito M, Serra D. Duodenal subepithelial hyperechoic lesions of the third layer: Not always a lipoma. *World J Gastrointest Endosc* 2013; 5(10): 514-518 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i10/514.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i10.514>

INTRODUCTION

Endoscopic ultrasonography (EUS) has long been considered the most accurate procedure for the evaluation of subepithelial lesions^[1-3]. It provides important information, namely the layer of origin, size, borders and echogenic structure. Using Doppler findings it may also differentiate vascular structures from cysts or assess the tumor blood supply. These findings allow for a presumptive diagnosis in most cases, although histopathology remains the gold standard^[2].

Gastrointestinal (GI) lipomas are benign tumors that occur anywhere along the gut, most commonly in the colon^[4]. The typical EUS finding is a homogeneous, hyperechoic, well-delimited lesion, originating from the third layer of the GI tract (submucosa)^[3,5]. The only differential diagnosis for this EUS pattern reported in the literature is Brunner's gland hamartoma^[5,6].

This case series aims to broaden the spectrum of

Abstract

Endoscopic ultrasonography is the most accurate procedure for the evaluation of subepithelial lesions. The finding of a homogeneous, hyperechoic, well-delimited lesion, originating from the third layer of the gastrointestinal tract (submucosa) suggests a benign tumor, generally lipoma. As other differential diagnoses have not been reported, echoendoscopists might not pursue a definitive pathological diagnosis or follow-up the patient. This case series aims to broaden the spectrum of differential diagnosis for duodenal hyperechoic third layer subepithelial lesions by providing four different and relevant pathologies with this echoendoscopic pattern.

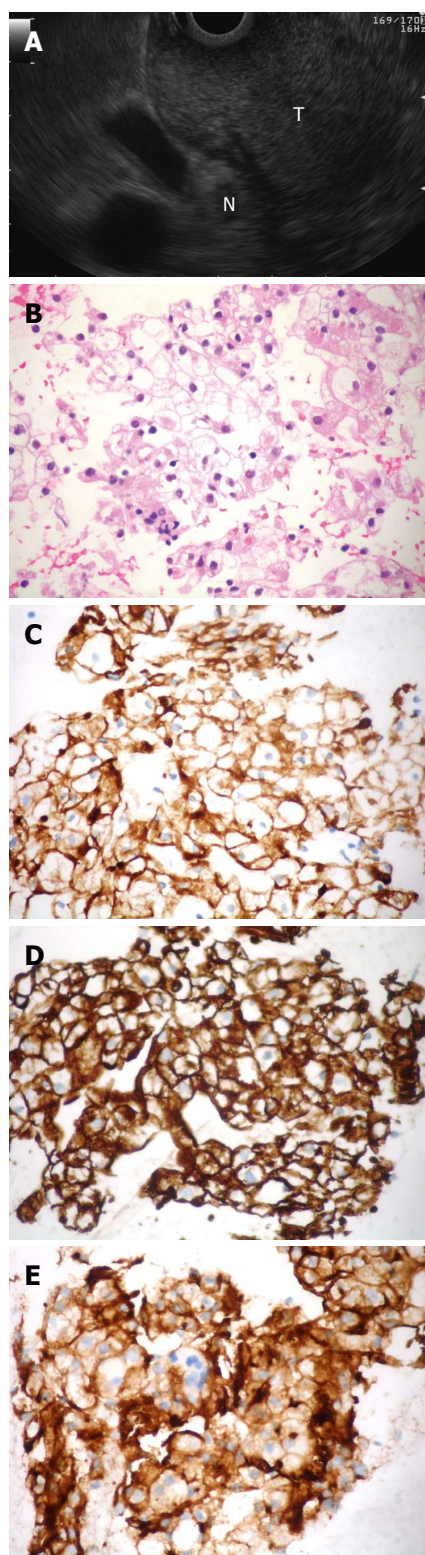


Figure 1 Endoscopic ultrasonography and cytology findings of a renal cell carcinoma metastasis. A: Hyperechoic mass in the duodenal bulb, apparently originating from the third layer. Adjacent, a small lymph node is noted; B-E: Fine-needle aspiration cell blocks, $\times 400$ magnification; Hematoxylin and eosin staining showing clear cell aggregates (B). Positive immunostaining for cytokeratin AE1/AE3 (C), vimentin (D) and CD10 (E): consistent with an epithelial carcinoma of renal origin.

EUS differential diagnosis for duodenal hyperechoic third layer subepithelial lesions.

CASE REPORT

Case 1: Renal cell carcinoma metastasis

A 58-year-old woman was admitted for melena and upper GI endoscopy revealed an ulcerated mass in the duodenal bulb. Biopsies using “bite-on-bite” technique were inconclusive. EUS with a linear echoendoscope (Olympus Medical Systems Corp., Tokyo, Japan) showed a well-delimited hyperechoic mass, apparently originating from the third layer at the bulb (Figure 1A). Fine-needle aspiration (FNA) was performed with a 22-gauge EZ Shot needle (Olympus Medical Systems Corp., Tokyo, Japan). FNA smear and cellblock sections showed clear cell aggregates with positive immunostaining for cytokeratin AE1/AE3, vimentin and CD10, which were consistent with an epithelial carcinoma of renal origin (Figure 1B-E). Three years before the patient had a left kidney nephrectomy for a Grawitz tumor and was referred for cephalic pancreatoduodenectomy to treat the disease recurrence.

Case 2: Ampullary carcinoma

A 64-year-old man presented with jaundice at the emergency department. An abdominal US and CT scan showed dilated bile ducts down to the level of the ampullary region, where a polypoid mass was found. Using a linear echoendoscope a mildly hyperechoic homogeneous lesion was found on the duodenal submucosa, adjacent to the ampulla, compressing the bile duct (Figure 2A). FNA with a 25-gauge EZ Shot needle (Olympus Medical Systems Corp., Tokyo, Japan) retrieved a cytology sample consistent with adenocarcinoma (Figure 2B, C). The patient was submitted to cephalic pancreatoduodenectomy which confirmed the diagnosis of ampullary carcinoma (Figure 2D-F).

Case 3: Hamartomatous duodenal polyp

A 62-year-old man was admitted for melena and upper GI endoscopy revealed an ulcerated semipedunculated polyp in the second portion of the duodenum (Figure 3A). EUS, performed using a radial echoendoscope, showed a homogeneous hyperechoic polypoid lesion originating from the submucosa (Figure 3B, C). Following polypectomy, histopathological examination unveiled fibroadipose tissue covered by intestinal mucosa, which was consistent with a hamartomatous polyp (Figure 3D).

Case 4: Gangliocytic paraganglioma

A 51-year-old woman was submitted to an upper GI endoscopy for dyspepsia. A 20 mm subepithelial lesion was found on the posterior wall of the second part of the duodenum. On linear EUS, this was shown to be a well-delimited slightly hyperechoic lesion apparently originating from the submucosa (Figure 4A). A tissue sample was obtained using a 22-gauge ProCore needle (Cook Endoscopy Inc, Limerick, Ireland) (Figure 4B-E). Cytopathological examination suggested a possible gastrointestinal stromal tumor (GIST) which led to the decision to perform endoscopic resection (Figure 4F). Further

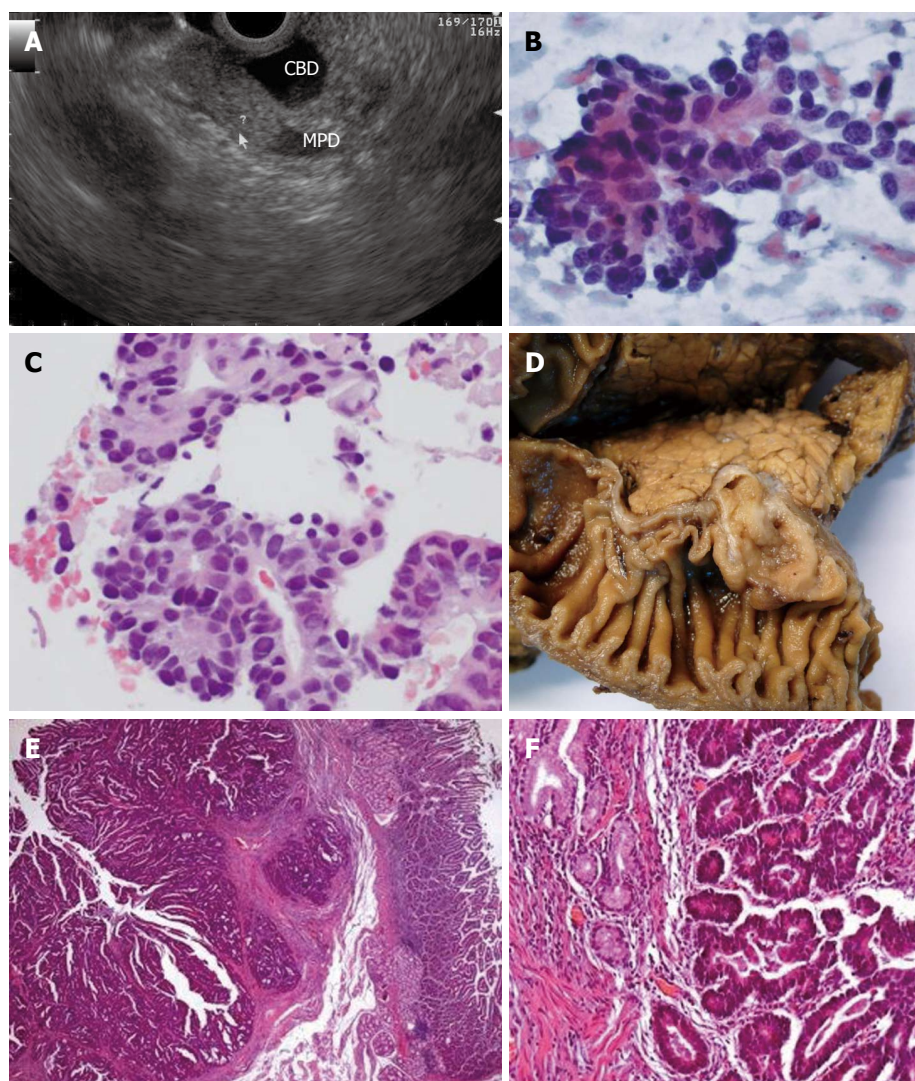


Figure 2 Endoscopic ultrasonography and pathological findings of an ampullary carcinoma. A: Mildly hyperechoic third-layer lesion adjacent to the ampulla, compressing the bile duct; B, C: Fine-needle aspiration, $\times 400$ magnification; B: Smears with acinar groups, irregularly distributed nuclei, coarse chromatin, conspicuous nucleoli (Papanicolaou); C: Cell-block preparation of aspirated sample [hematoxylin and eosin (HE)]; D: Surgical pathology specimen confirming the full excision of an ampullary carcinoma; E: Ampullary area well-differentiated adenocarcinoma, HE $\times 25$; F: HE $\times 100$.

histopathological analysis of the resected tumor brought about another diagnosis-gangliocytic paraganglioma (Figure 4G-I).

DISCUSSION

Although EUS does not provide gastroenterologists with a definitive diagnosis for subepithelial lesions, the ultrasonographic findings and knowledge of the epidemiology allow for an educated guess in many situations. This, along with the likelihood of malignancy, guides management decisions regarding biopsy and resection.

Both lipomas and Brunner's gland hamartomas are regarded as benign tumours, which are usually asymptomatic^[7,8]. Given their benign nature, treatment is only recommended if they become symptomatic^[9]. Moreover, in the absence of other differential diagnosis for hyperechoic lesions of the third layer of the GI tract, the ecoendoscopist might be tempted not to obtain a tissue sample or even not follow-up the patient.

In our case series, two subepithelial lesions presented with bleeding and a third one with jaundice. EUS favored the diagnosis of lipoma in all of these lesions and resection was required. In the first two cases, surgery was the preferred approach due to the tumors characteristics-size, ulceration and location. The surgical team required a histopathological evaluation to confirm the diagnosis and establish the therapeutic strategy, therefore EUS with FNA was performed. In the third case, the tumor was pedunculated and endoscopic resection was feasible, thus FNA was not required.

The fourth case was an incidental lesion. EUS features were felt suspicious for lipoma although the pattern was not typical. Based on these findings and our prior experience with the first three cases, a FNA was performed. The diagnosis was GIST, which is a fairly uncommon diagnosis in the third layer^[3]. Management options were discussed with the patient and the decision for resection was based on the tumor's size (2 cm), location (small bowel confers worse prognosis) as well as the

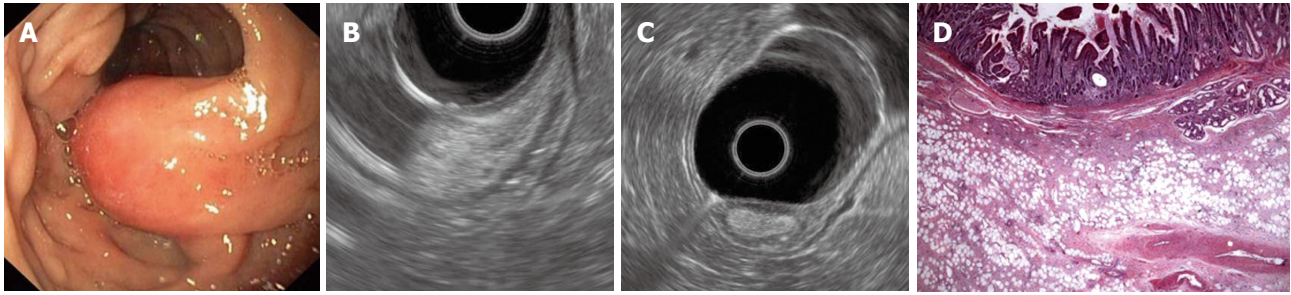


Figure 3 Endoscopic, endoscopic ultrasonography and pathological findings of hamartomatous polyp. A: Semipedunculated polyp in the second portion of the duodenum; B: Longitudinal view of the polyp's stalk-originating from the duodenal wall; C: Top of the polypoid lesion-cross-sectional view; D: Hamartomatous polyp, HE $\times 25$.

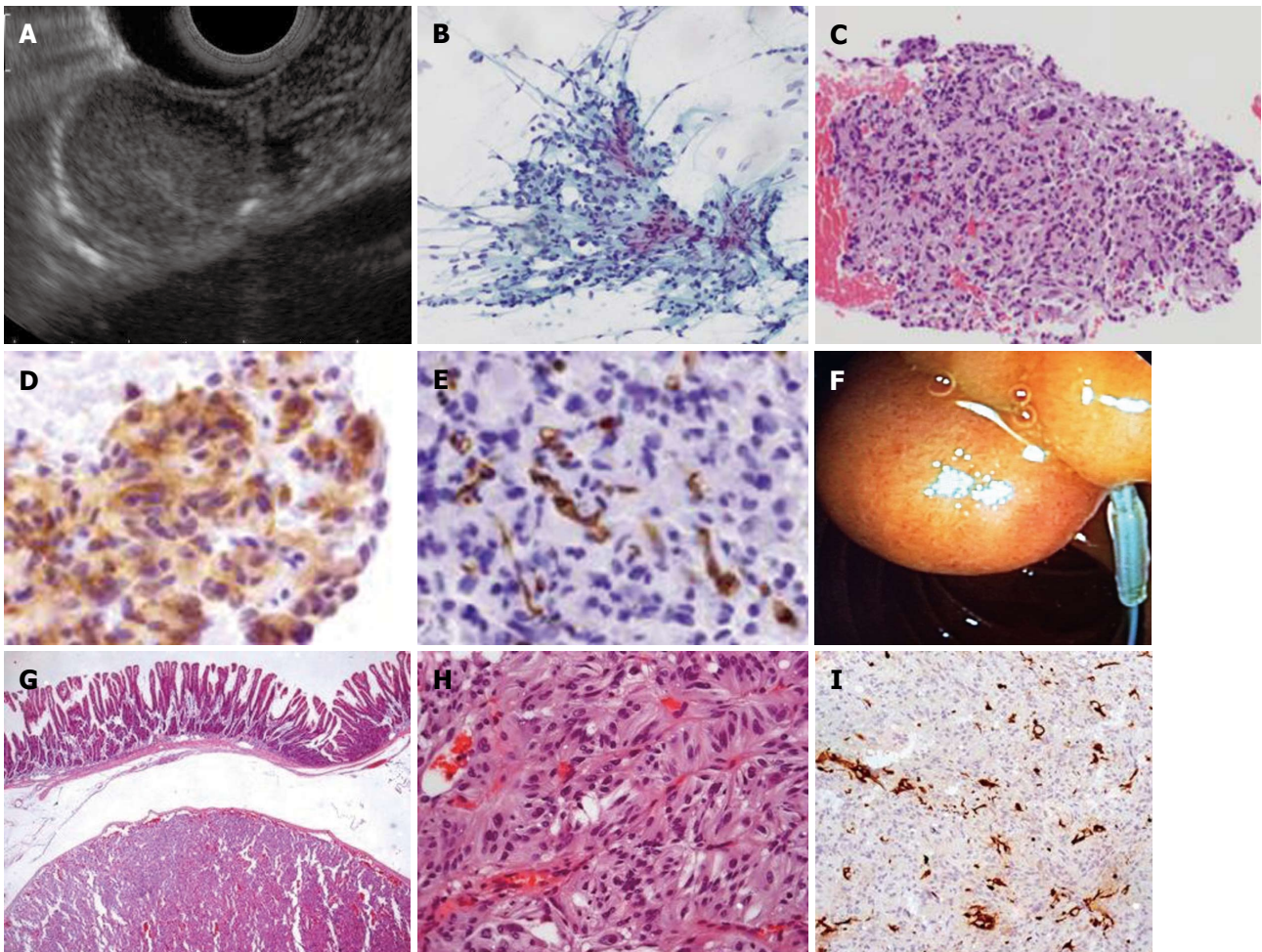


Figure 4 Endoscopic, endoscopic ultrasonography and pathological findings of gangliocytic paraganglioma. A: Slightly hyperechoic lesion of the third layer of the duodenal wall; B-E: Endoscopic ultrasonography-fine needle aspiration with cytological features suggestive of GIST; B: Few fragments of loose mesenchymal spindle cell tissue fragments (Papanicolaou staining $\times 100$); C: Cell block preparation of aspirated material, discrete nuclear atypia [Hematoxylin and eosin (HE) $\times 100$]; D: Most cells stain positive for CD117 ($\times 400$); E: Rare cells stained with CD34 ($\times 400$); F: Resection of the subepithelial lesion using endoloop; G-I: Histopathological analysis of the resected tumor; G: Duodenal gangliocytic paraganglioma (HE $\times 25$); H: Duodenal gangliocytic paraganglioma (HE $\times 200$); I: Sustentacular S-100 positive cells documented (S100 $\times 100$). GIST: Gastrointestinal stromal tumor.

patient's wish^[10]. The surgical specimen pathology report showed the lesion to be a gangliocytic paraganglioma—an exceedingly rare entity^[11]. Previous EUS reports described it as a hypoechoic or isoechoic homogeneous lesion, in the proximity of the duodenal papilla^[12,13]. Its characteristic triphasic microscopic appearance (epitheli-

oid cells, spindle cells, and ganglion cells) histological appearance might account for our inability to differentiate it from a GIST on FNA^[14].

In conclusion, this case series presents relevant and previously unreported differential diagnosis for duodenal hyperechoic subepithelial lesions in the third layer.

The EUS operator should always take time to assess the transition zone to assess the layer of origin and, in our opinion, have a low threshold to perform FNA, namely, if the EUS features are felt not typical.

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Contribution of endosonography in an uncommon case of pancreatic cysts

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Key words: Von Hippel-Lindau disease; Endosonography; Pancreatic cysts; Hereditary disease; Cysts

Core tip: This is a case of a rare clinical entity, Von Hippel-Lindau disease, with an unusual presentation. The patient had only pancreatic cysts without more common manifestations, particularly hemangioblastomas and malignancy. The imaging methods used in this case were important for the diagnosis, particularly endosonography, which showed the honeycomb appearance of the pancreatic serous cystadenomas. This case should alert endoscopists to the possible occurrence of this hereditary disease in the presence of multiple pancreatic cysts without other manifestations or family history.

Sousa AL, Sousa D, Figueiredo P, Marques PP, Guerreiro H. Contribution of endosonography in an uncommon case of pancreatic cysts. *World J Gastrointest Endosc* 2013; 5(10): 519-522 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i10/519.htm>
DOI: <http://dx.doi.org/10.4253/wjge.v5.i10.519>

Abstract

Here we present the case of a 35-year-old female patient with long standing dyspepsia and imaging studies showing the presence of multiple cysts in the head and tail of the pancreas. The patient underwent endosonography that confirmed the presence of multiple simple cysts throughout the entirety of the pancreas without dilation of the pancreatic duct. The majority of the cysts were less than one centimeter in size, and the largest cyst showed a honeycomb appearance. Cytology of aspirates from the two largest cysts was compatible with benign pancreatic cysts. Endosonography also revealed cysts within the left kidney and spleen. Genetic testing confirmed Von Hippel-Lindau disease. We highlight this case because it is unusual for Von Hippel-Lindau disease, a rare clinical entity, to present solely with cysts in the absence of more common manifestations, such as hemangioblastomas in the central nervous system and malignancy.

INTRODUCTION

Von Hippel-Lindau (VHL) disease is an autosomal dominant disorder caused by germline mutations in the VHL tumor suppressor gene. VHL mutations predispose patients to the development of a variety of tumors, which are most commonly retinal and central nervous system hemangioblastomas, clear cell renal carcinoma and pheochromocytomas^[1,2]. Hemangioblastomas are the most common tumors associated with VHL disease and affect 60% to 84% of patients^[3]. There are few studies assessing pancreatic lesions in VHL disease^[4-7]. Hammel *et al*^[4] found pancreatic involvement in 77.2% of patients with

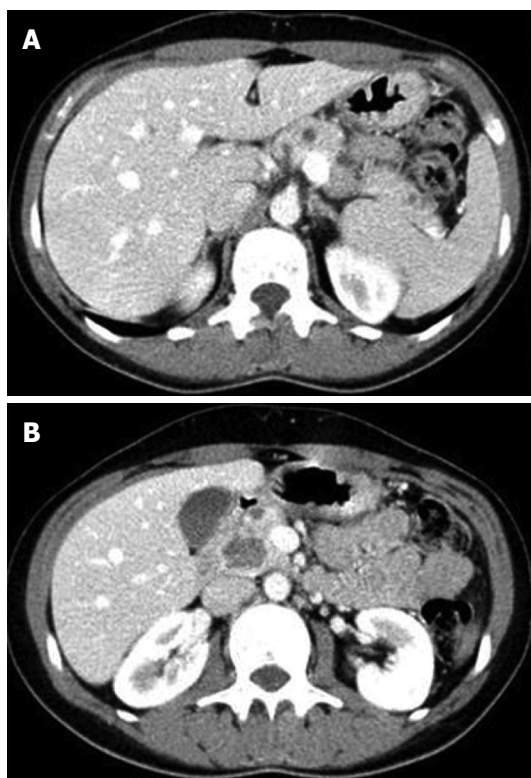


Figure 1 Computed tomography abdominal scan. A: Small cystic lesions dispersed throughout the pancreas; B: The largest lesion.

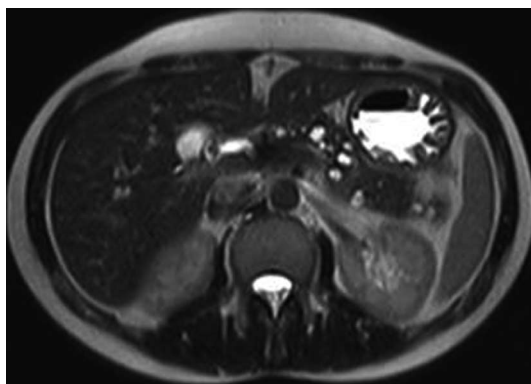


Figure 2 Magnetic resonance imaging. Cyst lesions are bright on T2-weighted images.

VHL, and these pancreatic lesions can manifest as cysts (91.1%), serous cystadenomas (12.3%), neuroendocrine tumors (12.3%) or combined lesions (11.5%). However, the frequency of the pancreas as the only organ affected is low (7.6%), and the majority do not require treatment^[4].

CASE REPORT

This case concerns a 35-year-old woman referred to our Gastroenterology Department with long-standing dyspepsia and pancreatic cysts detected by ultrasound examination. There were no other symptoms, such as abdominal pain, weight loss, visual or hearing changes,

headache or urinary complaints. The past medical and family histories were not of significance. There were no abnormal findings on examination.

The patient underwent an abdominal computed tomography (CT) scan (Figure 1), which showed an enlargement of the pancreas, especially in the cephalic region, with heterogeneous density due to the presence of multiple hypodense nodules dispersed throughout the parenchyma. The majority of these lesions were small, but one larger contrast-enhancing lesion of 22 mm was present in the uncinate process.

Given the findings of the CT scan, we performed an abdominal magnetic resonance imaging (MRI) (Figure 2), which revealed several cysts that had a high signal intensity on T2 weighted images.

The patient underwent endosonography that confirmed the presence of multiple simple cysts throughout the entirety of the pancreas. The majority of the cysts were less than 1 cm in diameter, but two cysts were larger than 1 cm. One of the larger cysts was 16 mm in diameter and was located at the isthmus-body transition. This cyst did not communicate with the main pancreatic duct and was aspirated. The content had a serous appearance, and cytological analysis revealed amorphous material, few erythrocytes and inflammatory cells (Figure 3).

The largest cyst was 23 mm in diameter and was located in the head of the pancreas. The cyst had a honey-comb appearance characteristic of serous cystadenomas (Figure 4A). The cytology did not show evidence of cellular atypia (Figure 4B). The carcinoembryonic antigen was < 0.6 ng/dL, and the amylase in the cystic content was 135 U/L.

The endosonography also showed cysts in the left kidney and in the spleen (Figure 5). The findings described were compatible with simple cysts and pancreatic serous cystadenomas and provided an indication for genetic testing for VHL. The sequencing of the VHL gene revealed one pathogenic heterozygous mutation in exon 1 (c.269A > T), confirming the diagnosis of VHL disease.

The patient underwent a MRI of the brain and entire spine and no hemangioblastomas were detected. The abdominal MRI scan excluded renal carcinoma. The plasma and urinary catecholamines and the urinary vanilmandelic acid were normal, excluding pheochromocytoma. The patient was also referred for examination of the retina and ear, nose and throat, including audiometry. There were no abnormal findings, which excluded angiomas of the retina and endolymphatic sac tumors, respectively.

Her family was genetically tested, and the same mutation was found in her 7 year-old daughter.

DISCUSSION

This case is important not only due of the rarity of VHL disease but also because the only manifestation in this patient was cysts diagnosed by imaging tests. This

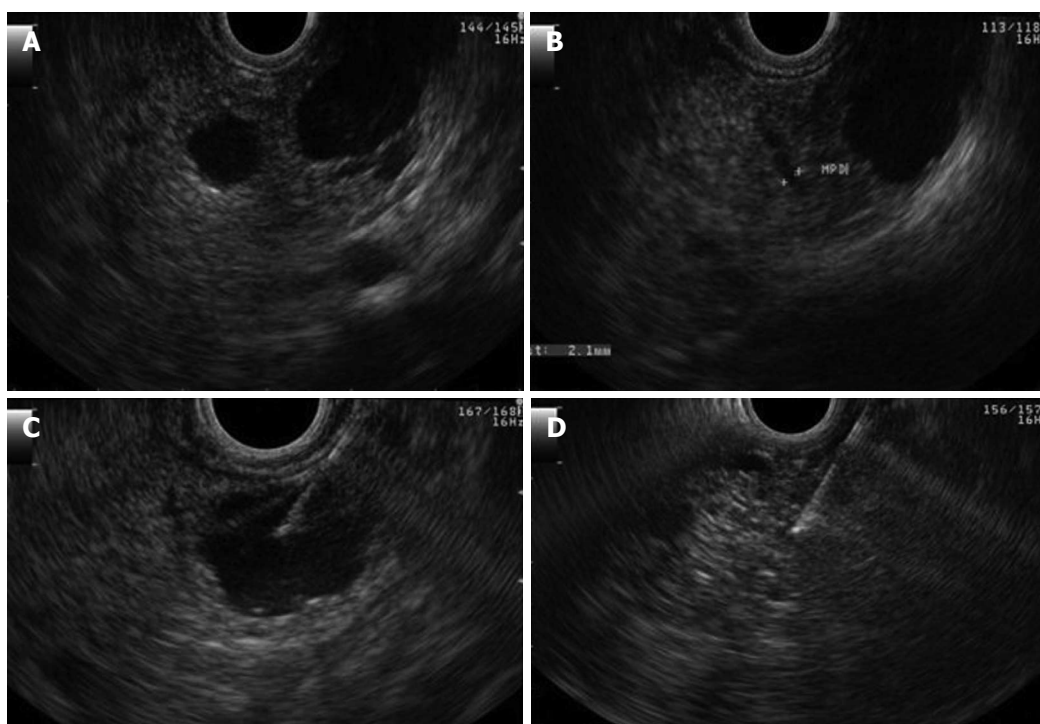


Figure 3 Endosonography. A, B show a large cyst of 16 mm in diameter without communication or dilatation of the pancreatic duct; C: Demonstrates aspiration of the cyst; D: Demonstrates its appearance after total aspiration.

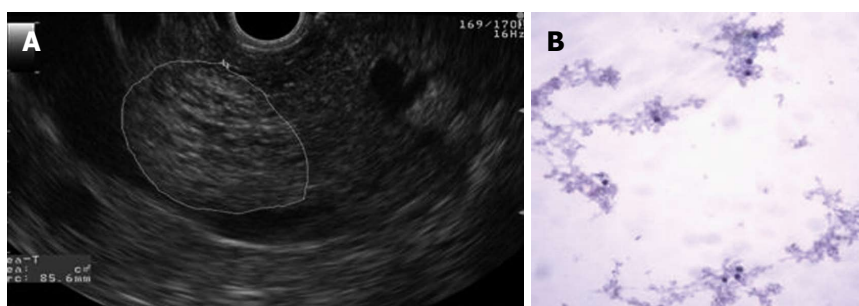


Figure 4 The largest cyst was 23 mm in diameter and was located in the head of the pancreas. A: Endosonography. Cyst with a honeycomb appearance; B: Cytology (papanicolaou stain, $\times 100$). Benign pancreatic cysts.

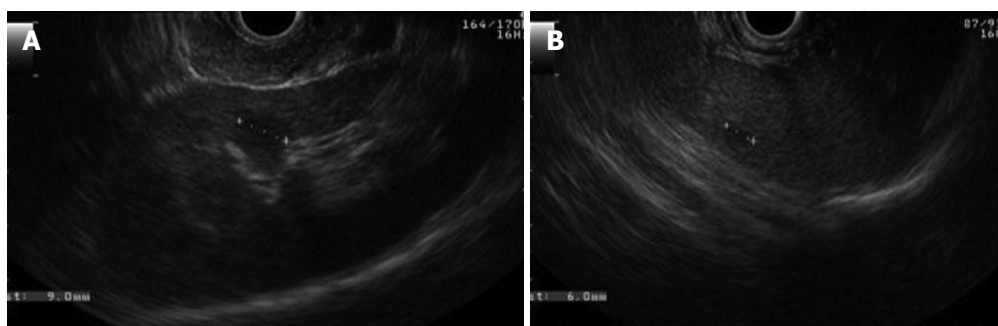


Figure 5 Endosonography. A: A cyst in the renal cortex; B: A cyst in the spleen.

finding emphasizes the importance of endosonography for better characterization of lesions, particularly in the absence of family history or more common manifestations.

According to criteria from Massachusetts General Hospital, if patients are found to have more than one pancreatic serous cystadenoma or have multiple pancreatic cysts and any VHL associated lesion (including

pancreatic serous cystadenoma), they should be referred to a VHL specialist clinic^[8]. Serous cystadenomas are rare pancreatic exocrine tumors that occur at an unusually high frequency in patients with VHL disease. They account for nearly 10% of pancreatic lesions^[4]. This percentage may actually be higher due to the difficulty in distinguishing this tumor from a cluster of multiple small true cysts, although the differentiation between the two does not modify the approach to management. Hammel *et al*^[4] found that VHL disease was discovered by chance in 6% of patients during abdominal imaging performed for unrelated reasons. Therefore, the possibility of VHL disease must be considered when pancreatic lesions are observed. Isolated pancreatic involvement can be a key factor in establishing the diagnosis of VHL when there is no family history or the concomitant existence of more conventional lesions, such as hemangioblastomas. Most of the pancreatic cysts in VHL are clinically indolent and generally do not require treatment^[4,5,7]. In our case, imaging studies, such as endosonography, revealed the characteristic appearance of pancreatic serous cystadenoma and was crucial for the diagnosis of VHL disease. This diagnosis has multiple implications, including requiring an adequate annual surveillance and the possibility of transmission of this disease to descendants. Pancreatic lesions can be the first manifestation in some VHL patients. The mean age of initial detection is 37 years and precedes hemangioblastomas in the central nervous system by 5-7 years. This result emphasizes the importance of surveillance with an annual MRI of the brain and spine^[7]. However, the series by Mukhopadhyay *et al*^[5] retrospectively evaluated the pancreatic lesions in 17 VHL disease patients and found the lesions were not the presenting feature in any patient. *De novo* mutations of VHL are estimated to occur in approximately 20% of

probands^[2], which most likely occurred in our case. Unfortunately, her daughter was born with the same mutation. With a diagnosis of VHL more than 7 years earlier, our patient could have been offered prenatal screening.

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Migration of a biliary stent causing duodenal perforation and biliary peritonitis

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the stent in each patient.

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INTRODUCTION

The use of biliary stents was introduced in the late 1970s, and since then endoscopic and percutaneous insertion of biliary stents is the treatment of choice as a palliative measure for patients suffering from obstructive jaundice secondary to unresectable malignant hepatobiliary tract tumors and to relieve obstruction of the bile ducts secondary to benign stricture or choledocholithiasis^[1,2].

Biliary stents however are not without complications. The complication rate ranges between 8% and 10%, with a mortality rate below 1%^[3-5]. Complications specific to the stents include migration, occlusion, and intestinal perforation. Migration of endoscopically placed biliary stents is a well-recognized complication of endoscopic retrograde cholangiopancreatography (ERCP). Serious complications can result from stent migration but fortunately less than 1% of migrated stents cause intestinal perforation. Of those that do perforate the bowel, the vast majority occur in the duodenum^[5-7]. There have been several case reports of intestinal perforation distal to the duodenum including the small intestines, cecum, right side of colon and sigmoid colon^[8-15]. Although the majority of migrated stents pass spontaneously or can be retrieved using endoscopy and fluoroscopy, few of them can cause biliary peritonitis necessitating an emergency laparotomy. This report describes an unusual case of biliary stent migration where part of the stent remained in the common bile duct and the rest perforated the

Abstract

Migration of endoscopically placed biliary stents is a well-recognized complication of endoscopic retrograde cholangiopancreatography. Less than 1% of migrated stents however cause intestinal perforation. We present a case of a migrated biliary stent that resulted in duodenal perforation and biliary peritonitis.

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Key words: Biliary stents; Migration; Duodenal perforation; Biliary peritonitis

Core tip: Biliary stent migration complicated by duodenal perforation is rare and should be included in the differential diagnosis of those presenting with abdominal pain after endoscopic retrograde cholangiopancreatography with stent placement and physicians caring for these patients should be aware of such complication. To reduce the chance of stent migration, endoscopists should assess for the size and shape of

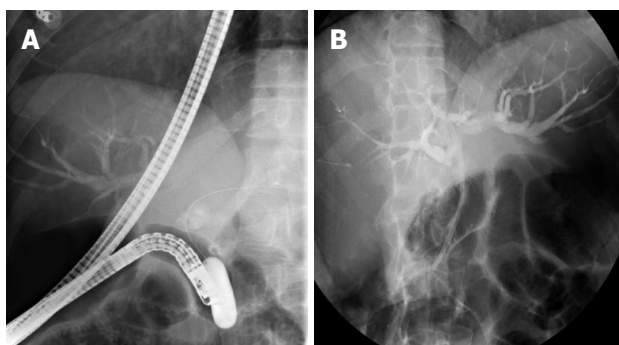


Figure 1 Endoscopic retrograde cholangiopancreatography which showed dilated common bile duct (A) and intra hepatic biliary radicles dilation (B) followed by insertion of 10 Fr \times 10 cm endobiliary plastic stent.

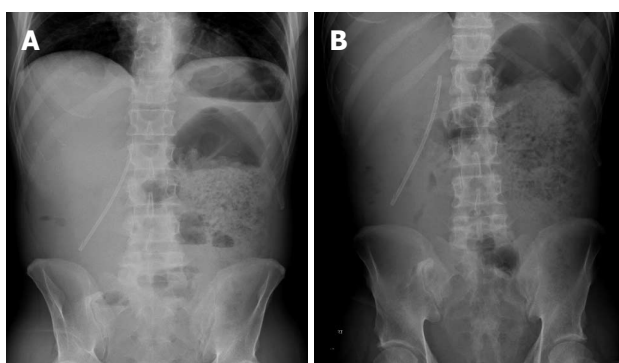


Figure 2 Abdominal X-rays showing an abnormal position of the biliary stent highly suspicious of distal migration with free air (A) and markedly dilated left side of colon and retained fecal material (B).

duodenum causing biliary peritonitis.

CASE REPORT

A 51-year-old male presented to the emergency department complaining of severe abdominal pain, constipation, vomiting and progressive jaundice over a period of 3 d. He underwent an abdominal ultrasound and computed tomography (CT) scan which showed distended gallbladder with no stones, dilated common bile duct up to 17.5 mm with a 9 mm stone in the distal common bile duct (CBD) and intra hepatic biliary radicles dilation. He underwent an ERCP in his primary hospital which failed due to an abnormal anatomy as reported. A second ERCP two weeks prior to his presentation was technically difficult, prolonged with a lot of manipulation and maneuvers to gain a biliary access. Sphincterotomy was done and there was a suspicious distal biliary stricture for which controlled radial expansion balloon dilation up to 15 mm was done followed by insertion of 10 French, 10 cm long endobiliary plastic stent (Figure 1). At the time of presentation to our hospital, he was ill looking, in pain, deeply jaundiced. His temperature was 37.3 °C, blood pressure 122/60 mmHg, and pulse 120 per minute. Abdominal examination showing distended abdomen with diffuse tenderness and rigidity, and sluggish bowel

sounds. Cellular blood count showed leucocytosis 21.56×10^9 /L, Hb 14 g/dL, Platelets 368×10^9 /L. Liver panel showed total bilirubin 74.65 μ mol/L, direct bilirubin 35 μ mol/L, alkaline phosphatase 269 U/L, γ -glutamyl transpeptidase 417 U/L, alanine aminotransaminase 50 U/L, aspartate aminotransferase 73 U/L. Abdominal X-ray showed an abnormal position of the biliary stent highly suspicious of distal migration with markedly dilated left colon segment (Figure 2). Urgent abdominal CT-scan was done which confirmed the inferior migration of the biliary stent causing perforation of the second part of duodenum, with protrusion of the stent into the peritoneal cavity causing biliary peritonitis (Figure 3). He was covered with antibiotics and underwent an urgent laparotomy which showed the stent penetrating the second part of duodenum and draining bile into the peritoneal cavity causing biliary peritonitis (Figure 4). The perforation was closed and the closure was reinforced using an omental patch. Postoperatively, he did well and was discharged on the 12th postoperative day.

DISCUSSION

In 1980 Soehendra *et al*^[16] introduced transpapillary biliary drainage using plastic biliary stent. Since then biliary stents are often used for the treatment of benign obstructive biliary disease. Biliary stents nevertheless causes serious complications and one of these is stent migration which occurs in up to 10% of patients^[2-4]. This is more so in those with benign pathology without severe stenosis of the bile duct or papilla. Malignant strictures, larger diameter stents, and short stents are known to be associated with proximal biliary stent migration. Stent related factors such as the type of stent, length and caliber of the stent offer potential avenues to minimize the risk of migration. The presence of previous abdominal surgeries is an important factor for endoscopists to ascertain the location of a migrated stent. Fortunately, most of these stents can be retrieved using endoscopy and if the stent migrates to the intestines, then 43% pass spontaneously^[4,5]. Arhan *et al*^[5] in a review of 204 plastic biliary stents for benign biliary disease reported a migration rate of 13.4% with an equal proportion of stents found in the proximal and distal gastrointestinal tract. All of the migrated stents were retrieved without complication. This however is not the case always and occasionally biliary stents impact and perforate the intestines, usually in the fixed parts namely the duodenum and right side of the colon or in other fixed areas of the intestines because of adhesions due to a previous operation. There are also reports of biliary stents causing bowel perforation through bowel loops incarcerated in a hernial sac, in duodenal diverticula, in a colon diverticulum and also in healthy sigmoid colon^[8-10,14,15].

Biliary stent migration is not unusual and may result in intramural or transmural intestinal perforation. The perforation can be retroperitoneal in duodenal perforation causing bilioma or the perforation can be intra-

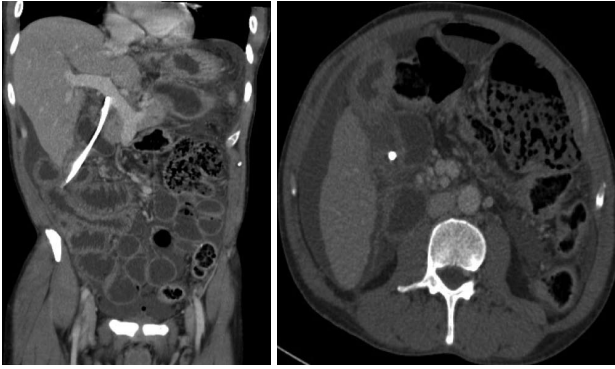


Figure 3 Computed tomography-scan of the abdomen which confirmed the inferior migration of the biliary stent causing perforation of the second part of duodenum, with protrusion of the stent into the peritoneal cavity causing biliary peritonitis.

peritoneal leading to biliary peritonitis^[13,17]. Our case is unique as the stent was found partly in the biliary duct and the rest perforated the duodenum causing bile leak with total bile diversion into the peritoneal cavity and biliary peritonitis. In these patients there are signs of peritonitis and radiological images will show the stent outside the intestinal wall. Ang *et al*^[18] described a case of duodenocolic fistula caused by a stent and Rosés *et al*^[17] described the case of a plastic stent perforating the duodenal wall causing a retroperitoneal duodenal perforation and bilioma. Figueiras *et al*^[19] reported a colocutaneous fistula secondary to the migration of a biliary stent.

The majority of migrating biliary stents pass spontaneously but whenever a perforation is suspected, operative extraction is the treatment of choice. There is a report stressing the successful endoscopic extraction of the migrating stent and clip placement in the duodenal perforation^[17]. This was however in a patient with a biliary stent causing a localized retroperitoneal duodenal perforation and bilioma. Others have reported the successful percutaneous extraction of migrating biliary stents^[20]. In our case, the perforation was in the peritoneal cavity and part of the stent was still in the biliary ducts causing biliary diversion into the peritoneal cavity and although percutaneous retrieval of the stent was possible, the fact that the patient was already having biliary peritonitis made operative extraction and closure of duodenal perforation the appropriate choice.

In conclusion, biliary stent migration complicated by duodenal perforation is rare and should be included in the differential diagnosis of those presenting with abdominal pain after ERCP with stent placement and physicians caring for these patients should be aware of such complication. Radiologically, it is possible to locate the site of stent migration and perforation and in the presence of peritonitis, surgery is the treatment of choice. To reduce the chance of stent migration, endoscopists should assess for the size and shape of the stent in each patient. A straight biliary stent may migrate since there is nothing to hold it in place, even though there are side flaps. Inappropriately long stent may exert pressure on



Figure 4 Intraoperative photograph showing the stent perforating the duodenum and protruding into the peritoneal cavity.

the duodenal wall causing tissue necrosis and perforation. Curved (Amsterdam) stent or a double pigtail biliary stent may be associated with less migration and perforation.

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Sedation-related complications in gastrointestinal endoscopy

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Abstract

Sedation practices for gastrointestinal endoscopic (GIE) procedures vary widely in different countries depending on health system regulations and local circumstances. The goal of procedural sedation is the safe and effective control of pain and anxiety, as well as to provide an appropriate degree of memory loss or decreased awareness. Sedation-related complications in gastrointestinal endoscopy, once occurred, can lead to significant morbidity and occasional mortality in patients. The risk factors of these complications include the type, dose and mode of administration of sedative agents, as well as the patient's age and underlying medical diseases. Complications attributed to moderate and deep sedation levels are more often associated with cardiovascular and respiratory systems. However, sedation-related complications during GIE procedures are commonly transient and of a mild degree. The risk for these complications while providing any level of sedation is greatest when caring for patients already medically compromised. Significant unwanted complications can generally be prevented by careful pre-procedure assessment and preparation, appropriate monitoring and support, as well as post-procedure management. Additionally, physicians must be prepared to manage these complications. This article will review sedation-related complications during

moderate and deep sedation for GIE procedures and also address their appropriate management.

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Key words: Sedation; Complication; Gastrointestinal; Endoscopy

Core tip: Gastrointestinal endoscopic (GIE) procedures are relatively safe. However, these procedures have been shown to cause various effects on cardiorespiratory systems. Sedation-related complications while providing any level of sedation can occur. Fortunately, these complications during GIE procedures are commonly transient and of a mild degree. In addition, significant unwanted complications can generally be prevented by careful pre-procedure assessment and preparation, appropriate monitoring and support. Periodical assessment of the level of sedation and continuous monitoring of cardiovascular and respiratory systems provides timely information. Standardized discharge criteria should be used to determine the patient's readiness for discharge.

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INTRODUCTION

Gastrointestinal endoscopic (GIE) procedures are relatively safe and now performed routinely because of their minimal invasiveness and diagnostic and therapeutic capabilities. These procedures have been shown to cause various effects on cardiorespiratory systems, which can increase the risks of the procedure in patients with underlying cardiorespiratory diseases^[1,2]. Additionally,

complications attributed to moderate and deep sedation levels are more often associated with cardiovascular and respiratory systems. Most predictors of sedation-related complications are patient-centered factors and do not vary significantly from procedure to procedure, although the procedure is complex^[3].

Providing sedation has been the most effective strategy employed, with most patients preferring the use of sedation during endoscopy. The use of sedative agents has been found to improve the performance of the endoscopy, enhancing the successful completion of the procedure. The incidence of sedation-related complications associated with a GIE procedure is relatively low. Risk factors for these complications are age > 60 years, high American Society of Anesthesiologists (ASA) physical status, inpatient status and the involvement of a trainee in the procedure^[4,5]. Sedation-related complications during GIE procedures are usually transient and of a mild degree. The risk of these complications while providing any level of sedation is greatest when caring for patients already medically compromised. Significant unwanted complications can generally be prevented by careful pre-sedation assessment and preparation, appropriate monitoring and support, as well as post-sedation management.

PRE-SEDATION ASSESSMENT

All patients scheduled to receive sedation should have an up-to-date history and relevant physical examination. Many risk factors to be aware of are a history of sleep apnea, alcohol or substance abuse, adverse reaction to sedative drugs, and prolonged duration of procedure. Patients should be classified using the criteria of the ASA^[6]. Cardiorespiratory problems which could occur during the GIE procedure should be carefully evaluated.

Before undertaking any GIE procedure, endoscopists should obtain informed consent from the patient, be familiar with the latest guidelines on sedation, be aware of any medical, surgical and drug history elicited in the pre-admission process, and risk factors should be identified in both out-patients and in-patients^[7,8]. Additionally, physicians must be prepared to manage sedation-related complications. Respiratory depression and oxygen desaturation from the sedative agents used to achieve sedation are thought to be important risk factors for these complications. So, safety and monitoring should be part of a quality assurance program for endoscopy units. This article will review sedation-related complications during GIE procedures and also address their appropriate management.

POST-SEDATION PERIOD

Most sedation-related complications occur during the GIE procedure. Standard monitoring, including non-invasive blood pressure, heart rate, pulse oximetry and ECG, is also routinely used in the post-sedation period. Post-procedural nausea/vomiting and pain need to be

resolved, especially in ambulatory patients. Fortunately, a lower incidence of procedural nausea/vomiting and pain after the GIE procedure is observed even in a therapeutic endoscopy^[9]. Opioid and cyclo-oxygenase-2-inhibitors can be safely and effectively used for procedural pain in GIE patients^[10].

Sedated patients are discharged from the recovery area when the discharge criteria are met. My previous study showed that periodic objective evaluation of home-readiness revealed that the majority of patients would achieve a satisfactory score on or before 1 h after the GIE procedure^[11]. So, patients that have undergone GIE procedures should be admitted to the recovery room unit for at least 30-60 min before discharge. The time to home-readiness by objective evaluation correlates with the type of procedure. Most delays after satisfactory home-readiness scores were reached were due to non-medical reasons.

Sedation-related cardiorespiratory complications also occur immediately after the GIE procedure. The types of complications in the post-sedation period are similar to the intra-sedation period. Patients who receive benzodiazepine and/or opioid antagonists should be closely observed in the recovery room unit longer than the other patients. If the patient received a reversal agent, the patient must be in a recovery room for at least 2 h after the last administration of that reversal agent.

REVERSAL DRUGS

Naloxone

Naloxone is a pure mu-opioid antagonist with a high affinity for the receptor. It can reverse both the analgesic and respiratory effects of opioids^[12]. Naloxone may be administered intravenously, intramuscularly, subcutaneously and *via* an endotracheal tube. The dosage of intravenous naloxone is 1 mcg/kg to 2 mcg/kg every 2-3 min with a maximum dose of 0.1 mg/kg, up to 2 mg. Because of its rapid removal from the brain, naloxone has a short duration of action and one dose typically only lasts for 30-45 min. The patient should be monitored for at least 2 h after administration of naloxone to ensure that re-sedation does not occur. Potential adverse reactions of naloxone include reversal of opioid withdrawal, nausea/vomiting, hypertension, tachycardia, pulmonary edema and cardiac dysrhythmias.

Flumazenil

Flumazenil is a benzodiazepine antagonist that can safely reverse the sedative and respiratory effects caused by benzodiazepines^[1]. It is a highly specific benzodiazepine receptor antagonist. The usual adult dose is 0.01 mg/kg, up to 1 mg. Its clinical duration of action is approximately 1 h^[12]. However, its effects are reversible, so it is not recommended for routine use. Similar to naloxone, patients should be monitored for at least 2 h after administration of flumazenil to ensure that re-sedation does not occur. Potential adverse reactions of flumazenil include sweating, flushing, nausea/vomiting, hiccups, agitation,

abnormal vision, paresthesia and seizures.

CARDIOVASCULAR-RELATED COMPLICATIONS

The autonomic nervous system plays an important role in maintaining normal hemodynamics and an adequate coronary blood flow. The sympathetic nervous system regulates the heart rate and rhythm and increases the excitability of the myocardium. The parasympathetic nervous system regulates the heart rate and rhythm, which when stimulated can lead to sinus bradycardia^[13]. Cardiorespiratory complications account for about 50% of potentially serious morbidity and about 50% of all procedure-related deaths associated with the GIE procedure. In many cases, these complications are a direct or indirect consequence of elderly or at risk patients being given unnecessarily high doses of sedative and analgesic drugs^[1].

Hypotension

A significant decline in blood pressure from baseline should alert clinicians. Hypotension is defined as systolic blood pressure less than 90 mmHg which is due to a fall in either cardiac output or total peripheral resistance, lowering the patient's mean arterial pressure^[14]. Episodes of hypotension in clinical practice are most commonly associated with vasovagal events and are generally transient. However, they may become prolonged in the presence of central nervous system depressants^[1]. Blood pressure is a reflection of cardiac output and total peripheral resistance and a fall in either or both will lower the patient's mean arterial pressure. In general, a systolic blood pressure of 90 mmHg should sustain mean arterial blood pressure sufficiently to perfuse tissues in the recumbent patient. Blood pressure lower than this, combined with evidence of inadequate perfusion, requires intervention.

The evaluation of tissue perfusion is the most significant component of cardiovascular assessment. Hypotension encountered during sedation is usually attributed to either vasovagal episodes or the use of sedative and anesthetic agents that depress sympathetic outflow to the cardiovascular system. Benzodiazepines, such as midazolam and diazepam, have a mild vasodilator effect and usually produce a slight fall in arterial blood pressure, even in normal sedative doses. The combination use of a benzodiazepine and an opioid can profoundly drop blood pressure. Propofol has been shown to be safe and effective for sedation during endoscopic retrograde cholangiopancreatography, endoscopic ultrasonography and small bowel enteroscopy because these procedures require more time and patient co-operation^[15-19].

Cardiovascular effects of propofol include decreases in cardiac output, systemic vascular resistance and arterial pressure. A fall in heart rate and/or cardiac stroke volume will also lower blood pressure. Additionally, more profound falls in blood pressure occur in a hypovolemic patient. Propofol has also been proven to reduce post-procedural hypoxemic events, which may be of signifi-

cance in critically ill elderly patients^[20,21] and sick pediatric patients^[22,23]. Prevention of this complication is to take a relevant medical and drug history before the procedure with particular detail required regarding current antihypertensives, antianginal and antiarrhythmic therapy and the use of systemic corticosteroids. The use of volume supplementation might be beneficial and could therefore be recommended in order to avoid propofol-induced hypotension. Additionally, blood pressure and heart rate should be recorded before, during and after the endoscopic procedure.

Hypertension

Blood pressure continuously fluctuates due to the cyclic nature of the pumping action of the heart. The highest pressure occurs during ventricular contraction. The lowest pressure occurs during ventricular relaxation^[24]. Generally, hypertension is defined as the systolic blood pressure greater than 160 mmHg. Sudden elevations of systolic blood pressure ≥ 180 mmHg or diastolic blood pressure ≥ 110 mmHg are generally regarded as an acute hypertensive episode^[25]. The causes of hypertension are background systemic hypertension, anxiety or pain, and a reflex pressure response from intubation of the esophagus. Generally, asymptomatic patients and patients without acute end-organ symptoms should not receive antihypertensive agents in the endoscopy unit.

Cardiac arrhythmias

Autonomic control of the heart rate will respond to demands placed on the patient and may be initiated *via* several baroreceptor-mediated reflexes^[20]. Electrocardiogram (ECG) is also a useful monitor for heart rate and a better assessment of heart rhythm. Continuous ECG monitoring is recommended for a high risk patient with relevant cardiac history. Cardiac arrhythmias are frequently observed during GIE procedures. Fortunately, most of them are not clinically significant.

In healthy patients, a heart rate of up to 120 beats/min will usually allow adequate filling. Sinus tachycardia can be caused by a patient's anxiety or be related to pain, a compensatory mechanism in patients who are hypotensive as a result of either dehydration or blood loss, and following intravenous anticholinergic drugs such as buscopan. Heart rate < 50 beats/min in healthy patients may allow for more time in diastole, but ventricular filling becomes maximized^[24]. Sinus bradycardia is most frequently seen in patients who are taking beta blockers. It can also be induced by vagal stimulation, which occurs at the time of intubation of the esophagus or the stretching of the sigmoid mesentery during colonoscopy or flexible sigmoidoscopy.

Myocardial ischemia/infarction

Myocardial infarction occurs either during or in the few days after endoscopic procedures with or without sedation. A proportion of these are undoubtedly causally related to the endoscopic procedure. The causes of angina

or myocardial infarction are two factors: increased myocardial oxygen demand and reduced myocardial perfusion^[26].

Increased myocardial oxygen demand is due to an increase in the mean arterial blood pressure and heart rate. This can cause angina in patients with ischemic heart disease or occult symptomless myocardial ischemia. Additionally, marked hypertension and/or tachycardia increase myocardial oxygen consumption. On the other hand, hypotension and/or bradycardia reduce myocardial perfusion. Stress-induced myocardial ischemia can occur even in patients with or without clinically significant coronary disease^[27]. This myocardial ischemia is related to the activation of the sympathetic nervous system, resulting in hemodynamic changes causing an increase in cardiac demand.

Prevention or minimization of myocardial ischemia/infarction during GIE procedure: (1) pre-oxygenation in at risk patients and give continuous supplemental oxygen; (2) give patients their normal anti-hypertensive and/or antianginal therapy right up to the time of the endoscopy; (3) angina developing during an endoscopy is usually best managed by giving sublingual nitroglycerine, oxygen supplementation and discontinuing the examination; and (4) if angina or myocardial infarction is suspected during or following an endoscopy, arrange an ECG to exclude an myocardial infarction.

RESPIRATORY-RELATED COMPLICATIONS

Airway management is the most important aspects of patient care and examination of the patient's airway is an essential component of the preoperative assessment. Mallampati score correlates with increased difficulty in airway management. High oxygen concentration is indicated for patients who are spontaneously breathing, regardless of their level of consciousness during medical urgencies and emergencies. The equipment required to provide supplemental oxygen includes a 100% oxygen source, a regulator, tubing and either a nasal cannula or mask. Every office should be equipped with a portable E-cylinder of oxygen.

Respiratory depression

A higher dose of benzodiazepine and/or opioid and the greater the percentage benzodiazepine and/or opioid receptor occupancy in the central nervous system, the greater is the degree of depression of consciousness. Intravenous benzodiazepines such as midazolam and diazepam can cause respiratory depression. Intravenous opioids, such as meperidine and fentanyl, occupy opioid receptor sites within the brain and brainstem and can similarly cause respiratory depression^[26]. Drug induced hypoventilation may cause both hypoxemia and carbon dioxide retention.

Pulse oximetry is a very useful indicator of oxygenation but not ventilation. However, when supplemental

oxygen is used, the fall in SpO₂ may be significantly delayed for between 30-90 s, so continuous capnography monitoring is recommended in patients being deeply sedated with propofol^[1]. As for over-sedation, loss of verbal contact due to a reduced conscious level may be the first sign of impending respiratory depression. Reduction in SpO₂ on pulse oximetry is a good indicator but it can be a late sign of respiratory depression. Increased PaCO₂ is the most sensitive early warning of respiratory depression^[28]. However, several controlled randomized studies showed a beneficial effect of capnography regarding some surrogate parameters of patients, such as the occurrence of hypoxemia detected by pulse oximetry, but a clear effect on patient outcome has not been demonstrated. Therefore, most national guidelines do not recommend its routine use currently.

Management of over-sedation is to stimulate the patient, both verbally and/or by light shaking, to wake up and take deep breaths. If the patient is not responding, then a benzodiazepine antagonist such as flumazenil and/or opioid antagonist such as naloxone may be required. The airway may need to be protected with chin lift, jaw thrust and, if necessary, airway or laryngeal mask^[26].

Airway obstruction

Obstruction may result in hypoventilation and hypoxia. However, airway obstruction must be distinguished from respiratory depression. Hypoxia is common in patients undergoing an upper GIE procedure with or without sedation. Sedation significantly increases the incidence of desaturation and hypoxia. Supplementary nasal oxygen at 3 L/min in sedated patients abolishes desaturation and hypoxia. Upper airway obstruction may be attributed to anatomical structures or a foreign body^[29]. Independent predictors of airway modifications include male sex, ASA class of III or higher, and increased body mass index^[1].

Laryngospasm is a reflex closure or spasm of the glottic muscles, including the false and true vocal cords. It is more likely to occur during deep sedation. Laryngospasm occurs more frequently in adults who are smokers. Bronchospasm is a lower airway obstruction due to contraction or spasm of the bronchial smooth muscle. It may be a result of an anaphylactoid reaction or a consequence of a hyper-reactive airway in asthmatic patients^[30]. Management of laryngospasm and bronchospasm depends on the severity and the cause.

Hypoxia

Hypoxia may be a consequence of respiratory depression or airway obstruction. The incidence of hypoxia is 1.5% to 70%, which makes it the most common cardiorespiratory complication during endoscopy^[31]. Hypoxemia can lead to several complications, depending on the severity of hypoxemic attack. The use of supplemental oxygen during a GIE procedure is routinely used by many endoscopists. However, oxygen supplementation will delay the detection of apnea and hypoxia^[5]. Additionally, in patients given supplemental oxygen, saturation may be maintained

in the progression of hypercapnia.

Multivariable logistic regressions revealed that independent risk factors for hypoxemia include high body mass index, hypertension, diabetes, gastrointestinal diseases, heart diseases and procedures that combined esophagogastroduodenoscopy (EGD) and colonoscopy^[32]. Hypoxemia occurs typically within 5 min of medication administration or endoscope intubation and only one third of all apnea and abnormal ventilation events eventually lead to hypoxemia^[31].

Pulmonary aspiration

Aspiration of gastric contents into the lungs during a GIE procedure is relatively common. It may cause pneumonia and may result in death. Risk factors for aspiration are the elderly, over-sedated patients, patients with gastrointestinal bleeding, gastric stasis, gastric outlet obstruction, hepatic encephalopathy and a full stomach. Aspiration can also occur when a local anesthetic spray is used in combination with intravenous sedation^[26].

Aspiration may be suspected when a patient starts coughing violently either during or soon after an endoscopic procedure and cyanosis may occur. The higher incidence of pulmonary aspiration is because of the better sensitivity of 2-[¹⁸F] fluoro-2-deoxy-D-glucose positron tomography. However, the low incidence of clinical events needing intervention may still reflect the safety of sedation used for the GIE procedure^[33]. Treatments of pulmonary aspiration includes suction of fluids from oral cavity and throat, increasing the rate of supplemental oxygen, encouraging the patient to cough, chest film, antibiotics and physiotherapy.

ALLERGIC REACTIONS

Pre-sedation assessment includes a comprehensive evaluation of the patient's allergic history. Generally, it is important not to confuse an increased sensitivity or side effect of a drug. Although rare, severe allergic reactions can occur during anesthesia or sedation. The spectrum of allergic reactions can include a minor local reaction to more severe anaphylactic reactions. The diagnosis of anaphylactic reaction is not always easy to establish.

The potential risk of propofol administration in patients with a known allergy against soy beans and egg should be stated^[34]. In addition, propofol usually produces a burning sensation at the injection site. Some opioids such as meperidine can cause a transient red wheal which is caused by local release of histamine. However, this reaction is a transient phenomenon with no sequelae. Anaphylactic reactions can present with mild dyspnea in mild cases or lead to hypotension and shock in severe cases. When a life threatening anaphylactic reaction does occur, it simulates an acute cardiac, respiratory and metabolic crisis and requires urgent acute critical care. Treatment for anaphylactic reactions includes the discontinuation of the suspected allergen, airway management, fluid resuscitation, anti-histamine drugs, hydrocortisone and epinephrine.

OTHER COMPLICATIONS

Nausea and vomiting

Nausea and vomiting are common side effects of opioids. Additionally, the over distension of the stomach or colonic loop can produce nausea and vomiting after the endoscopic procedure. The prevention of this complication is to reassure the patient and to minimize the opioid dose. In severe cases, anti-emetic agents such as metoclopramide and ondansetron may be required^[35].

Paradoxical reactions

Paradoxical reactions are characterized by combativeness, agitation, talkativeness, disorientation and tachycardia. This reaction frequently occurs with benzodiazepines, in particular midazolam and diazepam, and is more common in children^[36]. Inadequate sedation or cerebral hypoxia may mimic paradoxical reactions. Early recognition of paradoxical reactions is imperative for proper management. The administration of a benzodiazepine antagonist such as flumazenil has been shown to be effective in managing paradoxical reactions with minimal side effects.

PREVENTION OF SEDATION-RELATED COMPLICATIONS

Generally, GIE procedures can be performed by using topical anesthesia, intravenous sedation and general anesthesia^[17,37,38]. Topical anesthesia and intravenous sedation techniques can be effectively done by non-anesthetic personnel. Most national guidelines and several studies from the literature demonstrate that non-anesthetic personnel can safely perform propofol sedation^[39-41]. However, non-anesthetic personnel should sedate patients only to mild and moderate (conscious) sedation levels^[42]. Several previous studies demonstrated the feasibility and safety of computer-assisted personalized sedation (CAPS) to facilitate propofol sedation by non-anesthetic personnel in patients who underwent EGD and colonoscopy procedures^[43-45]. The SEDASYS System is the first CAPS system designed for physicians to provide minimal to moderate sedation levels with propofol. The system continuously monitors and records patient parameters, including oxygen saturation, blood pressure, heart rate, respiratory rate, end tidal carbon dioxide and patient responsiveness.

The risk of GIE procedures can be associated with sedation. The depth of sedation level is one of the risk factors of sedation-related complications. High sedation depth can significantly create sedation-related complications greater than a low sedation depth. Patients with mild hypotension, with co-morbidities and the elderly should be carefully sedated. The titration technique should be used to sedate these patients. Additionally, physicians should continuously monitor the depth of sedation^[46,47].

Prevention of complications in the first place is the best form of management. It is also the professional responsibility of health providers to prevent the avoidable

risks by following national standards for safe sedation. Patients under sedation must have physiological monitoring, including heart rate, blood pressure, oxygen saturation and an expired concentration of carbon dioxide. An anesthesiologist consultation should be done in patients with moderate to severe hypotension (systolic blood pressure < 90 mmHg), patients with severe cardiac and/or respiratory abnormalities, patients with a history of failed sedation, alcoholic or drug addicted patients, phobic or uncooperative patients, such as children, dementia and psychiatric patients, patients being sedated with intravenous propofol, and patients with a high risk of aspiration and requiring endotracheal tube with general anesthesia, including patients with depressed levels of consciousness and patients associated with encephalopathy^[48,49].

CONCLUSION

Sedation-related complications are relatively common. However, the majority of these complications are transient and easily treated. Serious complications are rare for GIE procedural sedation. Sedation-related complications may be severe if physicians do not detect and treat patients earlier. Appropriate pre-sedation assessment and proper patient selection, preparation and optimization of patients, as well as the availability of skilled professionals for sedation administration are key components to provision of quality patient care. Periodical assessment of the level of sedation and continuous monitoring of cardiovascular and respiratory systems provides timely information. Pulse oximetry and oxygen supplementation are recommended for the reduction of hypoxemia. Capnography monitoring is considered in patients undergoing prolonged endoscopic procedures who are at risk of deep sedation. Additionally, standardized discharge criteria should be used to determine the patient's readiness for discharge. Lastly, physicians should remember that the risk for an unintended deeper level of sedation may be more common after the stimulation of the endoscopic procedure has been removed.

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Recent advances in photoacoustic endoscopy

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technical details of the ultrasonic transducer incorporated into the photoacoustic endoscopic probe.

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Key words: Photoacoustic techniques; Tomography; Endoscopy; Endosonography; Gastrointestinal neoplasm

Core tip: Photoacoustic imaging is an emerging modality, and provides image information of optical contrast or functional properties by detecting ultrasonic waves. The major advantage of photoacoustic imaging is the greater penetration depth, of millimeters to centimeters, in tissue. The aim of this article is to introduce the technological improvements in photoacoustic endoscopy (PAE) for possible clinical application in endoscopic gastrointestinal imaging. In addition, the technical details of an integrated PAE and endoscopic ultrasound imaging system are discussed.

Abstract

Imaging based on photoacoustic effect relies on illuminating with short light pulses absorbed by tissue absorbers, resulting in thermoelastic expansion, giving rise to ultrasonic waves. The ultrasonic waves are then detected by detectors placed around the sample. Photoacoustic endoscopy (PAE) is one of four major implementations of photoacoustic tomography that have been developed recently. The prototype PAE was based on scanning mirror system that deflected both the light and the ultrasound. A recently developed mini-probe was further miniaturized, and enabled simultaneous photoacoustic and ultrasound imaging. This PAE-endoscopic ultrasound (EUS) system can offer high-resolution vasculature information in the gastrointestinal (GI) tract and display differences between optical and mechanical contrast compared with single-mode EUS. However, PAE for endoscopic GI imaging is still at the preclinical stage. In this commentary, we describe the technological improvements in PAE for possible clinical application in endoscopic GI imaging. In addition, we discuss the

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COMMENTARY ON HOT TOPICS

Photoacoustics is described as laser induced ultrasound^[1]. Imaging based on photoacoustics uses short light pulses (nanosecond range) as the source. As pulsed light is absorbed by tissue absorbers, such as hemoglobin or melanin, a transient temperature increase is generated, resulting in local thermoelastic expansion, giving rise to ultrasonic waves^[2]. These ultrasonic waves are then detected by ultrasonic detectors placed around the sample (Figure 1). An important advantage of photoacoustic imaging is that the method can overcome the high degree of scattering of optical photons in biological tissue, resulting in high spatial resolution deep within tis-

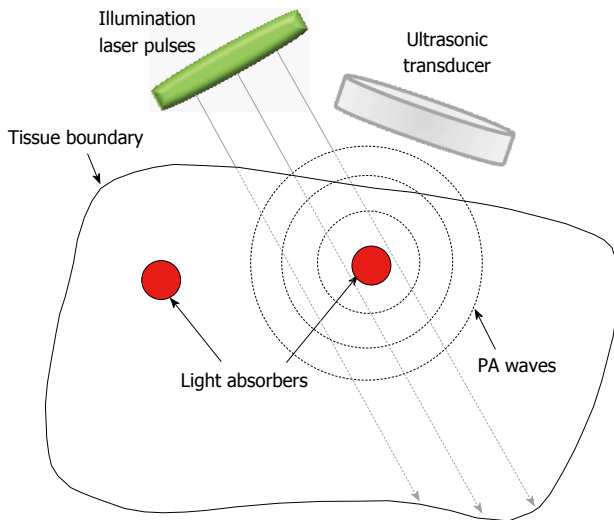


Figure 1 Illustration of the photoacoustic effect and photoacoustic imaging. Reproduced with permission from Yao *et al.*^[6]. PA: Photoacoustic.

sue^[3]. Although photoacoustic spectroscopy and simple imaging was developed in the 1970s, only recently has photoacoustic imaging become important in biomedical research^[4]. A major photoacoustic imaging for biomedical applications is photoacoustic tomography (PAT). PAT is similar to conventional ultrasound imaging, because image information is provided by capturing the ultrasonic waves using mechanical scanning or by detection arrays^[2]. However, while conventional ultrasound imaging measures only mechanical contrasts, PAT detects optical and thermoelastic contrasts^[5]. Currently, PAT has four major implementations: raster-scan based photoacoustic microscopy (PAM), inverse-reconstruction based photoacoustic computed tomography (PACT), rotation-scan based photoacoustic endoscopy (PAE), and hybrid PAT systems with other imaging methods (Figure 2)^[6].

Recently, Yang *et al.*^[7] showed photoacoustic images of the rat gastrointestinal tract *ex vivo* using a novel photoacoustic endoscope with a miniaturized imaging probe, which integrated a light-guiding optical fiber, ultrasonic sensor, and mechanical scanning unit for circumferential sector scanning. More recently, the same group^[8] developed an integrated PAE and endoscopic ultrasound (EUS) imaging system for simultaneous photoacoustic and ultrasonic imaging of internal organs *in vivo*. In this commentary, we describe the technological improvements in PAE for possible clinical application in endoscopic gastrointestinal (GI) imaging. We also discuss the technical details of the ultrasonic transducer incorporated into the photoacoustic endoscopic probe.

PAT

PAT is cross-sectional or three-dimensional imaging using photoacoustic effect, an emerging optical imaging modality that can offer volumetric images of biological tissues *in vivo* with high spatial resolution and deep tissue optical contrast^[5]. PAT is similar to ultrasound imaging in that both use detected ultrasonic waves to produce

images^[8]. However, PAT uses optical absorption-based contrast of tissue. PAT can provide high spatial resolution because ultrasonic scattering coefficients in tissue are two to three orders of magnitude less than optical scattering coefficients^[5]. Additionally, unlike ultrasonography or optical coherence tomography, PAT produces speckle-free images. As mentioned above, “PAT” includes PAM, PAE, PACT (Table 1). While PAM and PAE can image millimeters deep at microscopic resolution, PACT is available for microscopic and macroscopic imaging. In addition, PAT has been integrated into other imaging modalities, including ultrasound imaging^[9], optical coherence tomography (OCT)^[10], confocal microscopy^[11], two-photon microscopy^[6], and magnetic resonance imaging^[12].

Single-wavelength photoacoustic measurements of hemoglobin, a prominent light absorber in tissue, can provide images of blood vessels without exogenous contrasts. Deeper-seated vascular structures can be detected using a red or near infrared wavelength shift^[2]. In addition, the technique can evaluate oxygen saturation inside blood vessels because oxyhemoglobin and deoxyhemoglobin have significantly different optical absorption spectra^[13]. Other endogenous optical absorbers, such as melanin and other tissue chromophores, can contribute to photoacoustic signals. Sound reflectors such as calcification are useful in images of some tumors, including leiomyomas, leiomyosarcomas, or mucinous adenocarcinomas^[2].

Multispectral optoacoustic tomography (MSOT) with multiple illumination wavelengths can help differentiate extrinsic contrast agents (such as common fluorochromes, or photoabsorbing nanoparticles) from intrinsic contrasts (such as hemoglobin or melanin) by their unique spectral signatures^[14]. This imaging modality can offer differentiation of physiological conditions with the combination of each image of different absorbers^[2]. Using this method, Oh *et al.*^[15] reported three-dimensional images of subcutaneous melanomas and their surrounding vasculature in nude mice by dual-wavelength reflection-mode PAM, in which melanin distribution was imaged with a near-infrared light source and vascular system surrounding the melanoma with visible light. Extrinsically administered contrast agents for MSOT should have a sufficiently high optical absorption to be detected in tissues^[3]. Such agents include near-infrared cyanine dyes, such as indocyanine green^[16], reporter gene products^[17], and light-absorbing nanoparticles, such as gold nanoparticles^[18] and carbon nanotubes^[19]. Several nanoparticles produce significantly stronger photoacoustic signals than organic dyes^[2]. However, they also have limitations, including their larger size and safety concerns. MSOT can also detect activatable contrast agents, such as “smart probes” or molecular beacons, that are dark in their base state but produce fluorescence after target interaction^[20]. MSOT can provide functional, genetic, and molecular imaging using these extrinsic contrast agents^[5].

In recent years, PAT has been used in a number of preclinical applications, including imaging of angiogenesis, the microcirculation, drug responses, brain func-

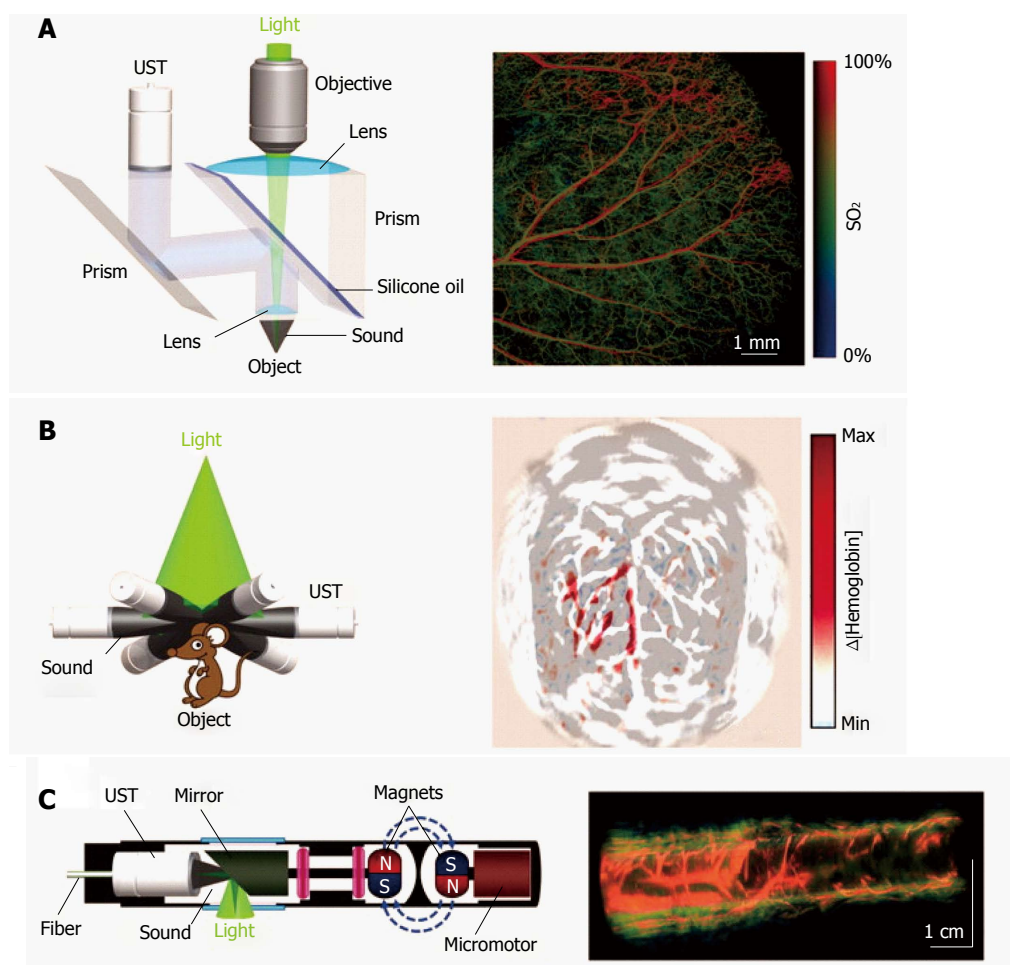


Figure 2 Three major implementations of photoacoustic tomography, with representative *in vivo* images. A: Optical-resolution photoacoustic microscopy and an image of hemoglobin oxygen saturation (SO_2) in a mouse ear; B: Circular-array photoacoustic computed tomography and an image of cerebral hemodynamic changes, $\Delta[\text{hemoglobin}]$, in response to one-sided whisker stimulation in a rat; C: Photoacoustic endoscopy and an image of a rabbit esophagus and adjacent internal organs, including the trachea and lung. Reproduced with permission from Wang *et al.*^[6]. SO_2 : Oxygen saturation; UST: Ultrasonic transducer.

tion, tumor microenvironments, biomarkers, and gene expression^[5]. PAT is also in the early stages of clinical application including breast cancer diagnosis^[21], melanoma imaging^[22], prostate cancer treatment^[23], and non-invasive sentinel lymph node imaging^[24]. Further developments in photoacoustic imaging techniques may provide better diagnosis of diseases and patient-management strategies.

PAE

Conventional white light endoscopic imaging of GI tract allows direct visualization of morphological changes and lesions, and subsequent histological analysis of tissue is the gold standard for final diagnosis. However, this method is limited by human vision and the lack of sensitivity to subsurface activity^[2]. Recent advances in optics and digital imaging techniques have been introduced in GI endoscopy. Several methods, including narrow-band imaging, autofluorescence imaging, confocal endomicroscopy, OCT, and two-photon microscopy, have been developed and are under investigation. Some of these methods have been used in clinical practice; however, their diagnostic accuracy and efficacy need to be confirmed in large-scale clinical trials. Additionally, these imaging methods cannot

achieve greater penetration depth^[25]. EUS-based imaging can penetrate for several millimeters to centimeters in tissue. However, its limitations include poor contrast and difficult interpretation of data^[2]. In addition, the mechanical contrast in EUS images often does not provide the required sensitivity and specificity^[26].

PAE may be useful as a new, minimally invasive diagnostic imaging tool because it provides functional optical contrast with high spatial resolution and maintains the benefits of traditional ultrasound endoscopy^[7]. Although the penetration depth of PAT can provide images that are centimeters deep, internal organs, such as the gastrointestinal tract and cardiovascular system, are not reachable^[6]. The photoacoustic probe must be positioned close to the area of interest by means of endoscopy in hollow organs^[7]. Viator *et al.*^[1] first developed a photoacoustic endoscopic probe for 1D sensing. Sethuraman *et al.*^[27] demonstrated photoacoustic images of rabbit blood vessels *ex vivo* using a high-frequency intravascular ultrasound imaging catheter. However, the system was not truly endoscopic because it used external illumination.

PAE has been investigated intensively as a tool of GI tract imaging. A prototype PAE system with a miniatur-

Table 1 Overview of currently available photoacoustic imaging technologies

Technology	Full name	Brief physics	Current applications	Future applications	Additional value to standard endoscopy
PAT	Photoacoustic tomography	Optical excitation of light absorbers in tissues by a pulsed laser and ultrasonic detection using mechanical scanning or detector arrays	Three major implementations include PAM, PACT, PAE	Functional information with the aid of an exogenous contrast	-
MSOT	Multispectral optoacoustic tomography	Utilization of multiple illumination wavelengths, spectral separation of optical reporter of interest from background absorption	Functional imaging of blood vessels, melanoma imaging of primary tumors and metastasis, characterization of atherosclerotic plaques, <i>etc.</i>	Tissue anatomy, function, molecular biomarkers, and gene expression	-
PAM	Photoacoustic microscopy	Based on a scanning focused ultrasonic transducer	Anatomical images of cutaneous microvasculature	Noninvasive imaging of individual cell nuclei	-
PACT	Photoacoustic computed tomography	Based on an array of unfocused ultrasonic transducers, use of an inverse algorithm to reconstruct a tomographic image	Tumor boundaries and connections with surrounding blood and lymphatic vessels	Same as PAT	-
PAE	Photoacoustic endoscopy	Probe that combines light delivery, acoustic sensing, and mechanical scanning in one small unit placed at the distal end of the endoscope	Gastrointestinal tract imaging	Improve the accuracy of cancer staging	Optical absorption-based contrast with high spatial resolution at depths
PAE-EUS	Photoacoustic endoscopy and Endoscopic ultrasound	Integrated system for ultrasonic images produced with conventional pulse-echo imaging and photoacoustic images formed through detection of acoustic waves	Gastrointestinal tract and lymphovascular imaging	Early-stage tumor detection or <i>in situ</i> characterization of diseased tissues	Angiographic and spectral imaging function would enhance EUS's role

PAT: Photoacoustic tomography; MSOT: Multispectral optoacoustic tomography; PAM: Photoacoustic microscopy; PACT: Photoacoustic computed tomography; PAE: Photoacoustic endoscopy; EUS: Endoscopic ultrasound.

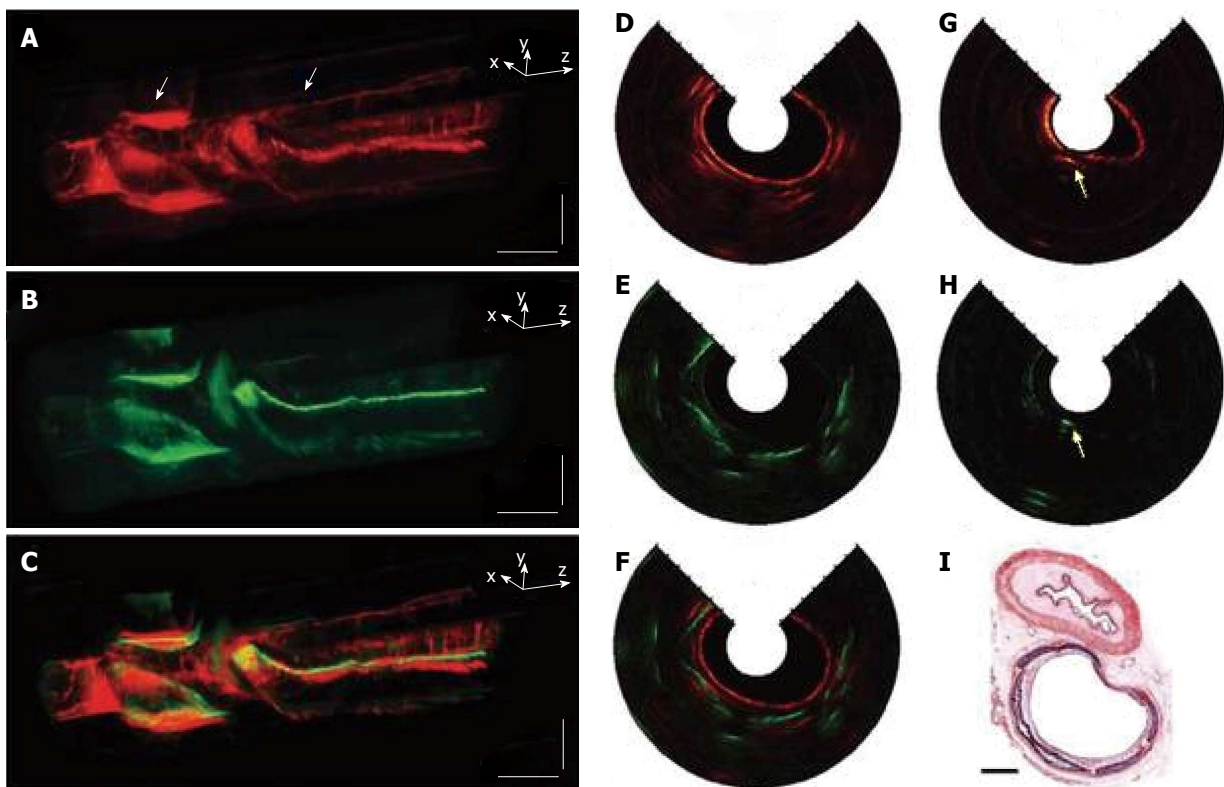


Figure 3 Simultaneous, co-registered, photoacoustic endoscopy and endoscopic ultrasound images of rabbit esophagus. A: Three-dimensionally rendered photoacoustic structural image. The left- and right-hand sides of this image correspond to the lower and upper esophagus, respectively, and the lower portion (-y axis) to the ventral side of the rabbit; B: Co-registered ultrasonic structural image for the same volume of A; C: An overlaid images of A and B. In A-C, horizontal and vertical scale bars represent 2 cm and 5 mm, respectively; D: A representative photoacoustic x-y cross-sectional image (18 mm in diameter) near the lung, as indicated by the left arrow in A; E: Corresponding ultrasonic cross-sectional image of D; F: A combine image of D and E; G: A photoacoustic x-y cross-sectional image near the trachea, as indicated by the right arrow in A; H: Corresponding ultrasonic cross-sectional image of G. In G and H, the dotted arrows indicate the contact point between the trachea and the esophagus; I: Histology of the esophagus (top) and the trachea (bottom) (HE stain). Scale bar, 1 mm. Reproduced with permission from Yang *et al*^[9].

ized imaging probe integrates a light-guiding optical fiber, an ultrasonic sensor, and a mechanical scanning unit into one small unit placed at the distal end of the endoscope^[7]. This probe used a scanning mirror system instead of conventional flexible shaft-based mechanical scanning, enabling circumferential sector scanning without moving other illumination optics or the ultrasonic detector. The large intestinal tract of a rat was imaged *ex vivo* with this probe. However, probe diameter was 4.2 mm due to the larger transducer size. One recently developed probe is 3.8 mm in diameter and approximate 38 mm in length, enabling simultaneous photoacoustic and ultrasound imaging using a single device^[8]. In this endoscopic system, a focused ultrasonic transducer detects one-dimensional, depth-resolved signals (or the A-line). Additionally, cross-sectional images (or B-scan) can be achieved by constant rotation of a scanning mirror that directs both optical and acoustic waves. This system records and shows a set of dual wavelength photoacoustic to differentiate oxy- and deoxyhemoglobin, two of the dominant absorbers of visible light in soft biological tissues, and ultrasonic B-scan images in real time. It provides anatomical information about a rabbit esophagus and organs surrounding the esophagus, covering an approximately 14-cm long and 18-mm diameter volume (Figure 3). Volume rendering enabled three-dimensional visualization of the morphology and configuration of tissues and proximal organs surrounding the esophagus. Also, simultaneous, co-registered PAE-EUS colonoscopic pseudo-color images of the rat colon *in vivo*, and images of the lymphovascular system near the rat colon, could be achieved using the same scanning parameters as imaging of the esophagus. Thus, PAE-EUS system can provide high-resolution information on the GI tract vasculature and display differences between optical and mechanical contrast compared with single-mode EUS. However, the probe was too large to fit in the working channel (usually approximate 2.8- or 3.7-mm diameter) of a standard endoscope. More recently, a newer generation probe was further miniaturized, with probe diameter of 2.5 mm and a approximate 35 mm rigid length^[28]. This mini-probe may be inserted into the working channel of a standard endoscope and be used with endoscopic guidance.

In conclusion, PAE is an emerging modality, and provides image information of optical contrast or functional properties by detecting ultrasonic waves. The major advantage of PAE is the greater penetration depth, of millimeters to centimeters, in tissue. It has great potential for *in vivo* endoscopic applications, such as early-stage tumor detection, accurate diagnosis of submucosal lesions, and *in situ* characterization of diseased tissues. Targeted contrast agents may improve the capabilities of endoscopic imaging, resulting in the earlier and more accurate detection of malignant and premalignant lesions, and further extend PAE to molecular imaging. Several technical challenges regarding the use of PAE in biomedical applications must be overcome. High-repetition lasers with fast wavelength tuning at each scan position are required

for high-speed multicontrast PAE. Additionally, further miniaturization of the PAE probe is essential so that it can be inserted into the working channel of a standard endoscope. Although PAE for GI endoscopic imaging is at the preclinical stage, it would become an important imaging modality with further technological improvements.

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Imaging pancreatobiliary ductal system with optical coherence tomography: A review

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Abstract

An accurate, noninvasive and cost-effective method of *in situ* tissue evaluation during endoscopy would be highly advantageous for the detection of dysplasia or early cancer and for identifying different disease stages. Optical coherence tomography (OCT) is a noninvasive, high-resolution (1-10 μm) emerging optical imaging method with potential for identifying microscopic subsurface features in the pancreatic and biliary ductal system. Tissue microstructure of pancreatobiliary ductal system has been successfully imaged by inserting an OCT probe through a standard endoscope operative channel. High-resolution OCT images and the technique's endoscopic compatibility have allowed for the microstructural diagnostic of the

pancreatobiliary diseases. In this review, we discussed currently available pancreatobiliary ductal imaging systems to assess the pancreatobiliary tissue microstructure and to evaluate varieties of pancreatobiliary disorders and diseases. Results show that OCT can improve the quality of images of pancreatobiliary system during endoscopic retrograde cholangiopancreatography procedure, which may be important in distinguishing between the neoplastic and non-neoplastic lesions.

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Key words: Optical coherence tomography; Endoscopy; Common bile duct; Main pancreatic duct; Sphincter of Oddi; Benign and malignant strictures

Core tip: Optical coherence tomography is a high-resolution diagnostic tool for pancreatobiliary system during endoscopic retrograde cholangiopancreatography procedure.

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INTRODUCTION

Outstand from various existing diagnosis methods such as, endoscopic retrograde cholangiopancreatography (ERCP), percutaneous transhepatic cholangiography (PTC), magnetic resonance cholangiopancreatography (MRCP), computed tomographic cholangiography (CTC), endoscopic ultrasound guided fine-needle aspiration (EUS-FNA), available for the assessment of pancreatic

Table 1 Imaging methods for diagnosis of bile duct strictures *n* (%)

Techniques	SEN (%)	SPEC	PPV	NPV	Accuracy
BC/FNA ^[2,11,23]	30 (30-60)	95 (90-100)	100 (90-100)	28 (28-50)	48 (30-50)
Forceps biopsy ^[2,11,23]	43 (40-70)	90 (90-100)	95 (90-100)	31 (30-50)	48 (30-70)
BC + FNA + biopsy ^[2,11,23]	62 (60-75)	90 (90-100)	96 (90-100)	39 (35-60)	55 (45-75)
ERCP/MRCP ^[9,17,32,50-52]	70 (67-90)	75 (70-80)	80 (68-90)	88 (70-95)	70 (50-80)
ERCP-BC/BX ^[9,11,33,38]	43 (36-60)	80 (75-100)	95 (94-100)	90 (56-100)	70 (60-75)
EUS ^[17,32,33,47,53]	80 (70-100)	80 (75-100)	80 (76-100)	80 (54-90)	80 (78-90)
EUS-FNA ^[9,23]	85 (80-100)	95 (90-100)	95 (95-100)	80 (60-90)	85 (80-90)
IDUS ^[32,38]	90 (85-100)	85 (80-100)	85 (80-100)	90 (80-100)	90 (83-90)
IDUS + ERCP/biopsy ^[32,33,38,54]	91 (90-100)	93 (90-100)	94 (84-100)	90 (84-95)	92 (90-100)
OCT ^[11,2]	79 (75-90)	69 (65-90)	75 (70-90)	73 (70-90)	74 (70-85)
OCT-BC/BX ^[2]	84 (80-90)	69 (70-90)	76 (70-90)	78 (70-100)	77 (70-90)

True positive (TP) and true negative (TN) represent the accurate diagnosis of biliary and non-biliary strictures respectively; False positive (FP) reflects the incorrect diagnosis of non-malignancy, whereas, false negative (FN) reflects incorrect diagnosis of the benign strictures; Sensitivity, specificity, positive predictive values and negative predictive values were calculated as Ref. [54]. BC: Brush cytology; BX: Forceps biopsy; FNA: Fine-needle aspiration; ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancreatography; EUS-FNA: Endoscopic ultrasound-guided FNA biopsy; IDUS: Intraductal ultrasonography; OCT: Optical coherence tomography; SEN: TP/(TP + FN); SPEC: TN/(TN + FP); PPV: TP/(TP + FP); NPV: TN/(TN + FN).

and biliary disorders; optical coherence tomography (OCT) shows great potential for identifying dysplastic or early malignant epithelial changes and for differentiating between neoplastic and non-neoplastic lesions^[1,2]. This is because ERCP and PTC are not risk free and in some cases, patients must undergo subsequent surgical or percutaneous procedures^[3-5]. Additionally, diagnosis accuracy of ERCP-based tissue sampling (brush cytology and/or forceps biopsy) is relatively low (less than 70%) and highly variable^[6-11]. Sometimes, tissue specimens collected with forceps biopsy and/or brushes may contain superficial tissue layers that are inherently insensitive to diagnosis and prone to false-negative results. MRCP^[12-16] method is noninvasive, and is apparently less operator-dependent and its diagnostic accuracy is comparable (or slightly less) to ERCP. However, MRCP is expensive which requires additional tests for data analysis and diagnose diseases. Computed tomography^[15-18] may provide better diagnostic information, but usually should be avoided due to the radiation exposures and contrast materials.

EUS-FNA is used for diagnosing cholangiocarcinoma and/or tumors in the biliary duct, especially in patients with negative brush cytology and forceps biopsy findings^[19-27]. The technique shows diagnosis accuracy over 80%, however, the performance is hindered by system resolution; additionally expensive equipments are required during procedure. Intraductal ultrasonography (IDUS) is another safe and effective method performed during ERCP to diagnose localized stenosis and early malignant changes in main pancreatic duct^[28,29], common bile duct stone^[30,31] and to identify malignant biliary strictures^[32-39]. During IDUS, a high-frequency ultrasound probe is placed into the pancreaticobiliary duct under ERCP guidance. IDUS shows diagnosis accuracy over 90% in patients with biliary strictures^[31-38]. The major drawbacks of IDUS are the impossibility of tissue sampling and IDUS findings that might have showed limited reproducibility^[30]. Therefore, more reliable and adequately sensitive diagnostic procedure is on demand for early

detection of pancreatic and biliary diseases.

OCT an optical modality shows great potential for identifying dysplastic or early malignant epithelial changes and for differential diagnosis between neoplastic and non-neoplastic lesions. OCT is a noninvasive, high-resolution, cross-sectional *in vivo* imaging method based on the principle of low-coherence interferometry^[40,41]. This technology has been widely used in various clinical and pathological applications, such as, in the field of ophthalmology^[40,42], cardiology^[43], gastroenterology^[44,45], oncology^[46], respiratory airways^[47,48] and oral cavity disorder^[49]. Main limitation OCT is its shallow penetration depth (2-3 mm) of imaging which depends upon the tissue structure, depth of focus of the probe used and absorption and/or scattering properties of the tissue sample.

General criteria (accuracy, sensitivity and specificity, positive and negative predictive values) of various imaging methods used to diagnose biliary duct strictures (malignant and benign) are summarized in Table 1. The advantages and disadvantages of these imaging modalities are listed in Table 2.

In this review, we focused on the feasibility of OCT approach that improves the diagnostic accuracy of the ductal epithelial changes, with a potential to diagnose neoplastic and non-neoplastic lesions as well as pancreatic cysts. We discussed the mechanism of an OCT imaging system and then image pancreatobiliary ductal system with OCT. The images of pancreatobiliary ductal system are divided into two categories: normal pancreatobiliary ductal system and pathological (neoplastic) ductal structure. Various pancreatic cysts with OCT are also discussed at the end of this review.

OCT IMAGING OF THE PANCREATOBILIARY DUCTAL SYSTEM

Introduction to OCT imaging system

Figure 1 shows the schematic diagram of an endoscopic

Table 2 Comparison of various imaging modalities

Imaging modality	PTC	ERCP	MRCP	US/HFUS/EUS/IDUS	CT	OCT
Projection/ tomograph	Projection	Projection	Projection or tomo- graphic	Tomographic	Tomographic	Projection or tomo- graphic
Resolution	1-2 mm	1-2 mm	Fairly poor 3-5 mm	US/EUS 100-250 μ m HFUS/IDUS 50-100 μ m	300-500 μ m μ CT: 3-125 μ m	Fairly high 1-10 μ m
Imaging depth	1-5 mm	5-60 mm	Entire biliary tree	US/EUS: 5-10 cm HFUS/IDUS: 1-3 cm	Entire biliary tree	1-3 mm
Tissue sampling	++	+++	-	US + EUS +++	+	-
Portability	-	+	-	US +++ EUS ++	-	++
Therapy	+++	+++	-	US - EUS +	-	+
System cost	++	++++	+++	US - EUS ++	++	++
Operator depen- dence	High	High	Low	Very high	Low	Low
Staging of malign- ancy	-	-	++	US + EUS +++	+++	-
Safety	-	+	+++	++	++	+++
Experiment du- ration	2-4 h	30-120 min	10-30 min	20-40 min	15-30 s	5-10 min
Complications	+++ Risk (5%-10%) of Infection, bleeding and bile leaks	++ Risk (< 5%) Bleed- ing, perforationpan- creatitis cholangitis	- Claustrophobia in some patients	+	-	-
Comments pros	+ Diagnosis and therapeutic (treatment) procedure	+ Diagnosis and treatment procedure	Non-invasive + No ionizing radia- tion + Relatively operator -independent	Usually non-invasive (sedation) + Diagnosis tool combined with tissue and/or lesion sampling	Non-invasive + Faster method + High resolution + Operator-independent	Non-invasive + No ionizing radiation + High resolution + Faster method + Operator-inde- pendent
Cons	Invasive ion- izing radiation Operator- dependent	Invasive Ionizing radiation Operator dependent	Expensive-poor reso- lution Solely diagnostic method Motion sensitive claustrophobia	Operator dependent Highly motion sensitive Thermal effects and cava- tations	Ionizing radiation Solely diagnostic method	Low imaging depth 3 mm Motion sensitive

PTC: Percutaneous transhepatic cholangiography; ERCP: Endoscopic retrograde cholangiopancreatography; MRCP: Magnetic resonance cholangiopancreatography; US: Ultrasound; EUS: Endoscopic ultrasound; HFUS: High frequency ultrasound (> 10 MHz); IDUS: Intraductal ultrasonography; CT: Computed tomography; OCT: Optical coherence tomography.

OCT system. Light generated from a low coherence infrared light source splits into two parts: the sample and reference arms. The back-reflected light from the tissue interferes with the reference signal which then fed to a detector and then sent the signal to a computer for visualization. OCT is analogous to the ultrasound imaging^[1], but uses light waves rather than ultrasound waves. Therefore, OCT provides high resolution (1-10 μ m) which is at-least ten times better than the currently available high-frequency ultrasound imaging system. For investigating the epithelial layers of the main pancreatic duct (MPD), common bile duct (CBD) and sphincter of Oddi (SOD) an OCT probe (guide wire) is inserted through the working channel of an endoscopic catheter (Figure 1). The outer diameter of this endoscopic catheter can be made as small as 1.2 mm. Repeated frames are taken by the “pull-back” technique while connecting the catheter with a rotator, giving a large number of transitional-rotational

images. Diagnoses of the intraductal pathology of the pancreatobiliary system, such as biliary and/or pancreatic stricture, are improved with OCT method where the conventional biopsy is technically difficult and is associated with risk^[6,7]. After the targeted tissue is identified with a conventional endoscopy, a narrow-diameter (about 1.2 mm) OCT probe is inserted through the operating channel of the endoscope and positioned on the site of interest. No special patient preparation is required during OCT imaging and images can be acquired within several minutes (5-10 min). Three different types of OCT systems are widely used in various research and clinical applications (Table 3). Companies currently produce OCT systems are: Novacam, Biopigen, Heidelberg Engineering, Alcon/LenSx, Canon/Optopol, Volcano Crop, Optovue, Thorlabs, Topcon, Imalux, Nidek, Tomey, Schwind, Watschphotonics, OptiMedica, Optos/OTI, Volcano Crop, LightLab Imaging, Shenzhen Moptim Imaging, Techno-

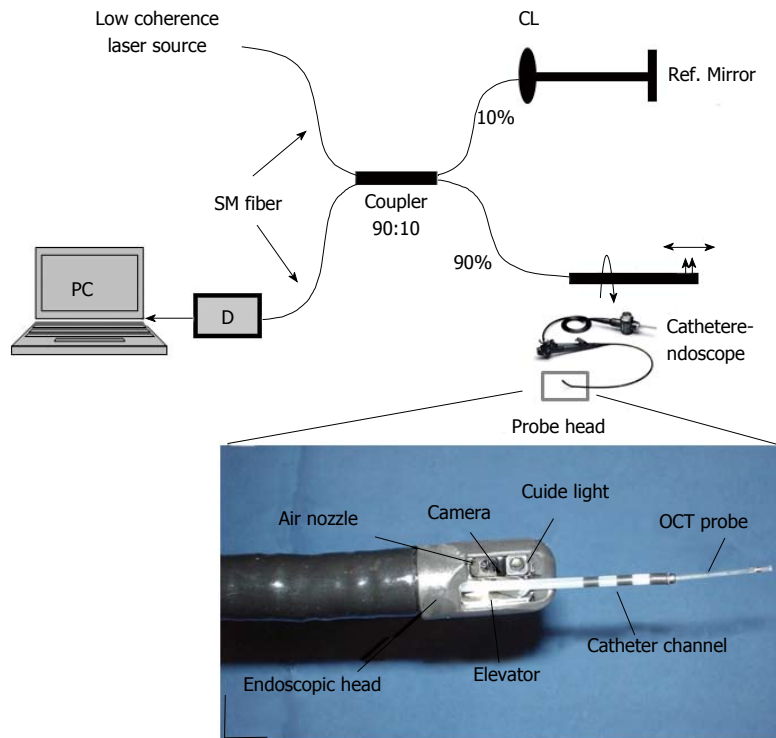


Figure 1 Schematic diagram of an endoscopic optical coherence tomography system. The endoscopic probe is connected to the sample arm (Color online). Light generated from a low coherence laser source splits into two parts, the sample arm and reference arm. Both back-reflected lights from sample and reference arms recombine in a fiber coupler (10:90). If both back-reflected reference and sample light travels the same distance (optical) then interference will occur and the interference signal will be fed to a detector (D). Magnified region of interest in the second image is the endoscopic probe head, consisting primarily of an optical fiber (OCT probe), catheter channel, elevator, video camera and aiming light^[55]. Scale bar: 10 mm.

Table 3 Comparison of different types of optical coherence tomography systems

Parameters	TD-OCT	SD-OCT	SS-OCT/OFDI
Mechanism	Interference signals are detected as a function of optical time delay between obj. and ref. arm.	Interference signals are detected with a camera as a function of optical frequency	Spectral fringes are mapped to time domain by use of a swept laser and are measured with a detector as a function of time
Major components	Broadband laser, optical delay line and a detector	Broadband laser, spectrometer and camera	Tunable laser, digitizer and a balanced detector
Spectrum	800 nm, 1000 nm, 1300 nm	800 nm, 1000 nm, 1300 nm	800 nm, 1000 nm, 1300 nm
Imaging depth	1-3 mm	1-3 mm	1-3 mm
Resolution	$\geq 10 \mu\text{m}$	1-10 μm	1-10 μm
Imaging speed (axial scan rate)	Slow ($\leq 5 \text{ kHz}$)	Fast (20-150 kHz)	Fairly fast (20-400 kHz)
SNR	Low	High	High
Image quality	Moderate	Fairly high	High
Sensitivity	Low (70-90 dB)	High (85-105 dB)	High ($\geq 100 \text{ dB}$)
Phase stability	Low	High	Moderate
Portability	Yes	Yes	Yes
System cost	Low	High	Moderate

SNR: Signal-to-noise ratio; dB: Decibel; TD-OCT: Time domain OCT; SD-OCT: Spectral-domain OCT; OFDI: Optical frequency domain imaging; SS-OCT: Swept source OCT.

las Perfect Vision, and Carl Zeiss Meditec. Cost of an OCT system varies with imaging engines (consisting of an interferometer, light source, and detector) and imaging devices (or OCT probes) and ranges from \$20000-\$80000. The cost per correct diagnosis (or procedure cost) is approximately \$100 (100-200).

Normal pancreatobiliary ductal system

Visualization of epithelium layer structure of main pancreatic duct has been obtained from post-mortem^[56] and *ex vivo* in humans^[57-60], while *in vivo*, it comes from single study in animals^[61] and another in humans^[62]. Normal biliary ductal system was investigated in humans, *ex vivo*

in a study^[58,60], post-mortem^[56] and *in vivo* and *ex vivo* in animals^[61,63] and *in vivo* in ERCP-based OCT studies^[2,64,65]. The SOD structure was investigated in normal and pathological conditions either in *ex vivo* or *in vivo* studies^[2,58,65].

Human pancreatobiliary duct studies: Tearney *et al.*^[56] first performed *ex vivo* OCT imaging from the post-mortem cadaveric pancreatobiliary tissue. OCT images obtained from CBD-wall were able to identify layered structures and could resolve the submucosa-muscularis and muscularis-adventitia boundaries. Mucosa, submucosa, muscularis propria and adventitial layers, serosa in the gallbladder and biliary duct were visualized due to different back-

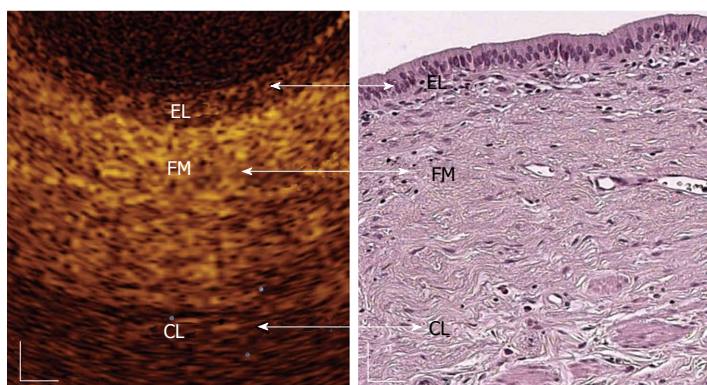


Figure 2 *In vivo* optical coherence tomography image of a normal common bile duct wall. Three recognizable layers were observed from the surface of the duct to a depth of 1 mm (Color online). The inner single layer of epithelial (EL) cells (400-600 μm thick) is visible as a superficial, hypo-reflective layer. The intermediate connective fibro-muscular (FM) layer surrounding the epithelium is visible as a hyper-reflective layer (350-480 μm thick) and the outer connective layer (CL) is visible as a hypo-reflective layer with longitudinal relatively hyper-reflective strips (smooth muscle fibers)^[58]. White scale bar: 150 μm .

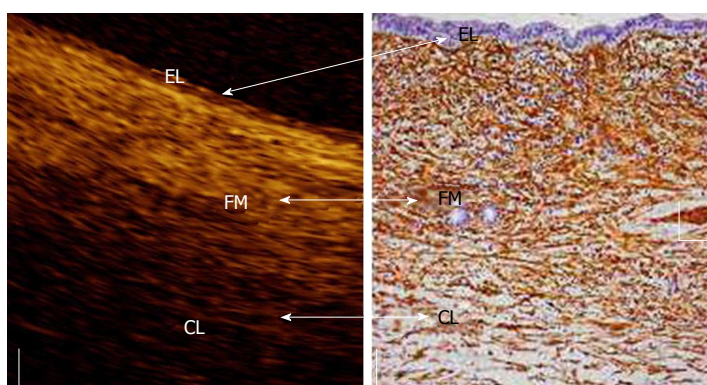


Figure 3 *In vivo* optical coherence tomography image of a normal main pancreatic duct wall compared with histology. Three recognizable layers were observed from the surface of the duct to a depth of 1 mm (Color online). The inner single layer of epithelial (EL) cells (400-800 μm thick) is visible as a superficial, hypo-reflective layer. The intermediate, connective fibro-muscular (FM) layer surrounding the epithelium, is visible as a hyper-reflective layer (350-600 μm thick). The outer connective-acinar (CL) structure close to the ductal wall epithelium is visible as a hypo-reflective layer^[58]. White scale bar: 150 μm (right image).

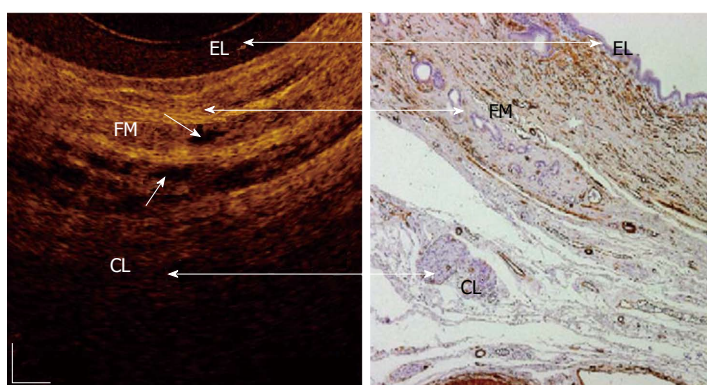


Figure 4 *In vivo* optical coherence tomography image of a normal sphincter of Oddi wall. Three recognizable layers were observed from the surface of the duct to a depth of 1 mm (Color online). The inner single layers of epithelial (EL) cells are visible as a superficial, hypo-reflective layer (400-800 μm thick). The intermediate connective-muscular (FM) layer surrounding the epithelium is visible as a hyper-reflective layer (250-400 μm thick). The outer connective layer (CL) is visible as a hypo-reflective layer with longitudinal relatively hyper-reflective strips (smooth muscle fibers). Within intermediate and outer layer, vessels could be visualized (marked with arrows) as nonreflecting areas. The boundaries between the intermediate and outer layers are not clearly recognizable due to irregular distribution of the connective and muscular structure^[59]. White scale bar: 150 μm .

scattering characteristics within each layer. For example, submucosa and/or muscularis layers showed higher intensities and regular scattering pattern than the adventitial layer, most likely due to the presence of adipose tissue into the adventitial layer. The tissue microstructure, such as secretions within individual glands (glandular structure), and cross-sectional imaging of islets Langerhans cells were visualized. The pancreatic duct appeared as a highly backscattering band near the lumen of the tissue and the pancreatic stroma was seen beneath the pancreatic duct.

Testoni *et al.*^[58,59,62,66] further studied *in vivo* MPD, CBD and SOD wall structures with OCT. Three different layers (Figures 2-4) were recognized from the surface of the duct to a depth of about 1 mm. The inner layer defined from the surface to the lumen, consisting of single layers of epithelial cells. The intermediate layer is homogeneous, consisting of connective fibro-muscular layer

surrounding the epithelium. The outer layer is less definite and corresponds to the smooth muscular structure within a connective tissue in the CBD and at the level of the SOD, and connective-acinar structure in the MPD.

The inner hypo-reflective layer showed a mean thickness of 500 μm (range: 400-800 μm). Layer thickness, surface roughness and reflectance of inner layer were not substantially differing in CBD, MPD and SOD. Thickness of the intermediate hyper-reflective layer (about 400 μm) is substantially similar to MPD and CBD, whereas it reduces by 25% at the level of SOD^[55]. Tiny, multiple, nonreflective areas can be appeared within the intermediate MPD layer and at the level of SOD (Figures 3 and 4). The outer hypo-reflective layer was recognizable up to a depth of about 1 mm (focus distance of the OCT probe) from the lumen. Multiple, smooth-muscle longitudinal strips appeared within hypo-reflective layer at the level of CBD and SOD and were particularly more

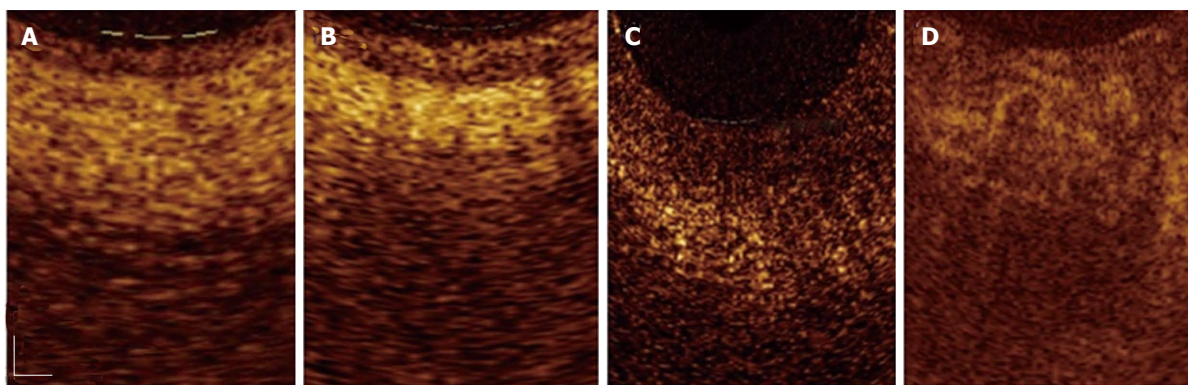


Figure 5 Magnified optical coherence tomography images. A: Sections with normal main pancreatic duct (MPD) wall; B: The presence of chronic pancreatitis; C: Low-grade dysplasia; D: Adenocarcinoma. Three differentiated layer architecture with a linear, regular surface, and a homogeneous back-scattered signal from each of the layer was observed in the normal condition. In the presence of chronic pancreatitis the optical coherence tomography (OCT) image still showed three-layer architecture, however, the inner epithelial layer appeared slightly larger than normal and the intermediate layer appeared more hyper-reflective; probably due to the presence of the dense mononuclear cell infiltrate. In the presence of dysplasia, OCT image showed thickened, strongly hypo-reflective and hetero-geneous inner MPD layer. Irregular surfaces were observed in the whole MPD structure. None of these layers were recognizable in the presence of adenocarcinoma^[60]. Scale bar: 200 μm (Color online).

pronounced in SOD than in CBD. Furthermore, OCT images can identify veins, arteries and/or secondary pancreatic ducts which were characterized by hypo- or non-reflective, well delimited areas.

All of these layers showed linear, regular surface and each layer had a homogeneous back-scattered signal in every frame. However, the differentiation between outer and intermediate layer appeared more difficult than that of between inner and intermediate layer. The muscular and connective-acinar structure was visible until the focus distance (about 1 mm) of the OCT probe into the tissue.

Other biliary ductal studies: Singh *et al.*^[61] reported *in vivo* OCT images of animal (dog) pancreatic biliary ducts. Hwang *et al.*^[63] observed the normal structures of an *ex vivo* pig pancreas including small pancreatic ducts and pancreatic acini. OCT image identified biliary duct wall structure, features within lamina propria and some of the surrounding fibrous tissue. But OCT could not identify the nuclei or subcellular structures and/or adjacent structures such as blood vessels. A thin, low-scattering superficial layer appeared on the majority of the images, corresponding to the cuboidal epithelium. The lamina propria appeared as highly reflecting layer underneath the mucosal surface. Irregular reflections from layers underlying the lamina propria were from the dense connective tissue. Low reflected peribiliary glands were viewed as large open spaces with a single layer epithelium. The pancreatic duct in dogs has a flat mucosal layer composed of cuboidal epithelium and virtually has no lamina propria. OCT was able to image wall of the pancreatic duct but not the surrounding parenchyma. The pancreatic duct images were homogeneous and moderately reflective.

Pathological (dysplastic/neoplastic) pancreatobiliary ductal system

Imaging pathological pancreatic ductal system with OCT

was first investigated by Testoni *et al.*^[59,60] in humans in two *ex vivo* studies. MPD chronic inflammatory changes showed a conserved, three-layer architecture. However, the inner hypo-reflective layer was slightly larger than the normal tissue layer and the intermediate layer was more hyper-reflective than normal condition. Additionally back-scattered signal from each layer is more heterogeneous than the normal layer condition.

In the presence of dysplasia, OCT showed thickened, strongly hypo-reflective and hetero-geneous inner layer of MPD (Figure 5C). Irregular surfaces were observed between the inner and intermediate layers. The intermediate layer is strongly hyper-reflectance, particularly close to the inner layer. The outer layer was homogeneously hypo-reflective and did not differ from normal condition. The agreement between OCT and histology in chronic pancreatitis and dysplasia were 62% in these cases. Overall, approximately one-third sections of normal wall structure and chronic inflammatory/low-grade dysplastic changes were not distinguishable with OCT.

In the presence of adenocarcinoma, MPD wall structure with OCT is shown in Figure 5D. All three layer structures and their linear, regular surface were not recognizable. No clear identifiable margin was seen between connective fibro-muscular layer and acinar tissue. The back-scattered signal was strongly heterogeneous with multiple nonreflective areas in the disorganized pancreatic microstructure. The OCT and histology were 100% concordant for sections with adenocarcinoma. OCT images from sections of MPD with normal tissue, tumor-associated chronic inflammation, low-grade dysplasia, and adenocarcinoma are shown in Figure 5.

OCT can differentiate three-layer architecture in either normal MPD or chronic pancreatitis; however, in a neoplastic lesion the layer architecture is totally subverted with heterogeneous light back-scattering. In addition, OCT can distinguish non-neoplastic from neoplastic lesions of MPD and can gave 100% accuracy for

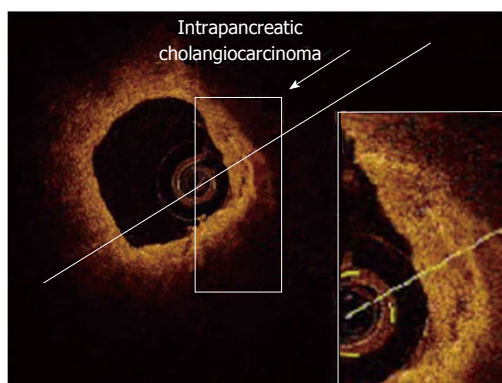


Figure 6 Adenocarcinoma (neoplasia) of the common bile duct at early stage, detected with optical coherence tomography probe maintained inside the endoscopic retrograde cholangiopancreatography catheter. In the presence of Adenocarcinoma (neoplasia), optical coherence tomography (OCT) patterns showed distorted common bile duct (CBD) wall structure (Color online). All three-layer architecture and their linear and regular surface, normally giving a homogeneous back-scattered signal, are not recognizable. OCT image shows heterogeneous back-scattered signal with minute, multiple, nonreflective areas (necrotic areas) in the highly disorganized CBD microstructure. Therefore, epithelial structure and various biliary disorders in early-stage of cancer can be distinguishable with OCT^[67].

detection of neoplastic tissue compared with 66.7% for brush cytology^[62]. MPD layer architectures derived from different back-scattered signals from each layer were confirmed as a reliable OCT parameter for distinguishing non-neoplastic from neoplastic tissue. However, this technology is unable to discriminate between a normal MPD structure and other MPD benign lesions. Further studies are necessary which might improve the diagnostic accuracy of OCT in this challenging imaging scenario.

OCT imaging during ERCP can identify CBD layer structure and diagnose neoplastic lesions and/or adenocarcinoma at early stages which is usually missed by cytology and X-ray imaging^[55-67]. The normal CBD wall shows three recognizable layers, with a linear, regular surface and different homogeneous back-scattering of the light^[58]. These inner to outer layers are: epithelium, connective-fibromuscular, and muscular layer in normal CBD wall (Figure 2). However, with the presence of neoplastic tissue, OCT patterns showed distorted CBD wall structure with heterogeneous light back-scattering (Figure 6). Therefore, epithelial structure and various biliary disorders in early-stage of cancer can be distinguishable with OCT.

Arvanitakis *et al.*^[2] conducted biliary intraductal OCT during ERCP studies in thirty-seven patients with biliary strictures and assess the potential of this method for improving the diagnosis accuracy of the malignant biliary strictures. This study concluded to satisfactory accuracy levels regarding distinction between malignant and benign strictures, especially when combined to biopsies. Based on OCT images, two malignancy criteria were considered: (1) disorganized and subverted layer architecture and (2) presence of large nonreflective areas compatible with tumor vessels. Figure 7A shows the

cross-sectional OCT image of a patient with a benign stricture. The probe is surrounded by ERCP catheter (marked with arrow). The three-layered structure of the biliary wall is recognizable. Figure 7B-D show images of the malignant bile duct strictures. Disorganized layer architecture of the stricture wall which is one of the criteria for malignancy is shown in Figure 7B. Large, nonreflective, surface of at least 0.03 mm² tumor vessels were observed in Figure 7C. Malignant stricture due to hilar metastases of an esophageal squamous carcinoma was observed in Figure 7D.

Studies of pancreatic cysts with OCT

OCT modality shows great potential to reveal specific morphologic features of pancreatic cysts and thus to differentiate between the interior structures of low risk (*i.e.*, serous cyst adenomas) and high risk (*i.e.*, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms) pancreatic cysts with over 95% sensitivity and specificity^[68,69]. Fresh pancreatic specimens (pancreatic cysts) from patients were made available immediately after the surgery and then examined with OCT. An OCT probe was inserted into the cut surface of the pancreatic cysts. The main characteristics of each type of cystic lesion are shown in Figure 8.

Based on OCT images, the cysts were prospectively divided into two groups: mucinous (*i.e.*, Mucinous Cystic Neoplasms and Intraductal Papillary Mucinous Neoplasms) and non-mucinous (*i.e.*, Serous Cysts Adenomas and others). Multiple tiny cysts with well-defined outlines are seen in low-risk (*i.e.*, Serous Cysts Adenomas) of pancreatic cystic lesions. Thin septae between cysts create honeycomb appearance. The cyst content usually appears as dark due to lack of the scattering effect. Focal intra-luminal scattering can be found in some cysts which usually correspond to hemorrhage. In high-risk (*i.e.*, Mucinous Cystic Neoplasms, Intraductal Papillary Mucinous Neoplasms) pancreatic cyst multiple small cysts present (marked with white arrow), which may sometime surround the main cystic cavity (marked with red arrow). The cystic content may show some scattering due to presence of dead epithelial cells.

The above criteria mainly based on the visual appearance of the cystic wall morphology and on the scattering properties of the cystic fluid. Although relatively simple, they provide a very good discrimination between serous and mucinous pancreatic cysts. This *ex vivo* study suggests that OCT could be used by clinicians in future to more reliably differentiate between benign and malignant pancreatic cysts.

CONCLUSION

Limitations of standard endoscopic practices are addressed by the OCT technology described in this review. OCT identified layer structures of common bile duct, main pancreatic duct and sphincter of oddi and could resolve the submucosa-muscularis and muscularis-adven-

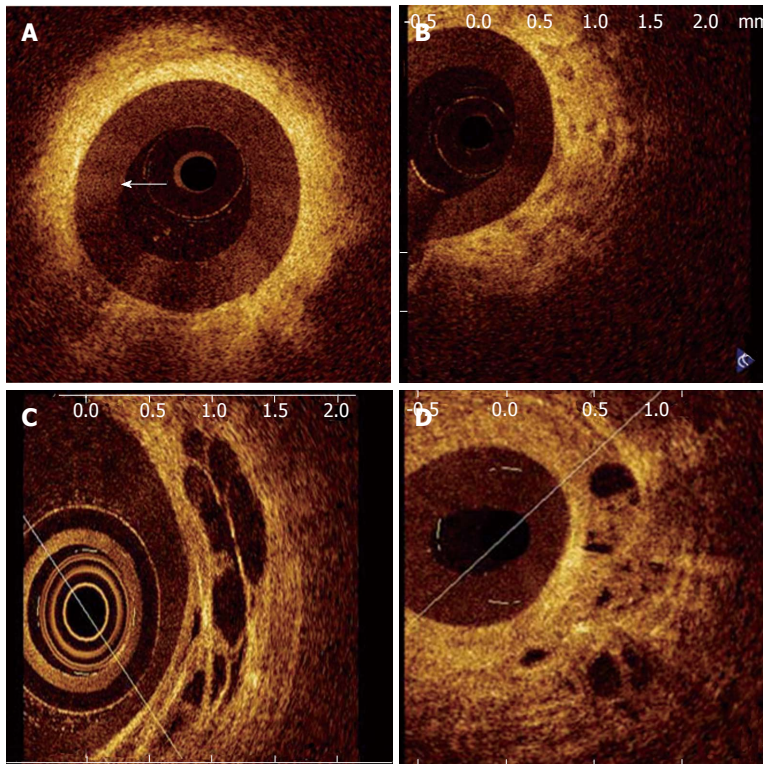


Figure 7 Optical coherence tomography image of a patient with a benign stricture. The three-layered structure of the biliary wall is recognizable (Color online). A-D shows images of malignant bile duct strictures. B: Disorganized layered structure with unidentifiable margins and a strongly heterogeneous back-scattering signal; C: Large, nonreflective areas in the intermediate layer suggesting the tumor vessels; D: Malignant stricture due to hilar metastases of an esophageal squamous carcinoma showing nonreflective areas and disorganized layer architecture^[2].

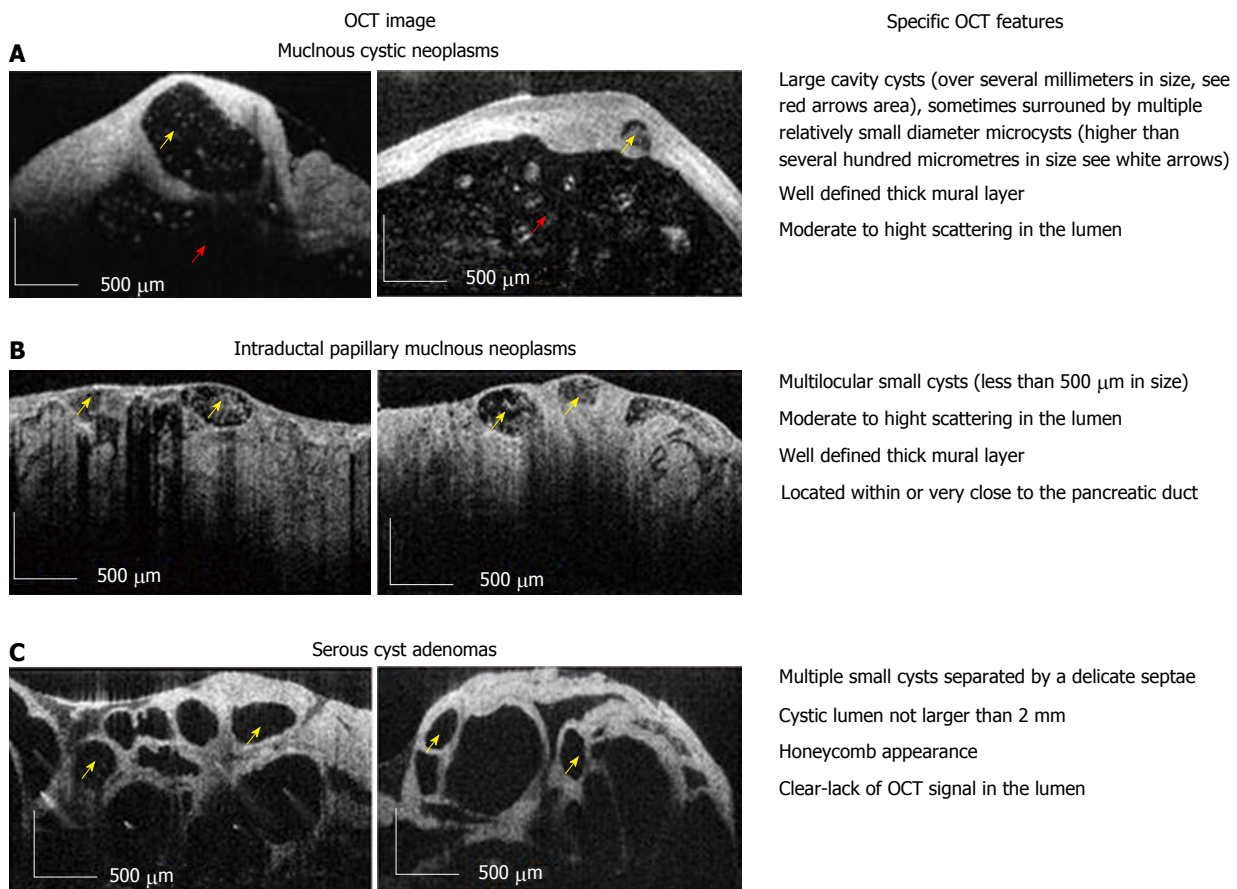


Figure 8 Optical coherence tomography image. A, B: Diagnostic criteria for high-risk (i.e., Mucinous Cystic Neoplasms, Intraductal Papillary Mucinous Neoplasms); C: Low risk (i.e., Serous Cysts Adenomas) pancreatic cysts. Multiple small cysts are marked with yellow arrow, while surrounded main cystic cavity is marked with red arrow. Scale bar = 500 μm^[69]. OCT: Optical coherence tomography.

titia boundaries. Layers of these biliary ducts showed linear, homogeneous and regular surface; however, the difference between hypo-reflective intermediate and hypo-reflective outer layer appeared more difficult than that of between the hypo-reflective inner and intermediate layer. Potentially, OCT shows real-time, high-resolution, cross-sectional images, or “optical biopsies” for detecting the early stages of pancreatobiliary diseases. OCT can improve the quality of images obtained during ERCP, which may be important in distinguishing between the neoplastic and non-neoplastic lesions. Further studies are necessary for the proper clinical applications of this promising method in the pancreatobiliary duct system and diagnosis of pancreatic cysts.

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Outcome in obscure gastrointestinal bleeding after capsule endoscopy

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comes were analyzed from electronic charts. Variables were compared by χ^2 analysis and Student *t* test. Risk factors of rebleeding were assessed by Log-rank test, Kaplan-Meier curves and Cox regression model.

RESULTS: There were 105 patients [45.7% women, median age of 72 years old (interquartile range 56-79)] and a median follow-up of 326 d (interquartile range 123-641) included in this study. The overall diagnostic yield of CE was 58.1% (55.2% and 63.2%, for patients with occult OGIB and overt OGIB, respectively). In 73 patients (69.5%), OGIB was resolved. Multivariate analysis showed that hemoglobin levels lower than 8 g/dL at diagnosis [hazard ratios (HR) = 2.7, 95%CI: 1.9-6.3], patients aged 70 years and above (HR = 2.1, 95%CI: 1.2-6.1) and significant findings in CE (HR = 2.4, 95%CI: 1.1-5.8) were independent predictors of rebleeding.

CONCLUSION: One third of the patients presented with rebleeding after CE; risk factors were hemoglobin levels < 8 g/dL, age \geq 70 years or the presence of significant lesions.

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Key words: Capsule endoscopy; Obscure gastrointestinal bleeding; Small bowel; Angiodysplasia; Enteroscopy

Core tip: This paper describes a large cohort of patients with obscure gastrointestinal bleeding who underwent a capsule endoscopy. The diagnostic yield was analyzed with further exploration motivated by the capsule findings, as well as the outcome during follow-up. Risk factors of rebleeding were also analyzed. Interestingly, old age, a lower hemoglobin level at diagnosis and significant lesions in capsule endoscopy were found to be predictors of rebleeding in this cohort.

Abstract

AIM: To investigate the clinical impact of capsule endoscopy (CE) after an obscure gastrointestinal bleeding (OGIB) episode, focusing on diagnostic work-up, follow-up and predictive factors of rebleeding.

METHODS: Patients who were referred to Hospital del Mar (Barcelona, Spain) between 2007 and 2009 for OGIB who underwent a CE were retrospectively analyzed. Demographic data, current treatment with non-steroid anti-inflammatory drugs or anticoagulant drugs, hemoglobin levels, transfusion requirements, previous diagnostic tests for the bleeding episode, as well as CE findings (significant or non-significant), work-up and patient out-

Cañas-Ventura A, Márquez L, Bessa X, Dedeu JM, Puigvehí M, Delgado-Aros S, Ibáñez IA, Seoane A, Barranco L, Bory F, Andreu M, González-Suárez B. Outcome in obscure gastrointestinal bleeding after capsule endoscopy. *World J Gastrointest Endosc* 2013; 5(11): 551-558 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i11/551.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i11.551>

INTRODUCTION

Since 2001, video capsule endoscopy (CE) has become an important tool for the diagnosis of small bowel diseases. Its most important indication is in the study of obscure gastrointestinal bleeding (OGIB), defined as persistent or recurrent bleeding from the gastrointestinal (GI) tract after a non-conclusive conventional endoscopic examination [upper-GI endoscopy (GIE)] and colonoscopy. Two different presentations of OGIB can be distinguished: obscure-occult GI bleeding [persistent or recurrent iron deficiency anemia and/or positive fecal occult blood test (occult-OGIB)] and obscure-overt GI bleeding [recurrent visible blood loss: melena or hematochezia (overt-OGIB)]^[1]. CE provides a non-invasive examination of the small intestine that is not accessible through conventional endoscopy or push or balloon enteroscopy. Several studies have shown good specificity and sensitivity of CE in the setting of OGIB and better diagnostic yield than other techniques (radiological or endoscopic procedures)^[2-5]. CE is well-tolerated and its rate of complications is very low. The disadvantages of CE are the impossibility to treat and the impossibility to obtain tissue biopsies. Although the diagnostic yield of CE is high, the impact on the outcome of the patients with OGIB after a CE is still unclear.

A single center retrospective study of a long follow-up cohort of 105 patients with OGIB who underwent a CE study is presented. The aim of this study was to evaluate the usefulness of CE, focusing on the subsequent treatment and the outcome of the OGIB episode. Secondary objectives were to define predictive factors of rebleeding.

MATERIALS AND METHODS

Patient inclusion

All patients with OGIB referred to the endoscopy unit (Hospital del Mar, Barcelona, Spain) between January 2007 and June 2009 were analyzed retrospectively. On all these patients, at least one upper-GIE and one colonoscopy were run. Those endoscopies were considered normal or the findings were insufficient to explain the patient's symptoms. By using the electronic charts of all patients, we collected data on the complete episode of OGIB; including previous procedures to CE and follow-up data. The collected variables were: demographic data, history of intake of non-steroidal anti-inflammatory drugs (NSAIDs), anticoagulant and antiplatelet therapy

(aspirin and clopidogrel), hemoglobin levels (Hb) at diagnosis, transfusion requirements, time from overt bleeding to CE procedure, and results of previous diagnostic tests [upper-GIE, colonoscopy, computed tomography (CT) scan, radiographic series of small bowel, angiography, Tc^{99m} red cell scan and Meckel's scan].

CE procedure

The procedure was performed in ambulatory and in-hospital patients, using PillCam SB2[®] (Given Imaging, Yoqneam, Israel). Bowel preparation consisted of an oral purge (two liters of polyethylene glycol-based solution) ingested the night before the procedure. CE was swallowed in the morning and the data recorder was removed 8-9 h later. Patients were allowed to drink fluids 2 h after the administration of CE and to eat 4 h after the ingestion. Patients were asked to verify the excretion of the capsule in the stool and to alert the endoscopy unit if it was not excreted.

In order to test small bowel patency, a previous exam was performed with Agile capsule[®] (Given Imaging, Yoqneam, Israel) on patients with a history of sub-occlusive intestinal episodes, chronic NSAID intake, *i.e.*, longer than 6 mo, established or suspected inflammatory bowel disease, previous abdominal surgery of small bowel or bowel strictures demonstrated by radiological techniques. Capsule retention was defined as the presence of the capsule in the GI tract for at least 2 wk after ingestion. Two gastroenterologists with extensive experience in small bowel endoscopy (González-Suárez B and Dedeu JM) evaluated the images recorded by CE.

Diagnostic and therapeutic strategy after CE

The CE findings were classified as significant and non-significant. Significant findings were those that explained the clinical situation (*i.e.*, ulcers, active bleeding, tumors and angiodysplasias). Non-significant findings were those where the mucosa was normal or with minimal changes with an uncertain relationship to the bleeding (*i.e.*, small erosions, small and isolated angiodysplasia).

Therapeutic strategy was classified into two different groups: (1) specific treatment focused on the main cause of bleeding: invasive therapies (*i.e.*, endoscopic treatment or surgery) and medical treatment (*i.e.*, proton-pump inhibitors (PPIs), NSAIDs or anticoagulant drugs withdrawal); and (2) non-specific treatment (*i.e.*, iron supplementation, blood transfusions, watchful waiting and NSAID withdrawal if CE findings were not significant or different to ulcer/erosion). Therapeutic strategy was chosen based on the patient's overall condition and the nature of the disease.

Follow-up

Complete follow-up information was obtained from electronic charts: hemoglobin levels, transfusion requirement after treatment, recurrence of OGIB and CE complications. Follow-up time was defined as the time between the CE and the date of rebleeding or the last

Table 1 Patients' baseline characteristics

Characteristics	Overall	Occult-OGIB	Overt-OGIB	P value
Patients	100.00%	63.80%	36.20%	-
Age [yr, median (IQR)]	72 (5-79)	71 (5-78)	73 (49-82)	0.800
Gender (female)	45.70%	55.20%	28.90%	0.014
Bleeding-related drugs	41.90%	37.30%	50%	0.200
NSAIDs	30.50%	26.90%	36.80%	0.300
Hemoglobin level [g/dL, median (IQR)]	7.5 (6.4-9.3)	7.4 (6.0-9.1)	7.6 (6.5-9.4)	0.600
Transfusion requirements	61%	55.20%	71.10%	0.080
Transfusion requirements (blood units, mean \pm SD)	2.01	1.7 \pm 1.7	2.5 \pm 2.3	0.037
Follow-up [d, median (IQR)]	326 (123-641)	330 (154-691)	217 (84-476)	0.500

NSAIDs: Non-steroidal anti-inflammatory drugs; OGIB: Obscure gastrointestinal bleeding; IQR: Interquartile range.

follow-up visit. Anemia was defined as Hb level < 13 g/dL in men and < 12 g/dL in women. A patient's outcome was considered favorable or resolved if no overt bleeding was present and the anemia was resolved completely after treatment. Rebleeding was defined as overt bleeding or reappearance of anemia.

Statistical analysis

Continuous data were expressed as median and percentiles [interquartile range (IQR) 25th-75th percentile] and were compared using the Student *t* test or the *U* test. Categorical data were expressed by percentages with a 95%CI and compared by the χ^2 test or the *F* test.

Independent predictors for rebleeding were first analyzed by univariate analysis using the Log-rank test in the Kaplan-Maier model (setting the rebleeding variable as "event"). All variables from the univariate analysis with a $P < 0.05$ were included in a Cox proportional hazards regression using the stepwise selection method. Results were reported as hazard ratios (HR) with 95%CI. All *P* values were two-sided and $P < 0.05$ was considered to indicate a statistically significant difference.

RESULTS

There were 108 patients included in the study. In two patients, the CE failed to achieve complete small bowel visualization: in one patient CE was retained for eight hours in the stomach and in the other one, bowel preparation was not optimal for image evaluation. In one patient, follow-up was not available because she moved back to her country the day after CE. Hence, 105 patients were available for data analysis (Figure 1).

According to the definition of OGIB, 67 patients (64.2%) with occult-OGIB and 38 patients (35.8%) with an overt-OGIB were identified. The baseline characteristics of patients included in the cohort are summarized in Table 1. Follow-up time and hemoglobin at diagnosis were similar in both groups. Mean of transfusion units was higher in the overt-OGIB group than in the occult-

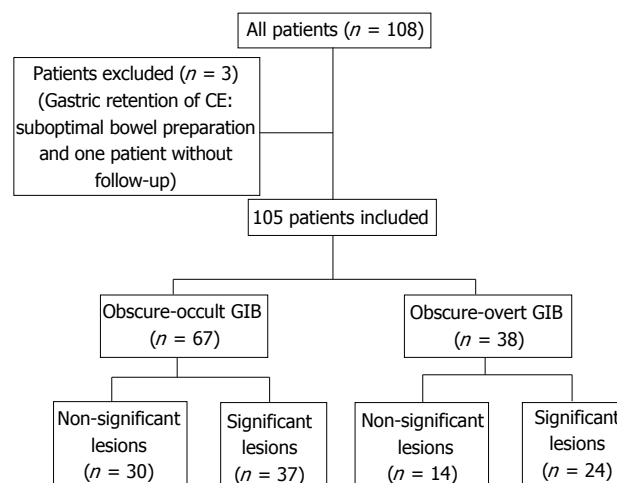


Figure 1 Patients included and group distribution. CE: Capsule endoscopy; GIB: Gastrointestinal bleeding.

OGIB group (2.5 *vs* 1.7 units, $P = 0.037$).

There were 44 patients (41.9%) that had been taken a bleeding-related drug before the OGIB episode: clopidogrel ($n = 8$); warfarin ($n = 9$) or NSAIDs (including acetylsalicylic acid) ($n = 26$), without statistical significant differences comparing the two groups ($P = 0.2$).

All patients were previously submitted to at least one upper-GIE and colonoscopy that were considered normal or whose findings were insufficient to explain the bleeding episode. Other procedures were performed before CE in 12 patients: four CT-scans focused on small bowel, two mesenteric angiographies, three Tc⁹⁹ red cell scans, three Meckel's scans, and all of them were negative for the diagnosis of cause of bleeding.

CE findings

CE findings were considered significant, according to previous definition, in 37 patients of the occult-OGIB group and in 24 patients of the overt-OGIB group, which represent a diagnostic yield of 55.2% and 63.2%, respectively ($P = 0.5$). The overall diagnostic yield of CE in our cohort was 58.1%. Intestinal angiodysplasia (21%) and small bowel ulcers (27%) were the most frequent lesions (Figure 2). A total of seven lesions (6.6%) were found in the upper GI tract of these patients: five ulcers and two erythematous duodenitis, classified as non-significant lesions.

In two patients, CE was retained in the small bowel. In one patient, retention was due to a pelvic relapse of a previous colorectal cancer that involved the ileum; the patient remained asymptomatic until surgery and the device was removed. Another patient was diagnosed with an intestinal T-cell lymphoma and CE was removed during an oral balloon enteroscopy performed to take biopsies.

All patients with overt-OGIB were submitted to a CE within the first three weeks after the bleeding episode. There were no differences between patients with significant and non-significant lesions regarding the time interval between bleeding and CE [8.5 d (95%CI: 11.4-5.6) *vs*

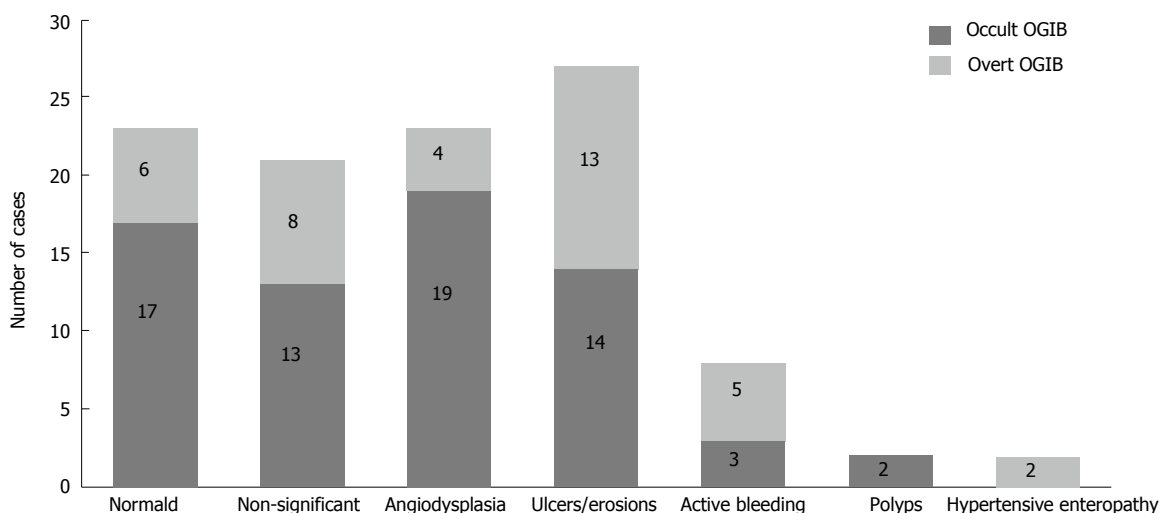


Figure 2 Capsule endoscopy findings according to obscure gastrointestinal bleeding presentation: occult or overt. OGIB: Obscure gastrointestinal bleeding.

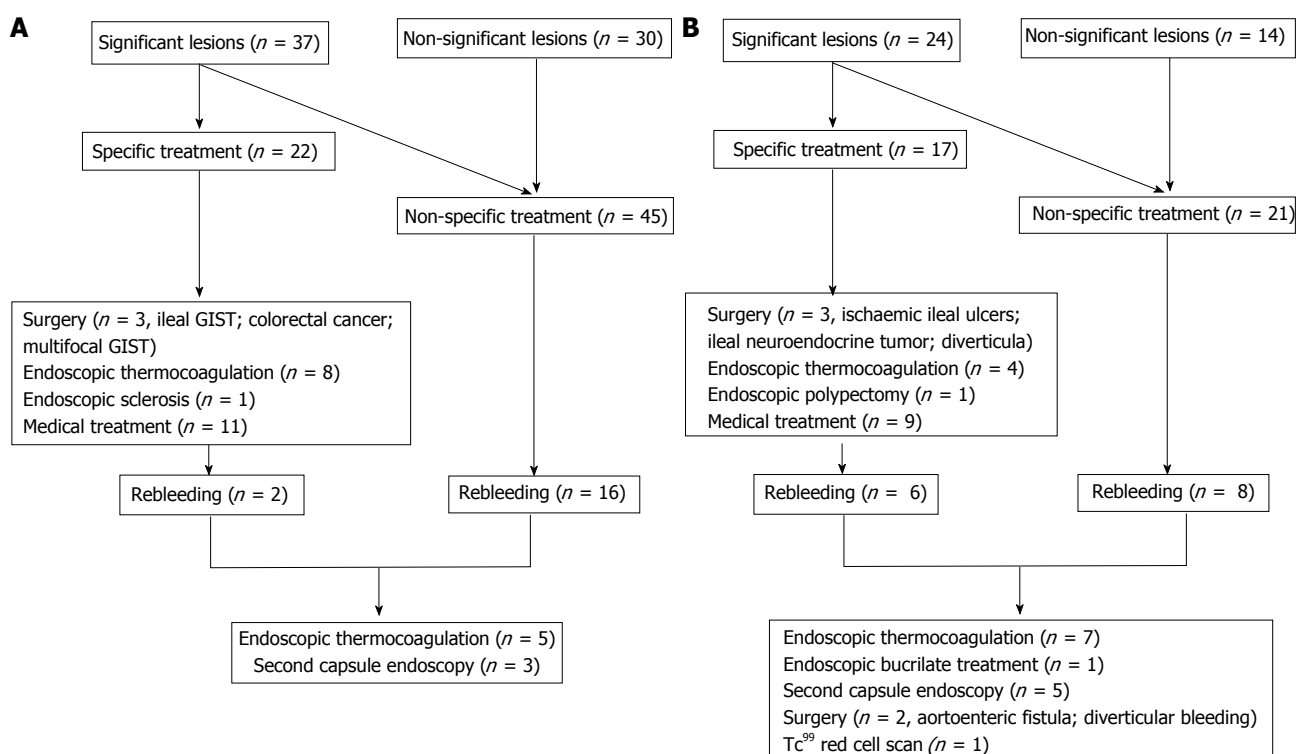


Figure 3 Therapeutic strategy and outcome: occult-obscure gastrointestinal bleeding group (A) and overt-obscure gastrointestinal bleeding group (B).

6.9 d (95%CI: 8.5-5.3), $P = 0.06$, respectively].

Therapeutic strategy

Therapeutic strategy after CE and outcome according to OGIB presentation and CE findings are detailed in Figure 3. Specific treatment was performed in 39 patients (37.5%): surgery ($n = 6$), endoscopic therapy with thermocoagulation or sclerosis ($n = 13$) and specific medical treatment ($n = 21$). Up to 87% of patients with significant lesions in CE received specific treatment. NSAIDs were withdrawn in 22 patients (21%): 9 of them with small bowel ulcers and 13 with normal capsule or non-

significant lesions.

Outcome

Overall follow-up time was 321 d (IQR 115-626). In the cohort, 73 patients (69.5%) had a favorable outcome according to the definition and hemoglobin levels improved significantly [Δ Hb 4.4 (95%CI: 5.0-3.9) g/dL, $P < 0.001$]. Surgery was curative in 100% of patients ($n = 6$). Endoscopic therapies ($n = 13$) such as thermocoagulation, sclerosis or polypectomy had a resolution rate of 61.5%.

There were 32 patients (30.8%) who had a recurrence of OGIB, in a median time of 157 d (IQR 81-326) af-

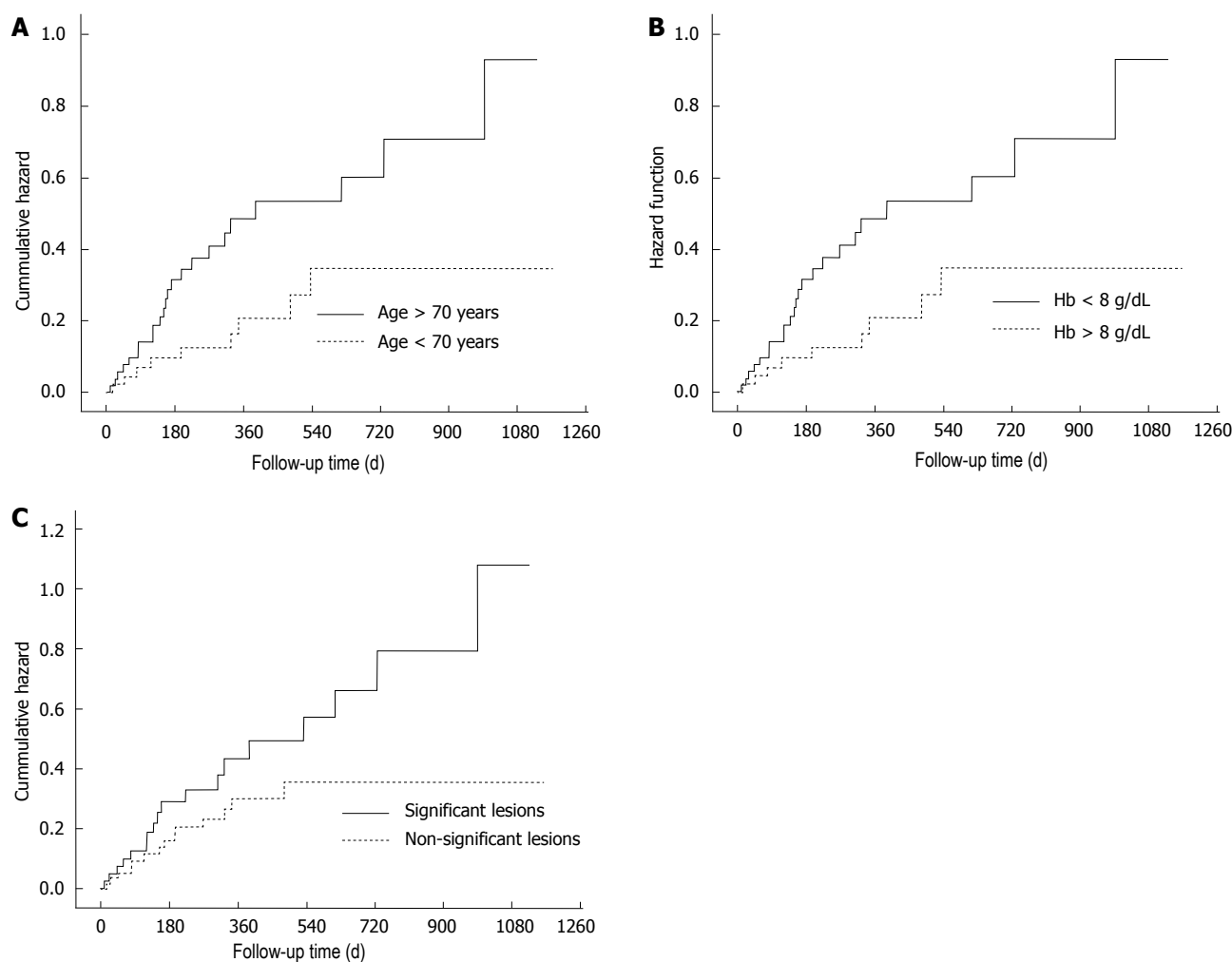


Figure 4 Hazard plots: Age (A), hemoglobin levels level (B) and significant lesions in capsule endoscopy (C). Hb: Hemoglobin.

ter the index episode. Rebleeding rates were 20.5% and 36.4%, depending on specific and non-specific treatment ($P = 0.8$).

In 8 of the 32 patients, a second-look capsule endoscopy was performed, which enabled the diagnosis of angiodysplasias in two patients with a previously normal CE. After rebleeding, specific treatment was performed on 15 of the 32 patients (46.8%): 12 endoscopic thermo-coagulation, one bucrylate injection and two surgeries.

In order to elucidate factors associated with a higher risk of rebleeding, univariate and multivariate analysis were performed. Association analysis is detailed in Table 2 and hazard plots are represented in Figure 4. In this study, Hb levels lower than 8 g/dL at diagnosis (HR = 2.7, 95%CI: 1.9-6.3), patients older than 70 years of age (HR = 2.1, 95%CI: 1.2-6.1) and significant findings in CE (HR = 2.4, 95%CI: 1.1-5.8) were independent predictors of rebleeding. The analysis depending on the type of lesion did not show differences. However, angiodysplasia was the lesion that rebled more frequently (8/32 patients, 25%). Moreover, angiodysplasia was diagnosed after rebleeding in another eight of the 32 patients (25%), whose cause of OGIB was different or unknown after the CE

in the index episode.

DISCUSSION

Diagnostic work-up and treatment of OGIB is an important challenge for gastroenterologists. Obscure gastrointestinal bleeding is the first accepted indication for capsule endoscopy and there are several diagnostic algorithms proposed by different medical societies^[1,6,7]. In the present study of 105 patients with OGIB, a high diagnostic yield of CE in patients with occult-OGIB and overt-OGIB is described.

Optimal bowel preparation is essential to improve CE diagnostic yield^[8] and a two liter, polyethylene glycol-based solution ingested the day before CE permitted adequate bowel visualization in almost all patients. Several studies have already shown the superiority of CE compared to other techniques^[5,9]. In this cohort, a diagnostic yield of 58.1% was observed, which is concordant with published data^[10-16]. However, differences between obscure-overt bleeding and obscure-occult bleeding^[17,18] were not observed. The time between the acute bleeding episodes and CE has been analyzed in previous stud-

Table 2 Risk factors for rebleeding

Risk factors	Univariate Log-rank test	Multivariate		
	P	HR	95%CI	P
Age > 70 yr	0.037	2.1	1.2-6.1	0.05
Gender	0.800	-	-	-
Overt OGIB presentation	0.130	-	-	-
Hb < 8.0 g/dL	0.027	2.7	1.9-6.3	0.03
Blood units transfused	0.180	-	-	-
Transfusions requirement	0.020	-	-	-
T ≥ 2 blood units	0.023	-	-	-
NSAID intake	0.900	-	-	-
Significant lesions in CE	0.036	2.4	1.1-5.8	0.01
Specific treatment carried out	0.500	-	-	-

OGIB: Obscure gastrointestinal bleeding; CE: Capsule endoscopy; NSAID: Non steroidal anti-inflammatory drugs; Hb: Hemoglobin; HR: Hazard ratios.

ies, showing that the diagnostic yield would be higher in ongoing bleeding cases if CE were performed within the first 48 h^[12,19,20], although this factor does not seem to influence the diagnostic yield in this study.

As has been previously described, the most frequent findings in capsule studies were angiodysplasia and intestinal ulcers^[12,21,22]. In seven patients (6.6%), CE diagnosed lesions in the upper-GI tract that were not seen in previous upper-GIE. These results suggest that the repetition of upper- or lower-GIE prior to a CE could be useful in diagnosing accessible lesions by conventional endoscopy^[20].

A favorable outcome after CE, reaching bleeding resolution, was observed in two-thirds of patients in this study. Capsule retention occurred in 1.9% of patients, which is consistent with previously published data^[23].

The diagnostic and therapeutic work-up were based on CE results in our series: patients with significant lesions received specific treatment more frequently compared with those who had no lesions or non-significant lesions. Nevertheless, this treatment was not associated with a higher resolution rate (20.5% *vs* 36.4% of rebleeding after specific or non specific treatment, $P = 0.8$, respectively). These results may have several explanations. Firstly, despite not finding differences according to the kind of lesions and risk of rebleeding, the lesion that most frequently rebled was angiodysplasia. Secondly, angiodysplasia often has a multifocal nature and it has a high rate of rebleeding, even when patients are treated by an endoscopy^[14,24].

Moreover, special attention is required in patients treated with NSAIDs and antiplatelet drugs. It is well established that a high percentage of NSAID consumers may present small bowel erosions or ulcers in CE^[25]. In this study's cohort, the use of NSAIDs was stopped in 22 patients after CE findings and 14 of them (14/22, 63.6%) achieved a resolution of the bleeding. However, in eight of these patients, CE findings were non-significant. It is important to remark that an accurate anamnesis regarding NSAID intake is important and its withdrawal should be individually evaluated.

In this study's cohort, one-third of patients presented with rebleeding episodes during follow-up. Hemoglobin levels lower than 8 g/dL at diagnosis, patients older than 70 years of age, and significant findings in CE were independent predictors of rebleeding, as has been described in previous papers^[20,26]. So far, the role of CE findings as a rebleeding risk factor remains controversial. Macdonald *et al*^[27] described a higher rebleeding rate in patients with significant lesions, although no regression analysis was performed in that study^[27]. On the contrary, Park *et al*^[28] did not find significant differences in the cumulative rebleeding rate between significant and non-significant findings in the CE. Type of lesion was not a predictor of rebleeding, probably due to stratification and the low number of relapses. However, nearly 50% of patients that presented with rebleeding had a final diagnosis of angiodysplasia in CE. Interestingly, second-look CE or conventional endoscopy after rebleeding revealed angiodysplasia not found in previous procedures, underlining the usefulness of a second-look CE in selected patients, as has been published before^[29,30].

The main limitation of this study is that it is a retrospective design. However, data were collected from electronic charts that permitted accuracy in terms of in-hospital and outpatient data, reducing data collection bias. Strengths of the study were the long follow-up that allowed the outcome to be evaluated and the regression analysis of rebleeding risk factors.

In conclusion, this study offers a long follow-up of a large, clinical based, cohort from a single tertiary hospital. Diagnostic yield of CE was high in both OGIB presentations. One-third of the patients presented with rebleeding after CE; risk factors of rebleeding were Hb < 8 g/dL, age ≥ 70 years or the presence of significant lesions in CE.

COMMENTS

Background

Capsule endoscopy (CE) is a device that allows visualization of the entire small bowel mucosa. It has become essential in the diagnosis work-up of gut pathologies, especially evaluation of obscure gastrointestinal bleeding (OGIB). Although published studies are focused on diagnostic yield of CE, outcome of patients that undergo a CE has not been analyzed extensively.

Research frontiers

CE is widely used in OGIB diagnosis. However, reports about patient outcomes presenting OGIB that received a CE are rare in the medical literature.

Innovations and breakthroughs

This study analyzed a large group of OGIB patients during a long follow-up time. The authors concluded that CE is useful in different types of OGIB and further treatments permitted the resolution of OGIB in a high proportion of patients. Ulcers and angiodysplasias were the most frequently diagnosed lesions by CE. The authors identified several risk factors of rebleeding: old age, a low hemoglobin level at diagnosis and the presence of significant lesions in the CE.

Applications

CE is safe, well tolerated and useful in the diagnosis of several gastrointestinal disorders. The risk factors described in this study should help physicians in OGIB management.

Terminology

CE is a device a little bit bigger than a pill that can be easily swallowed by patients. It is able to take photos as it passes through the gut that are saved in an external memory disk via wireless technology. Photos are studied later by a

gastroenterologist at a workstation.

Peer review

In this retrospective study, the authors investigated the outcome of obscure gastrointestinal bleeding after capsule endoscopy. They concluded that hemoglobin levels < 8 g/dL at diagnosis, patients > 70 years and significant findings in CE were independent factors of a high rebleeding rate.

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PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy

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Author contributions: All authors participated in the study; Negreanu L designed, wrote the article and made corrections; Sadagurschi R helped with article redaction and corrections.

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with tumors: 4 with colon cancers, 1 with gastric cancer and 1 with a small bowel cancer. The capsule findings were confirmed after surgery in all these patients. The capsule excretion rate in twelve hours was 77% with 54 patients having a complete examination. The rectum was not explored during CCE procedure, in 16 patients (23%, 95%CI: 13.7%-34.1%). Every patient accepted CCE as an alternative exploration tool and 65/70 (93%) agreed to have another future control by CCE. No complications were reported during or after CCE examination.

CONCLUSION: PillCam Colon 2 capsule was effective in detecting significant lesions and might be considered an adequate alternative diagnostic tool in patients unable or unwilling to undergo colonoscopy.

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Key words: Colon cancer; Colonoscopy failure; Colonoscopy refuse; Colon capsule; Pillcam Colon 2

Core tip: This is an important article on the second generation colon capsule endoscopy. It shows that it has a high diagnostic yield in an enriched population that have had incomplete colonoscopy or refused colonoscopy. We also diagnosed significant extracolonic lesions. The method had a high acceptability among patients and we did not encounter any complications.

Abstract

AIM: To assess the feasibility, accuracy and acceptability of PillCam Colon 2 in detection of significant lesions in colorectal cancer risk patients, unable or unwilling to perform colonoscopy.

METHODS: This is a prospective, single center study using the second generation of PillCam Colon capsule. In all patients the readers were instructed to review the entire colon capsule endoscopy (CCE) examination using Rapid 7 software and additionally to note significant extra-colonic findings. Colonic significant findings were described according to European Society of Gastrointestinal Endoscopy guidelines. CCE procedure completion rate, level of bowel preparation and rate of adverse events were assessed.

RESULTS: A total of 70 patients at risk of colorectal cancer were enrolled in the study. In three patients the procedure failed because the capsule was not functioning when entered the colon. PillCam Colon 2 showed positive findings in 23 (34%, 95%CI: 21.6%-44.1%) of the remaining 67 patients. Six patients were diagnosed

Negreanu L, Babiuc R, Bengus A, Sadagurschi R. PillCam Colon 2 capsule in patients unable or unwilling to undergo colonoscopy. *World J Gastrointest Endosc* 2013; 5(11): 559-567 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i11/559.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i11.559>

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer and second most common cause of cancer-related

deaths in Europe. CRC screening has been proven to reduce disease-specific mortality^[1]. The choice of a screening test takes into consideration parameters such as patient age and the presence of different risk factors for the development of CRC. Several European countries employ national screening programs. They rely almost exclusively on stool tests, with colonoscopy used as an adjunct in some countries. Colonoscopy has been shown to reduce colorectal cancer risk. Its increased use in the population aged 50 years and older in the United States since the 1980s is the reason for decreasing CRC incidence rates, particularly in the sigmoid, colon although some environmental factors may also have contributed to the decreasing risk^[2].

A prediction for 2012 expects a decline in mortality from colorectal cancer of 7% in men and 11% in women in the European Union compared with 2007 mainly due to the screening programs^[3].

Nevertheless the uptake of patients in the screening programs is disappointingly low. The degree of acceptance of colonoscopy is low because it is perceived by some patients/physicians as invasive and painful and with a degree of complications/risks. Another drawback is the rate of failed colonoscopic examinations. The caecal intubation failure rate is up to 20% of colonoscopies in clinical practice^[4]. No guideline exists for these patients but several options are being used with different success rates. Computed tomographic colonography (CTC) is a useful option and seems supported by recent studies^[5].

Colon capsule endoscopy (CCE) PillCam Colon was developed by Given Imaging especially for increasing the acceptability and safety of a colorectal examination. Although a bowel preparation similar to colonoscopy is necessary, this technique requires no intubation, insufflation or sedation and has minimal complication rates/risks^[6,7].

A second-generation, improved, CCE system (PillCam Colon 2) was developed to increase sensitivity for colorectal polyp detection compared with the first-generation system. A recent study using a second-generation colon capsule showed a higher sensitivity than the first generation, of almost 90% for detection of patients with significant colonic lesions^[8]. Recently the European Society of Gastrointestinal Endoscopy published an updated and extensive guideline regarding the current status of capsule endoscopy. It gives a clear perspective about the indications, bowel preparation, reporting and level of evidence^[9].

According to these guidelines, CCE is feasible and safe and appears to be an accurate screening tool when used in average-risk individuals. A CCE based screening may be cost-effective if it increases uptake compared with colonoscopy. In high risk patients (alarm symptoms or signs, family or personal history of CRC), which are at increased risk of advanced colorectal neoplasia or cancer, colonoscopy should be the first choice. However, in patients for whom colonoscopy is inappropriate or not possible, the use of CCE could be discussed with the patient^[9].

Study aim

We conducted a pilot trial to assess the feasibility, accuracy and acceptability of PillCam Colon 2 in detection of significant lesions in patients at risk of CRC which were unable or unwilling to perform colonoscopy. Following recent European Society of Gastrointestinal Endoscopy (ESGE) capsule endoscopy guideline, a significant colorectal lesion that requires colonoscopy follow-up was considered to be a colorectal polyp > 6 mm or presence of at least 3 colonic polyps^[9].

End points

Since we could not compare colon capsule endoscopy CCE to the gold standard (colonoscopy) we introduced a new end point of “positive” examination: the diagnostic utility index (findings directly explaining symptoms or requiring specific treatment in asymptomatic patients). Although using this end point even a normal examination can be considered successful for a certain patient if it is important for the clinical decision and follow up, we decided to consider significant the capsule findings that required medical or surgical treatment. Also a patient follow up of one year was mandatory. CCE procedure completion rate level of bowel preparation and rate of adverse events were also assessed.

MATERIALS AND METHODS

Patients

A total of 70 patients of mean age 58.3 years (range 29 to 87) were enrolled in this prospective, single center study.

Indications

Inclusion criteria were as follows: (1) patients at risk for CRC unable to undergo the colonoscopic examination because of the anesthetic risk and co-morbidities; (2) patients at risk for CRC who refused colonoscopy.

We considered as patients at risk for CRC, patients with personal or family history of adenomas or colorectal cancer, but also with digestive symptoms such as bleeding, recent bowel habits change, weight loss, anemia, abdominal pain, positive fecal occult blood test and suspect imaging-abdominal ultrasound, computed tomography (CT)/positron emission CT scan were included in the study.

Majority of patients unwilling to undergo the colonoscopic examination have had a negative experience with a prior colonoscopy (either an incomplete or failed colonoscopy because of the abdominal discomfort). The PillCam Colon 2 examination was proposed as an alternative tool to explore the colon to these patients. Exclusion criteria comprised: (1) patients with pacemakers; (2) patients with suspected digestive stenosis or intestinal occlusion; and (3) patients with dysphagia or swallowing disorders.

Ethical considerations

The study was approved by the Ethics Committee of the University Hospital of Bucharest and patients signed

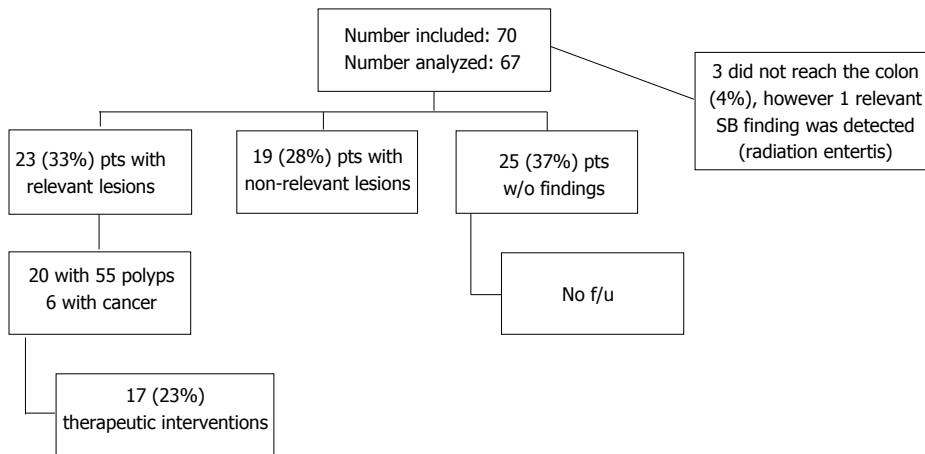


Figure 1 In all patients the readers were instructed to review the entire colon capsule endoscopy examination and additionally significant extra-colonic findings. All patients had at least one year follow up. The case no f/u will disappear.

an informed consent for the investigation. Enrollment started in February 2011.

PillCam Colon 2 procedure

The second generation PillCam Colon 2 capsule and Rapid reader 7 software were used in this study. The PillCam Colon 2 capsule is slightly longer than the previous generation with 11.6 mm × 31.5 mm in size. It has been designed to work for at least 10 h and it has a variable frame rate (from 4 to 35 frames/second in order to correctly visualize the mucosa when accelerated peristalsis). The angle of view was increased to 172 degrees in both capsule lenses, thus covering almost 360 degrees of the colonic surface. A new smaller and more ergonomic data recorder with a liquid crystal display allowing real time viewing was developed. It permits a bidirectional communication with the capsule and also is friendlier and easier to use by the patient providing automatic visual and audio signals for procedure activities (boost administration).

All the investigators reading the capsule videos had extensive experience in digestive endoscopy and they had previous experience using the small-bowel capsule. Before the study start a training session was organized by Given Imaging. This 2-d training session included several hours of sessions addressing different issues as preparation, procedure and software utilization. It was followed by a self-assessment test consisting of reading ten colon capsule videos. The first three examinations in the study were performed under supervision from Given Imaging.

Colon preparation and cleanliness estimation

Participating patients received written and oral explanations of colonic preparation details. The preparation consisted in a low-residue diet starting 48 h before investigation and a clear liquid diet 24 h before ingestion. A 4 L of split-dose polyethylene glycol (PEG) Fortrans® (Macrogol 4000, Ibsen, France) prep was administered in the evening and 2 h prior to capsule ingestion. Since in Romania oral sodium phosphate is not available, PEG was used as booster. Upon capsule exit from the stomach

a first liter of PEG was administered and a second boost of one liter of PEG was administered if the capsule was not excreted 3 h after the first one.

Colon cleanliness was graded using a two point scale. This scale was a development of the original 4-point scale used in previous studies and grades preparation as inadequate (poor or fair on the 4-point scale) or adequate (good or excellent on the 4-point scale)^[10]. The cleanliness was assessed in each of the five colon segments (cecum, right colon, transverse, left colon and rectum) and then a general estimate of the entire colon was made.

RESULTS

In all patients the readers were instructed to review the entire CCE examination and additionally significant extra-colonic findings (Figure 1).

Indications

The main indication for initial colonoscopy or for the otherwise contraindicated/refused colonoscopy had been: 35 symptomatic patients (abnormal transit 8, abdominal pain 4, anemia or overt bleeding 22, weight loss 1), 29 average and high risk colorectal cancer screening patients (familial 21 or personal history of polyps or cancer 5, acromegaly 1, long standing inflammatory bowel disease 1, screening 1) and 6 patients with abnormal imaging or tumor markers. The indications for referral of the patients are detailed in the Table 1.

The indication of capsule examination was: refusal of a colonoscopy in 37 patients, previous incomplete colonoscopy (mostly technical failures of initial colonoscopy) in 30 patients or unable to perform colonoscopy (the examination risks-cardiovascular or anesthetic were considered excessive by their own physicians) in 3 patients.

Findings

In three patients the procedure failed because the capsule was not functioning when it entered the colon. In the remaining 67 patients a significant diagnosis was made

Table 1 The main indication for initial colonoscopy or for the otherwise contraindicated/refused colonoscopy, the indications for referral of the patients

Patient	Sex	Age	Reason	Indication for CCE	Findings	Completion	Preparation
1	Female	85	Suspect CT	Refuse	3 pedunculated polyps in the descending colon 7-9 mm, voluminous diverticula in the sigmoid	c	a
2	Female	45	Transit troubles (diarrhea), family history	Failure	Diverticula	c	a
3	Male	76	Anemia	Failure	3 polyps 3-8 mm left colon	c	a
4	Male	39	Family history	Refuse	4 polyps 3-8 mm left colon	c	a
5	Male	52	Personal history of colorectal polyps	Refuse	4 polyps 4-8 mm left colon	c	a
6	Male	60	Abdominal pain weight loss	Failure	6 mm polyp cecum	c	a
7	Female	69	Transit troubles	Refuse	6 mm polyp right colon, diverticula	c	a
8	Female	57	Personal history of polyps	Failure	6 polyps 3-5 mm 2 transverse 4 left colon, diverticula	c	a
9	Male	80	Anemia severe, weight loss	Failure	Angiomas	c	a
10	Male	53	Transit troubles	Refuse	Diverticula	c	a
11	Female	61	Family history	Failure	Diverticula	c	a
12	Female	58	Transit troubles (diarrhea)	Refuse	Diverticula	c	a
13	Male	54	Family history (mother, aunt and uncle with CRC)	Refuse	Diverticula	c	a
14	Female	65	Abdominal pain history of resected transverse cancer history of urinary bladder cancer	Failure	Diverticula	c	a
15	Male	39	Family history	Refuse	Diverticula	c	a
16	Female	56	Family history (father with CC at 82) polyps	Refuse	Diverticula	c	a
17	Male	58	Personal history of cancer, colectomy	Refuse	Diverticula	c	a
18	Male	31	Family history (father CRC at 46)	Refuse	Diverticula	c	na
19	Male	62	Screening	Failure	Diverticula peridiverticular inflammation small erosion on the IC valve 3 mm polyp in the cecum	c	a
20	Male	69	Anemia weight loss	Refuse	Diverticula polyp 5 mm in the descendent colon internal hemorrhoids	c	a
21	Female	49	Transit troubles	Refuse	Diverticula small polyp 3 mm left colon some petechiae on the descendent colon	c	na
22	Male	75	Transit troubles	Failure	Diverticula, 16 mm ulcerated submucosal mass in the sigmoid	c	a
23	Male	59	Family history	Refuse	Diverticula, 4 mm polyp sessile left colon	c	na
24	Male	64	Family history CRC resection of polyps	Failure	Normal	c	a
25	Female	60	Family history (mother with rectal cancer)	Refuse	Normal	c	a
26	Female	55	Suspect mass on CT	Refuse	Normal	c	a
27	Female	77	Anemia	Failure	Normal	c	a
28	Male	64	Anemia weight loss	Failure	Normal	c	a
29	Female	60	Family history	Refuse	Normal	c	a
30	Female	56	Transit troubles	Refuse	Normal	c	a
31	male	36	Family history, transit troubles	Refuse	Normal	c	a
32	Female	39	Family history	Failure	Normal	c	a
33	Female	29	Anemia, grandmother with colon cancer constipation	Refuse	Normal	c	a
34	Female	44	Anemia	Refuse	Normal	c	a
35	Male	59	Family history (colorectal cancer in the mother at early age) abdominal pain	Failure	Normal	c	a
36	Female	39	Acromegaly	Refuse	Normal	c	a
37	Female	42	Tumoral markers	Failure	Normal	c	a
38	Female	59	Anemia weight loss diarrhea suspect CT	Cardiologist choice	Normal	c	a
39	Female	49	Abdominal pain	Refuse	Normal	c	a
40	Male	59	Transit troubles (diarrhea), family history	Refuse	Normal	c	na
41	Male	42	Family history	Refuse	Normal	c	na
42	Male	51	Family history	Failure	Normal	c	na
43	Female	43	suspect pet scan, ovarian cancer	Failure	Normal	c	na
44	Male	34	Family history (mother and father operated with ccr)	Refuse	Normal	c	na
45	Female	66	Tumoral markers	Failure	Normal	c	na
46	Female	65	Family history	Failure	Normal	c	na

47	Male	68	Bleeding, personal history of polyps	Refuse	Normal	c	na
48	Female	65	Personal history (colon resection)	Refuse	Normal resected colon	c	a
49	Female	41	Anemia, fh	Refuse	Polip cecum < 5 mm	c	a
50	Male	65	Long standing uc, renal transplanta- tion	Failure	Ulcerative colitis, pseudopolyps	c	a
51	Female	75	Anemia, suspect ultrasound exam	Refuse	Small bowel tumor 22 × 22 mm, 6 mm polyp descending	c	a
52	Female	56	Anemia weight loss	Failure	Ulcerated tumor in the cecum	c	a
53	Female	65	Anemia	Failure	Ulcerated tumor in the cecum	c	a
54	Male	45	Abdominal pain	Refuse	Ulceration on the ileon and ileal valve, Crohn's? diverticula	c	a
55	Female	78	Anemia	Failure	10 right transverse polyps 4-9 mm, angiomas, left side not seen, diverticula	i	na
56	Female	45	Family history	Failure	13 mm pedunculated polyp transverse colon, diver- ticula	i	na
57	Male	77	Anemia weight loss	cardiolo- gist Choice	3 polyps 10 mm and 5 and 4 mm left colon	i	na
58	Female	68	Family history	Failure	3 polyps 3-4 mm left colon,diverticula	i	na
59	Female	84	Personal history (hemicolectomy for right sided cancer)	Failure	4 polyps 5-7 mm left colon	i	a
60	Female	76	Family history of CRC (mother and brother)	Refuse	7 mm polyp on the ileo-caecal valve; caecal angiodys- plasia; multiple diverticula in the right and left colon	i	a
61	Female	87	Suspect CT and barium enema	Failure	Angiomatosis	i	a
62	Male	52	Bleeding, hematochezia	Refuse	Diverticula	i	na
63	Male	58	Anemia, suspect ct, personal and family history	Failure	gastric cancer, 5 polyps 3-4 mm left side, diverticula	i	a
64	Male	75	Weight loss	Refuse	Normal but cancer discovered after 3 mo	i	na
65	Male	73	Anemia weight loss	Refuse	Diverticula battery depleted	I battery	na
66	Female	61	Anemia	Refuse	Cancer	Impaction on cancer	a
67	Male	38	Anemia	Failure	Cancer two tumors	Impaction on cancer	na
68	Female	61	Anemia, weight loss, diarrhea	Failure	Impaction on radiation enteritis stenosis	Impaction on radiation enteritis	
69	Male	60	Family history	Refuse	Impaction	Retention gastric	
70	Male	65	Anemia melena, Normal endoscopy	Cardiolo- gist choice	Impaction	Retention small bowel	

a: Adequate; na: Non-adequate; c: Complete; i: Incomplete; CRC: Colorectal cancer; CCE: Colon capsule endoscopy; CT: Computed tomography.

in 23 (34%, 95%CI: 21.6%-44.1%). The significant lesions reported were: polyps > 6 mm in five patients, ≥ 3 polyps in 10 patients, multiple colonic angiomas in 2 patients, colon cancer in 4 patients, other digestive cancers in 2 patients, a newly discovered Crohn's disease in 1 patient and radiation enteritis in another. A total of 19 patients had insignificant lesions (17 with diverticulosis, 1 with ulcerative colitis and inflammatory pseudopolyps and 1 with a < 6 mm polyp).

Twenty five patients had no findings with normal colonic examinations. Fifty-five colonic polyps were identified by CCE in twenty patients. In the 15 patients with polyps over 6 mm or more than 3 polyps we identified 50 polyps with a median size of 5.8 mm (range 3 to 13 mm) and a median number of 3.5 polyp/patient (range 1 to 10), with locations in the right colon (3), transverse colon (13), left colon and rectum (34). We found 5 polyps < 6 mm in five patients (2 polyps located in the right colon and 3 in the left colon).

Four patients had colon tumors detected by CCE: (1) patient with two synchronous lesions in the cecum and ascending colon, (2) patients with ulcerated cecal tumors (Figure 2A and B) and 1 patient with a left angle

stenotic tumor (Figure 2C). Two other digestive tumors were discovered by the CCE examination. In one patient with iron deficiency anemia, suspect CT scan (abdominal mass) and failure of colonoscopy an ulcerated lesion was discovered by capsule in the stomach. An upper endoscopy with biopsies established the diagnosis of undifferentiated gastric cancer (Figure 2D). In another patient with anemia and suspect imaging (mass seen on ultrasound) and refusing a colonoscopy an ulcerated tumor in the small bowel was visualized at capsule (Figure 2E).

In one of the patients with capsule impaction in the small bowel, we made the diagnosis of radiation enteritis which was considered significant. For the other two patients where capsule did not reach the colon while functioning, no significant lesions were described in the examined segments.

Preparation

Bowel cleanliness was reported as adequate (good or excellent) in 48 of cases (72%, 95%CI: 60.8%-82.4%) and inadequate (fair or poor) in 19 cases (28%, 95%CI: 17.6%-39.1%). In the three cases where capsule did not reach the colon we could not analyze the preparation.

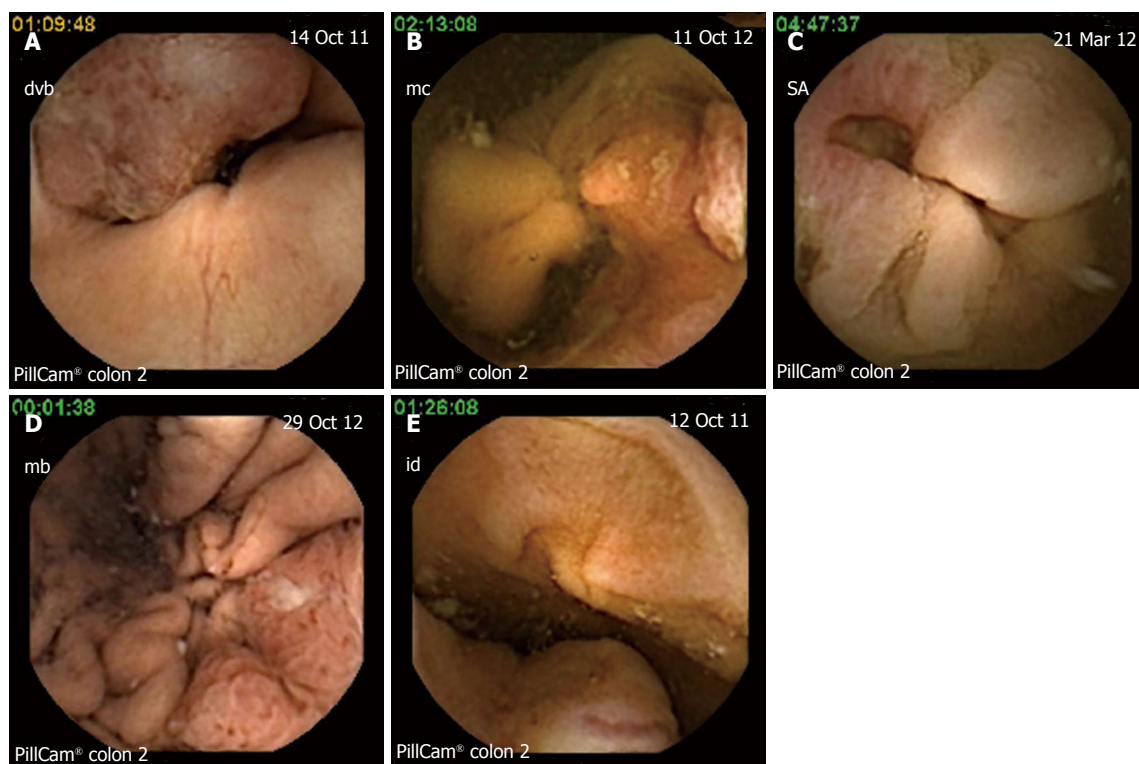


Figure 2 The results of colon capsule endoscopy examination. A: Cecum tumor-transvalvular vue; B: Ulcerated tumor in the cecum; C: Ulcerated stenosis of the left colon angle; D: Gastric cancer; E: Small bowel tumor.

Transit time and capsule egestion

The capsule excretion rate in 12 h was 77% with 54 patients having a complete examination. The median colonic transit time CTT was 189 min (range 3 to 665 min) with important differences between patients. The rectum was not explored during CCE procedure, in 16 patients (23%, 95%CI: 13.7%-34.1%). Of these 16 patients who did not have a complete capsule procedure, in 3 patients (4%) the capsule did not reach the colon at all. In 11 cases recording ceased in the left colon and in 2 it impacted above tumors of the right and left colon angle, respectively. In 9 of these 11 patients the capsule indication was a failure of a previous colonoscopy so we considered having a complete colonic examination.

All patients but two eliminated the capsule in the following 48 h. A true capsule retention (capsules remaining in the digestive tract more than 14 d and extracted during surgical treatment of the lesions) was seen only in 2 patients due to digestive stenosis. First impaction occurred in an ileal stenosis related to radiation enteritis. This patient was referred from another hospital for suspicion of colon cancer in the descending colon after a failed colonoscopy with impossibility to pass the sigmoid. She had no symptoms suggestive of a digestive stenosis or occlusion but a history of irradiation 24 years ago for uterine cancer. The other case was an impaction in a stenotic tumor of the left colonic angle in a patient referred for anemia and transit troubles and refusing colonoscopy. In both patients surgery was decided based on capsule findings and was successful and without complications

and realized in the following month.

We encountered another capsule transient impaction above a tumoral colonic stenosis in a young patient referred for iron deficiency anemia where two lesions of the cecum and right colonic angle were visualized during the examination. The patient eliminated the capsule in the following day. He had surgery after a complete pre operative check up including colonoscopy and CT scan which confirmed the two synchronous lesions. Besides the patient with radicle ileal stenosis, the other two where the capsules did not reach the colon while working, excreted the after 48 h without complications. In one patient with a history of colon cancer in both parents and refusing colonoscopy the capsule remained in the stomach during the entire battery lifetime. He refused an upper endoscopy to push the capsule. He remained asymptomatic during and after capsule passage. The other patient was morbidly obese and confined to bed and the capsule remained in the small bowel until battery depletion.

Follow up, clinical decision and treatment

Seventeen patients (74%) out of the 23 with relevant lesions diagnosed by CCE agreed to have a therapeutic intervention. The 4 patients detected with colon tumors had successful surgery. Only 2 of them had colonoscopies before surgery, for the other 2 patients the surgical indication being decided based single on CCE results. The capsule findings were confirmed after surgery. Diagnosis of adenocarcinoma was established in all cases and the tumor location was similar to the capsule findings.

One patient detected with small bowel tumor had surgery after the CCE and an ulcerated gist was removed. For the gastric ulcerated lesion visualized by capsule, an upper endoscopy with biopsies was realized. After histological confirmation of undifferentiated gastric cancer, the patient had a subtotal gastric resection.

In the two patients with severe iron deficiency anemia and multiple hospitalizations for transfusions and where previous colonoscopies failed, the CCE made the diagnosis of multiple angiomias. Before CCE both patients had extensive check ups including upper endoscopies, failed colonoscopies, CT scans and barium contrast enemas and they have at least three hospitalizations only in our institution. After CCE repeated séances of argon plasma coagulation were realized with a great deal of improvement of their anemia. In order to reach the cecum a single balloon enteroscope was used for one patient and a variable stiffness colonoscope was used for the other. Six patients with relevant lesions which previously denied colonoscopy accepted the examination after a discussion of the CCE results. Colonoscopy confirmed the findings of the CCE and polypectomy was performed in all cases.

In a patient with a suspicion of locally invading cecal tumor on CT scan, the CCE ruled out this diagnosis and showed only three colonic polyps one in the cecum and two in the descending colon. In this case the CCE had an important role in the clinical decision since it ruled out a colonic cancer. After careful examination of the imaging; exploratory laparotomy established a diagnosis of abdominal wall sarcoma was established. She had surgery soon afterwards. No colonoscopy for the three left side polyps was realized. The newly diagnosed Crohn's disease patient had a complete check up and he is currently under immune modulator therapy.

We had one clinical failure revealed by the follow up, 4 mo after CCE. A 76-year-old patient with family history and abnormal transit who refused colonoscopy had an incomplete colon examination by CCE caused by poor visualization due to low compliance to the preparation and the booster regimen. He refused a rectoscopy after CCE. Since he remained symptomatic he agreed to have a rectoscopy which revealed a small ulcerated rectal tumor. This patient had successful surgery after pre operative radiotherapy. Six patients either refused colonoscopy and polypectomy or decided to postpone the procedure. At the moment they are followed up in our center.

Acceptability

The patients included in the study had the indication of a colonoscopy that either failed or was refused. When offered the alternative of having a CCE examination all the 70 patients accepted it, although they were aware that the preparation regimen was more difficult than for a classic colonoscopy. Moreover the examination was subjectively appreciated by all patients as being non invasive and harmless and 65 of them were willing to have the next surveillance exam by CCE.

Adverse events

Capsule ingestion went smoothly in all patients. Although most patients had to ingest a total of six liters of PEG (preparation and boosters) no electrolyte disturbances or adverse effects related to bowel preparation were recorded. No other side effects related to capsule were encountered.

Technical failures

We had one CCE technical failure due to a recorder dysfunction which required another examination.

DISCUSSION

The existing national CRC screening programs are far from perfect due to different issues: lack of a universal screening policy despite recommendations, lack of uniform measures in all countries, cost issues. One major problem is the disappointingly low number of patients accepting the current screening tools. Furthermore is not negligible that a variable proportion (4%-20%) of patients will have an incomplete colonoscopy although the rate of completeness is as high as 97% in expert centers^[4].

After an incomplete examination with a standard adult colonoscope different approaches are available: variable stiffness colonoscope, use of gastroscope, single or double balloon enteroscopy (available in some centers). Changing the centre or the endoscopist is an alternative. However a first failed colonoscopy is significantly associated with a lower cecal intubation rate at further attempts, particularly when stopped in the sigmoid colon^[4].

Radiological procedures have been tested and they are proposed as a potential screening test in the average risk population^[11], for high risk patients' colonoscopy remaining the first option. For patients with colonoscopy failure or contraindication, radiological imaging is an option recommended by current guidelines^[11].

The use of double contrast barium enema (DCBE) was disappointing considering the low sensitivity for polypoid lesions and adenomas, when compared to colonoscopy or CTC^[12]. In a recent Italian meta-analysis, DCBE showed statistically lower sensitivity and specificity than CTC for detecting colorectal polyps ≥ 6 mm, and its use as an alternative imaging test is appropriate only when CTC is not available^[12].

Two studies reported varying results using computed CTC after a failed or an incomplete colonoscopy^[13,14], with an estimated sensitivity of 88% for advanced neoplasia ≥ 10 mm. Radiation exposure remains a concern despite the evolution of technique and improvement of examination protocols. The cost effectiveness of a CTC based screening program is debatable as the medical and economic impact of extra colonic findings remains unknown^[15]. We could not make a direct comparison in our population of patients, since CTC is not reimbursed by the Romanian health system and its availability is very

limited. The current ESGE capsule endoscopy guidelines take into consideration the utilization of CCE after failure or refuse of colonoscopy. According to these guidelines, CCE is feasible and safe and appears to be accurate when used in average-risk individuals and in high risk patients for whom colonoscopy is inappropriate or not possible. For these patients the use of CCE could be an alternative^[9].

We report the Pillcam Colon 2 use in high risk patients unwilling or unable to perform colonoscopy. Therefore we lack the comparison with colonoscopy which is the gold standard. The introduction of diagnostic utility index and the careful follow-up of the patients partially solved this issue. Clinical significant lesions were seen by Pillcam Colon 2 in 23 patients out of 67 analyzed (34%) CCE had a high clinical impact as endoscopic or surgical treatment was proposed in all these cases based on capsule results and seventeen patients (74%) of the 23 with relevant lesions agreed to and had a therapeutic intervention (Figure 1).

Complete colorectal examination was realized by CCE in 54 patients (77%, 95%CI: 67.3%-86.94%). The rate of complete examinations observed in our group is lower than in the study of Spada *et al*^[8] of 88% but much like the findings of Eliakim *et al*^[6] who reported a capsule egestion rate of 74% in their first generation capsule study. Several factors may have influenced the progression rate: in the absence of classic sodium phosphate boosters unavailable on the local market, the use of Macrogol as a booster has been a factor affecting the transit times. Also our study population included patients with previous difficult colonoscopies or with various co-morbidities and bed confined patients. The presence of fixed sigmoid loops in patients with previous colonoscopy failure might have contributed to slow transit times. Also in three patients with incomplete CCE examination, this was due to impaction over significant lesions (one post-radic stenosis and two cancers) during the procedure. Compared with CTC, CCE has the intrinsic advantage of directly visualizing the colonic mucosa. This may be very important as clinically relevant lesions like angiectasias or flat adenomas are missed by CTC and are easily visible in capsule endoscopy. This is confirmed in our study where capsule endoscopy established the definitive diagnosis of multiple angiomas in two patients who had previous CT scans and barium enemas in several occasions.

In a recently published multicenter (17 hospitals and private practices) study using first generation Pillcam Colon 1 in patients with failure or contraindications to colonoscopy, the CCE showed positive findings in 36 patients out of 107 analyzed (diagnostic yield 33.6%). The Pillcam Colon 1 was considered as having a high clinical impact as in 21% of patients a medical or surgical treatment was proposed. In this study the colon examination by CCE was complete in 83.2% of cases^[16]. Our results are comparable. However it is a single center study with a different study design. Also the classical boosts with sodium phosphate were not available for our population

leading to the lower excretion rates.

In our study the acceptability of the examination by CCE was extremely high. All patients with a previous failed colonoscopy proposed to take part in the study accepted the CCE examination. The method was perceived as non invasive and harmless by all patients. Moreover the vast majority of patients with significant findings, either failure or refusal of a colonoscopy, agreed to perform a therapeutic gesture (implying colonoscopy) after the discussion of the CCE findings.

The PillCam Colon 2 appears to be effective for the detection of clinically relevant lesions with great acceptability rate, and it might be considered as a useful tool for colorectal imaging in patients unable or unwilling to undergo colonoscopy. Further studies are necessary to validate the best approach to these patients.

The Given Imaging Research Grant supports innovative, original research in Gastroenterology with substantial involvement of capsule endoscopy and is awarded yearly by the European Society of Gastrointestinal Endoscopy. The project "Role of PillCam Colon 2 capsule in patients at risk of CRC unable or unwilling to perform colonoscopy" was awarded with the 2010 grant. The study design, data analysis, results and conclusions of the article are exclusively the investigators work. Given Imaging supported the study, by donating the capsules and loan of equipment.

COMMENTS

Background

There is growing evidence that colon capsule endoscopy is a reliable and well tolerated diagnostic method. A lot of technical improvements were made to the capsule endoscopy, including a second generation, more performant, colon capsule.

Research frontiers

Since the introduction of the second generation Pillcam Colon 2 very few studies addressed its use after colonoscopy failure or refusal.

Innovations and breakthroughs

This is a 70 patients' pilot study using the second generation of PillCam Colon capsule endoscopy to detect colon cancers as well as other tumors in the gastrointestinal (GI) tract. They included a heterogeneous population at risk of colorectal cancer that either failed or refused colonoscopy. This study indicated that PillCam Colon 2 capsule endoscopy is feasible and of high acceptance by patients.

Applications

This study suggests that PillCam colon 2 capsule endoscopy may eventually used for population-wide colon cancer screening, although more cost effectiveness studies are needed.

Terminology

Pillcam Colon 2 capsule has 11.6 mm × 31.5 mm in size and has been designed to work for at least 10 h with a variable frame rate (from 4 to 35 frames/second in order to correctly visualize the mucosa when accelerated peristalsis). The angle of view was increased to 172 degrees in both capsule lenses, thus covering almost 360 degrees of the colonic surface.

Peer review

This is an interesting manuscript describing a pilot lot study using the second generation of PillCam capsule endoscopy to detect colon cancers as well as other tumors in the GI tract. Although case controlled studies are ultimately needed to demonstrate the sensitivity and specificity of PillCam capsule endoscopy, this pilot study indicated that PillCam capsule endoscopy is feasible and of high acceptance by patients. This study suggests that PillCam capsule endoscopy may eventually used for population-wide colon cancer screening. This

is a descriptive paper on a new generation colon capsule. Since no comparison with the gold standard technique (colonoscopy) is made specificity and sensitivity of the method could not be assessed. One important point is that lesions outside the colon were found and this point should be underlined.

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A modified Rendezvous ERCP technique in duodenal diverticulum

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Abstract

AIM: To postoperative endoscopic retrograde cholangiopancreatography (ERCP) failure, we describe a modified Rendezvous technique for an ERCP in patients operated on for common bile duct stone (CBDS) having a T-tube with retained CBDSSs.

METHODS: Five cases operated on for CBDSSs and having retained stones with a T-tube were referred from other hospitals located in or around Istanbul city to the ERCP unit at the Haydarpasa Numune Education and Research Hospital. Under sedation anesthesia, a sterile guide-wire was inserted *via* the T-tube into the common bile duct (CBD) then to the papilla. A guide-wire was held by a loop snare and removed through the mouth. The guide-wire was inserted into the sphincterotome *via* the duodenoscope from the tip to the handle. The duodenoscope was inserted down to the duodenum with a sphincterotome and a guide-wire in the working channel. With the guidance of a guide-wire, the ERCP and sphincterotomy were suc-

cessfully performed, the guide-wire was removed from the T-tube, the stones were removed and the CBD was reexamined for retained stones by contrast.

RESULTS: An ERCP can be used either preoperatively or postoperatively. Although the success rate in an isolated ERCP treatment ranges from up to 87%-97%, 5%-10% of the patients require two or more ERCP treatments. If a secondary ERCP fails, the clinicians must be ready for a laparoscopic or open exploration. A duodenal diverticulum is one of the most common failures in an ERCP, especially in patients with an intradiverticular papilla. For this small group of patients, an antegrade cannulation *via* a T-tube can improve the success rate up to nearly 100%.

CONCLUSION: The modified Rendezvous technique is a very easy method and increases the success of postoperative ERCP, especially in patients with large duodenal diverticula and with intradiverticular papilla.

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Key words: Endoscopic retrograde cholangiopancreatography; Retained stones; Antegrade cannulation; Intradiverticular papilla; T-tube

Core tip: A postoperative endoscopic retrograde cholangiopancreatography (ERCP) is used as a treatment modality for common bile duct stone (CBDS) clearance when a laparoscopic common bile duct exploration has failed or retained stones are discovered after an operation. If a secondary ERCP fails, the clinicians must be ready for a laparoscopic or open exploration. Because of this, different techniques are required to exclude surgical intervention. We describe a modified Rendezvous technique for an ERCP in patients operated on for CBDSSs having a T-tube with retained CBDSSs and with intradiverticular papilla. The modified Rendezvous tech-

nique is a very easy method and increases the success of postoperative ERCP, especially in patients with large duodenal diverticula and with intradiverticular papilla.

Odabasi M, Yildiz MK, Abuoglu HH, Eris C, Ozkan E, Gunay E, Aktekin A, Muftuoglu MAT. A modified Rendezvous ERCP technique in duodenal diverticulum. *World J Gastrointest Endosc* 2013; 5(11): 568-573 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i11/568.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i11.568>

INTRODUCTION

Common bile duct stones (CBDs) can precipitate a variety of clinical events such as biliary colic, jaundice, and sepsis. In the treatment of this condition, stone removal is the primary intervention for dealing with clinical symptoms. The treatment options are an endoscopic retrograde cholangiopancreatography (ERCP) with endoscopic sphincterotomy (ES) and a laparoscopic or open surgical intervention^[1].

Postoperative ERCP is used as a treatment modality for CBDs clearance when a laparoscopic common bile duct exploration (LCBDE) has failed or retained stones are discovered after an operation (2.5%)^[2]. If a secondary ERCP fails, the clinicians must be ready for a laparoscopic or open exploration. A duodenal diverticulum is one of the most common failures of an ERCP, especially in patients with an intradiverticular papilla^[3]. Because of this condition, we need different techniques to exclude surgical intervention. Percutaneous techniques are used for this purpose. The Rendezvous technique combines an endoscopy with a percutaneous transhepatic cholangiography to facilitate cannulation of the bile duct when previous attempts have failed^[1,4]. We describe a modified Rendezvous technique for an ERCP in patients operated on for CBDs having a T-tube with retained CBDs.

MATERIALS AND METHODS

Five cases operated on for CBDs and having retained stones with a T-tube were referred to the ERCP unit at the Haydarpasa Numune Education and Research Hospital from other hospitals located in or around Istanbul city.

The preoperative findings were unclear because we could not obtain reliable information about the patients' preoperative status. All of the patients had a history of failed ERCP attempts at other ERCP units before surgery; five of these cases had papilla in their duodenal diverticulum. To prevent possible complications associated with a premature extraction of the T-tube, we waited three weeks before it was removed.

Technique

A contrast material was injected *via* the T-tube, and the

stone was observed in the common bile duct (CBD). Under sedation anesthesia with midazolam 3-5 mg and meperidine 30-50 mg by the intravenous route, a sterile guide-wire was inserted *via* the T-tube to the CBD then to the papilla (Figure 1). All of the patients with a diverticulum had a large diverticulum with an intradiverticular papilla. In our cases, the guide-wire was held by a loop snare and removed through the mouth (Figure 2). The sphincterotome was inserted into the working channel. The guide-wire was inserted into the sphincterotome *via* the duodenoscope from the tip to the handle (Figure 3). Subsequently, the duodenoscope was inserted down to the duodenum. Using the guidance of the guide-wire, the ERCP and sphincterotomy were successfully performed, the guide-wire was removed through the mouth, the stones were removed and the CBD was reexamined for retained stones by contrast (Figure 4). The T-tube was removed after 1-2 d because of the possibility of edema at the papilla.

RESULTS

In the time period between August 2009 and March 2012, 5 patients who underwent CBD exploration and who had retained stones with a T-tube were referred to the ERCP unit at our institution.

There were 1 man and 4 women ranging in age from 51 to 78 years with a mean age of 65 years. The patients all had a successful stone removal by a modified rendezvous technique.

The length of the hospital stay was 3.4 d. The T-tubes were removed. The patients were followed up for possible complications of the ERCP and T-tube removal. No morbidity or mortality occurred.

All the patients were followed up regularly through the first postoperative year. There has been no incidence of residual disease, and all the patients who were regularly followed-up have been asymptomatic.

DISCUSSION

An ERCP should be used as a therapy rather than a diagnosis; it should be therapeutic in more than 90% of cases^[5]. An ERCP can be used either preoperatively or postoperatively. Although the success rate in isolated ERCP treatments ranges from 87% to 97%, 5%-10% of patients require two or more ERCP treatments^[6]. This method is associated with morbidity and mortality rates of 15% and 1%, respectively^[7,8]. ERCP is not possible in 3%-10% of all patients^[9]. These patients need laparoscopic or open surgical intervention.

An LCBDE is the treatment of choice in many centers with successful stone clearance rates ranging from 85% to 95%, a morbidity rate of 4%-16% and a mortality rate of approximately 0%-2%^[10,11]. If this fails, alternate approaches such as an intraoperative or postoperative ERCP/EST, laparoscopic choledochotomy,

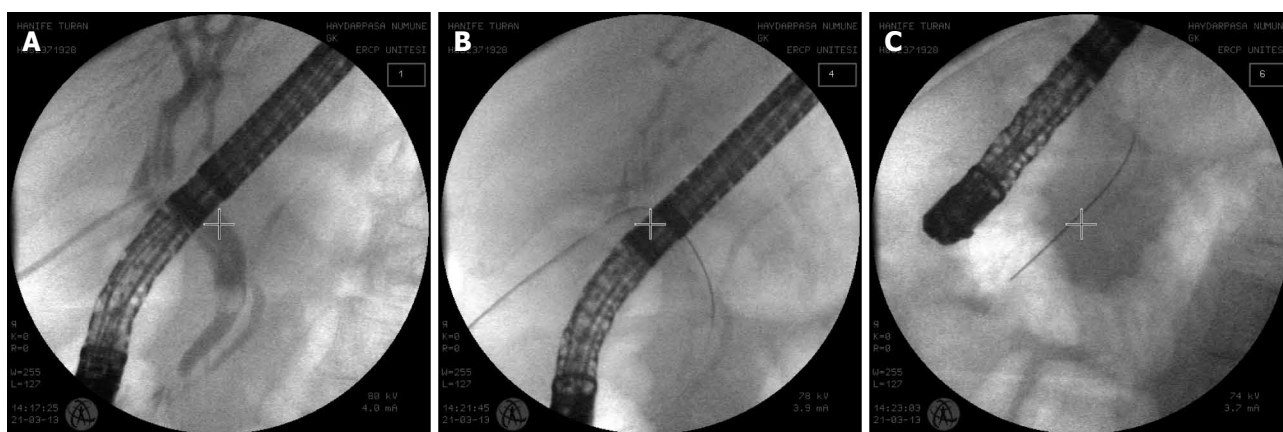


Figure 1 A sterile guide-wire was inserted *via* the T-tube to the common bile duct stone then to the papilla. A: Retained stone with a T-tube in the common bile duct; B: The antegrade insertion of a guide-wire through the T-tube; C: The extension of the guide-wire through the papilla into the duodenum.

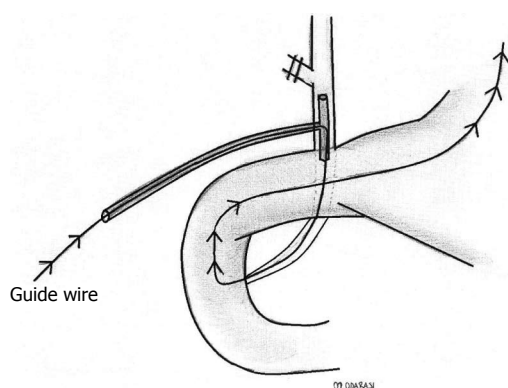


Figure 2 Schematic diagram of a guide-wire.

or open CBDE may be used^[12]. A transcystic approach is generally used for small stones in a small bile duct whereas a transductal approach is preferred for large occluding stones in a large duct, for intrahepatic stones, or a tortuous cystic duct^[9]. If the transcystic approach fails, a laparoscopic choledocholithotomy is recommended. After the stones are removed under endoscopic visualization, the ductotomy is usually closed either primarily or over an appropriately sized T-tube. The indication for a T-tube insertion is a decompression of the duct in patients with a residual distal obstruction, ductal imaging in the postoperative period to provide an access route for the removal of residual CBDs^[13-16]. When an LCBDS and a postoperative ERCP have failed, the surgeon must use the open approach to surgery. In the era of open cholecystectomy, open bile duct surgery was superior to ERCP in achieving CBD stone clearance. In the laparoscopic era, the data are close to excluding a significant difference between the laparoscopic and ERCP clearance of CBD stones. The use of an ERCP necessitates an increased number of procedures per patient^[14].

The routine use of intraoperative cholangiography (IOC) is still controversial. However, it can be a useful tool for identifying choledochal stones^[17]. Supporters of

the IOC routine claim that this practice ensures fewer retained stones, fewer postoperative ERCPs, and a reduction in the number of CBD injuries^[18]. One drawback is the consequent lengthening of the operation time by approximately 15 min^[19].

Although an LCBDE or open surgical explorations are performed, 2.5% of the patients still have retained stones^[2]. Percutaneous transhepatic therapies can be considered for CBDs under US guidance in selected patients^[17]. The extraction of stones, a sphincterotomy, or percutaneous drainage can be performed using this method^[20]. A percutaneous extraction is successful in more than 95% of the patients with retained stones; otherwise a postoperative ERCP can be required^[21].

A T-tube cholangiography should be performed before the removal of the tube (6-18 d postoperatively). The removal of the T-tube has been suggested as early as 5-6 d postoperatively and as late as 4-5 wk after surgery. Retained stones identified by a T-tube cholangiography may be effectively removed percutaneously after allowing for the maturation of the T-tube tract. Although all these techniques have high success rates, there is still a group of patients who need a second surgical intervention because of CBDs. A duodenal diverticulum is one of the most common failures of an ERCP, especially in patients with an intradiverticular papilla^[3]. The prevalence of a duodenal diverticulum is approximately 5% in postmortem studies, but endoscopic evaluations have documented higher rates (5%-23%)^[22]. For this small group of patients, antegrade cannulation *via* a T-tube can raise the success rate up to nearly 100%^[23].

When a selective CBD cannulation cannot be performed by ERCP despite trying various endoscopic techniques, a percutaneous transhepatic biliary drainage (PTBD) followed by a combined rendezvous technique is often successful. This combined technique increases the success rate of the biliary tract cannulation and facilitates the diagnosis and treatment of biliary tract diseases.

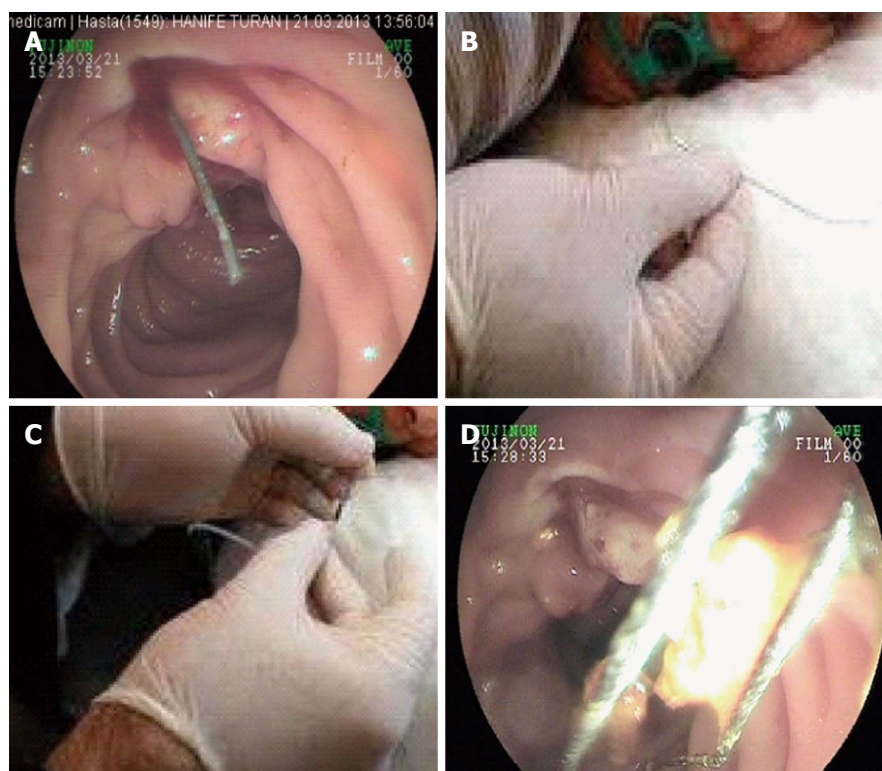


Figure 3 Appearance of the technique. A: A guide-wire through the papilla during an endoscopic sphincterotomy; B: The guide-wire taken out by a snare; C: The guide-wire inserted in the tip of the sphincterotome, which is inserted *via* the endoscope channel of the duodenoscope; D: The stone is extracted by a basket catheter.



Figure 4 Control images of the common bile duct stone after the extraction of the stone.

Antegrade cannulation *via* a T-tube is a modified rendezvous technique described by our ERCP unit. This technique can be performed using sedation anesthesia; this is a very easy technique that increases the success rate and decreases the complications of an ERCP. In this technique, because there is no false insertion of a catheter and a guide-wire to the pancreatic duct, the accidental occurrence of symptoms of pancreatitis is low and, unlike in a normal ERCP, the success rate appears to be higher^[24].

In other Rendezvous techniques, the guide-wire is grasped with a snare or forceps and pulled back through the working channel of the duodenoscope for subse-

quent over the wire cannulation^[25]. However, it is not always easy to grasp the guide-wire, which may be kinked, and its coating can be damaged during the withdrawal through the working channel of the duodenoscope, thus making it difficult, sometimes impossible, to pass a catheter over it^[26].

Although this patient group is small, this technique should be kept in mind. Percutaneous techniques are used worldwide but cannot be applied in all centers, and they require experienced personnel. Even beginners can apply our technique. You can examine the CBD with a contrast material *via* a T-tube. We recommend our technique, especially in cases of an intradiverticular papilla.

In conclusion, the antegrade cannulation of a guide-wire passing *via* a T-tube to the papilla is a very easy method and increases the success rate of postoperative ERCP, especially in patients with large duodenal diverticula with an intradiverticular papilla. Because the number of participants is small, this study must be supported by further studies. We recommend this modified technique for the centers that have an ERCP unit because other techniques are not appropriate for all clinical circumstances in all centers.

COMMENTS

Background

A postoperative endoscopic retrograde cholangiopancreatography (ERCP) is used as a treatment modality for common bile duct stone clearance when a

laparoscopic common bile duct exploration has failed or retained stones are discovered after an operation. If a secondary ERCP fails, the clinicians must be ready for a laparoscopic or open exploration. Because of this condition, the authors need different techniques to exclude surgical intervention. The rendezvous technique combines an endoscopy with a percutaneous transhepatic cholangiography to facilitate the cannulation of the bile duct when previous attempts have failed.

Research frontiers

The antegrade cannulation of a guide-wire passing via a T-tube to the papilla is a very easy method and increases the success of postoperative ERCP, especially in patients with large duodenal diverticula with an intradiverticular papilla.

Innovations and breakthroughs

Antegrade cannulation via a T-tube is a modified rendezvous technique described by our ERCP unit. This technique can be performed under sedation anesthesia, and it is a very easy technique that increases the success rate and decreases the complications of an ERCP. In this technique, because there is no false insertion of a catheter and a guide-wire to the pancreatic duct, the accidental occurrence of the symptoms of pancreatitis is low and, unlike a normal ERCP, the success rate appears to be higher.

Applications

The study recommends the modified technique for centers that have an ERCP unit because other techniques are not appropriate for all clinical circumstances at all centers.

Terminology

Rendezvous technique: The rendezvous technique combines an endoscopy with a percutaneous transhepatic cholangiography to facilitate the cannulation of the bile duct when previous attempts have failed.

Peer review

The concept of this technique seems logical and promising; the study conclusions are based on preliminary experience with a small number of participants. Therefore, caution should be taken in regard to the widespread use of the technique before further studies are pursued.

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Establishing a quality indicator format for endoscopic ultrasound

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evaluated. Quality indicators were evaluated prior to, during, and after performing EUS.

RESULTS: One hundred different EUS procedural reports were analyzed. The mean patient age was 59 years old. Indications for referral were mostly for pancreatic or biliary reasons. QC showed several strongly reported areas, including indications for EUS (97%), anesthesia given (94%), periprocedural pancreatic evaluation (87%), and an overall summary of the EUS examination (82%). Intermediately reported areas included patients' pertinent past medical history (71.7%), evaluation of the biliary tree (63%), and providing medical guidance about potential procedural adverse events, including pancreatitis and bleeding (52%). Half of the reports (50%) did not include a systemic organ evaluation. Other areas, including systematic reporting of screened organs (36%), description of fine needle aspiration (15%), tumor description *via* tumor-node-metastasis (5%), and listing of adverse events (0%) were largely lacking from procedural documentation.

CONCLUSION: Documenting specific EUS quality indicators including listing post-procedural recommendations may improve the quality and efficiency of future EUS examinations and subsequent patient follow-up.

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Key words: Endoscopic ultrasound; Quality indicators; Quality control; Fine needle aspiration; Malignancy

Core tip: Certain key points of quality control have been delineated as quality indicators by American and European Gastrointestinal Societies, which serve to establish and maintain high-quality gastrointestinal minimally invasive procedures and reports, minimize potential adverse events, and to optimize costs, resulting in savings for both hospitals and patients while optimizing patient care in the process. This national quality control study of endoscopic ultrasound (EUS) with expanded international comparison emphasized developing a

Abstract

AIM: To perform a quality control (QC) review of endoscopic ultrasound (EUS) with emphasis on current consensus established quality indicators.

METHODS: A national quality control study of EUS was performed with expanded international comparison. Ten different healthcare institutions in Israel participated in coordination with University of Chicago Medical Center. Each Israeli center provided ten patient reports, compared with twenty reports from University of Chicago Medical Center. Quality indicator forms were prepared with sections to be completed before, during, and after EUS. Physician compliance to all listed indicators was

standardized quality indicator table for EUS and subsequently evaluating physician adherence.

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INTRODUCTION

The advent of computerized documentation and electronic medical records (EMR) allows organized and effective quality control (QC) analysis of gastrointestinal procedures^[1]. The burgeoning costs of medicine have led to pushback efforts, including ensuring that value for cost is being delivered by high-quality examinations^[2]. Several studies have been undertaken by endoscopists have demonstrated the importance of QC in achieving these goals. One example of this effect was demonstrated for colonoscopy. A retrospective study by Imperiali *et al*^[3] in Northern Italy found wide variation in polyp detection rates and in the percent of procedural completion, both of which were significantly increased after offering more colonoscopy training sessions to less experienced endoscopists. As continuous quality control studies have shown to be useful in improving the effectiveness of colonoscopy, one can infer that other endoscopic procedures may be improved in a similar manner. QC analysis for endoscopic ultrasound (EUS)-guided fine needle aspiration (FNA) has also demonstrated several methods of improving the yield of tissue sample aspirates. Among these are simplified recommendations to take more passes from suspected lesions and to use newer flexible 25 gauge needles when attempting to biopsy masses that are very hard in consistency due to desmoplasia. Recent QC of EUS-FNA cytology has determined procedural FNAs to have 94% accuracy in diagnosing malignancy of the upper gastrointestinal tract and surrounding areas, further promoting its worth in medicine's evolving minimally invasive procedures^[4,5]. QC may identify remediable areas of practice for which low-cost solutions might be implementable to increase procedural efficiency.

One way to bolster QC of endoscopic procedures is by establishing quality indicators. Quality indicators are established by expert physicians possessing years of experience operating gastrointestinal endoscopy on a more or less daily basis while taking into account new emerging technology being integrated into gastroenterology. These quality indicators are a compilation of guidelines and/or instructions designed for optimal procedural performance and safety. One procedure in particular studied was colonoscopy, where the investigators emphasized the importance of performing a complete examination including a thorough evaluation of any discovered polyps and adenomas^[6]. In 2000, the American Society for

Gastrointestinal Endoscopy (ASGE) published the first listing of quality indicators for common gastrointestinal procedures, including upper endoscopy and colonoscopy^[7,8], which have also been set forth by the American College of Gastroenterology (ACG). These indicators also served to demonstrate to physicians areas of potential improvement and encourage periodic self-assessment. Therefore, this may lead to improved overall gastrointestinal (GI) procedural quality and efficiency.

Similar to quality improvement in EGD and colonoscopy, QIs also play a valuable role in endoscopic ultrasound. Perhaps as important as measuring the quality of EUS will be the measures found to be useful in raising the quality of less than optimal endoscopy. Although quality measures have been set by multiple well-known organizations including ACG, European Society of Gastrointestinal Endoscopy (ESGE)^[9], and ASGE quality indicator guidelines^[10], few healthcare centers have rigorously applied these guidelines and reported their results. Such an attempt was undertaken by Coe *et al*^[11], who studied adherence of physicians to EUS quality indicators over an eight year period and subsequent improvements in areas of poorer quality. The study's outcome resulted in statistically significant improvement in those areas of EUS found to be weakest by QC. This study aimed to investigate adherence to the aforementioned EUS QI guidelines across various medical centers in Israel along with a cross-sectional international comparison with the University of Chicago. The assessed quality indicators were studied based upon the aforementioned EUS quality indicator table, which allows identification of quantitatively weaker areas that may be remedied in a cost-effective manner to improve EUS performance and documentation. In doing so, this may increase the overall effectiveness of EUS, optimize treatment, and encourage patient follow-up.

MATERIALS AND METHODS

Data evaluation

A quality indicator table was assembled that emphasized important factors compiled after thorough literature review. The table was modeled after quality indicators presented by the various relevant societies including ASGE, ACG, ESGE quality indicators for EUS.

Population

Fifteen different healthcare centers in Israel that perform routine EUS examinations were asked to participate in this study. Each center was requested to send ten randomized consecutive EUS reports which would be evaluated for purposes of this research. Ten of these healthcare centers agreed to participate in this study which accumulated one hundred total reports. Twenty additional reports were sent in cooperation of the University of Chicago gastrointestinal department. Thus, this study represents a national cross-sectional assessment of EUS QIs with expanded international comparison.

Table 1 Endoscopic ultrasound quality indicators

Pre-EUS indicators
Indications for procedure
Detailed description of the patient by the referring physician
Patient completed procedural preparation of minimum 6 h NPO
Antibiotics per protocol were given in the need to perform FNA of pancreatic cysts
Listing of sedatives administered prior to and during EUS
Patient signed agreement of informed consent for EUS and/or if consented for research study
Intra-procedural indicators
A detailed description of the methods used to visualize routinely evaluated EUS organs. If there is any suspicion of organ pathology, the respective organ parenchyma should be described:
Suspected pancreatic lesions should include a parenchymal description including the body, head, tail, and duct
Common bile ducts and gallbladder contents should be detailed and a description of the biliary tree for sludge, stones, or other findings
If found, prominent lymph nodes should be described in detail as well as the kidneys and left liver lobe for the presence or absence of lesions
The celiac axis should be described for general arterial structure along with the aorta and superior mesenteric artery as well as the presence or absence of identifiable lymph nodes
Description of abnormal/pathological results:
Description of any tumor by the tumor, node, and metastasis system
Accurate detailing of the lesions and its surroundings in accordance with layers visualized by EUS
Degree of tumor penetration into organ mucosa and surrounding structures
Detailing the presence of lymph nodes when suspicious for malignancy and when performing FNA
Intra-procedural issues
Presence or absence of any mechanical problems or difficulties including past abdominal surgeries or ascites
Patient awakened/uncooperative during the procedure
Details of the number of FNAs performed with respective number of passes into each suspected lesion including:
Number of passes
Needle size
Number of needles
Impressions of aspirate (bloody, mucinous, color, <i>etc.</i>)
Cytology and/or histological examination
In-room tentative diagnosis
Post-procedural indicators
Summary of medical diagnoses
Examination findings, even if not relevant to the reason for EUS referral, should be listed
Physician recommendations shall be listed with respect to examination findings including instructions for the patient
Instructions for how patients will receive the results and for referring physician
After EUS, the incidence of adverse events should be listed, including pancreatitis, bleeding, and/or infections and the need for hospitalization

The above table is the standardized table of endoscopic ultrasound (EUS) quality indicators. This includes an itemized list for documentation prior to, during, and after performing EUS. FNA: Fine needle aspiration.

Research methods

Each EUS report was evaluated by the quality indicator table. QIs were evaluated prior to, during, and after performing EUS. Subsequent statistical analyses were then performed for the frequency of each indicator if listed or not listed in the various EUS reports. Reporting frequencies of each QI were calculated as percentages from which conclusions could be drawn. Each of the ten participating healthcare centers were provided with the results of this study so that they may be able to practically implement changes on their own respective terms that may improve the overall effectiveness of EUS as a whole. From the QI table, a sample EUS reporting document was proposed to be used by physicians performing EUS. Institutional Review Board approval was obtained prior to initiation of this study ensuring the privacy of all physicians, patients, and personal records. No direct patient contact took place nor were any patients harmed as a result of this research.

RESULTS

One hundred different EUS procedural reports were

collected from ten different healthcare centers of which each center contributed ten reports. These reports were evaluated for adherence to the quality indicator table developed, based upon the indicators presented by ACG^[9] (Table 1). The mean patient age was 59 years old, 52.8% of patients were female. The primary reasons for referral to EUS included suspected choledocholithiasis, suspicion of pancreatic tumor, suspicious lesions seen on imaging including ultrasound and computed tomography (Table 2).

Of the pre-procedural QIs, 71.7% of reports indicated patients' pertinent past medical history including cardiovascular disease, diabetes mellitus, gallstones, IBD, rheumatologic conditions, past surgeries, and malignancy among others. This is also to state that 29.3% of reports failed to mention the presence or absence of such conditions. Nearly of all the reports (97%) included indications for performing EUS, 82% included a detailed patient description, 61% of reports included that patients had signed a document evidencing informed consent, and 8% of reports mentioned the pre-procedural preparation. Ninety-four percent of patients received anesthesia with fentanyl combined with one or more sedatives includ-

Table 2 Indications for endoscopic ultrasound referral

Reason for EUS referral	Percent of cases
Suspected choledocholithiasis	31%
Pancreatic tumor suspicion	17%
Pathologic finding of imaging	16%
Suspicion of esophageal of stomach Tumor	12%
Pancreatic cyst	8%
Pancreatitis	3%
Obstructive Jaundice	3%
Other	19%

The above table displays the various main reasons for endoscopic ultrasound (EUS) referral. Although most commonly due to gallstone of pancreatic pathology, one can observe that EUS may be used to diagnose and to stage other areas in the gastrointestinal tract and surrounding areas.

ing propofol and midazolam. Three patients received ketamine and three patients received flumazenil (anexate) during the procedure. These agents were generally administered in the minimum accepted therapeutic intervals. For 6% of patients it was unknown which type of anesthesia, if any, which was administered (Table 3).

The most frequently documented intra-procedural QIs were pancreatic and bile duct pathology as these were the main reasons for referral. Thirty-six percentage of reports described the systematic evaluation of organs during EUS while half of the reports (50%) did not follow this systematic method. Therefore, 87% of reports included a thorough description of the pancreas including parenchyma and its different segments while 63% of reports included a description of the biliary tree. Thirty-four percent of reports outlined the evaluation of the celiac axis, and none of the reports mentioned the adrenal glands. Six percent of procedures documented intra-procedural problems which included insufficient anesthesia (2%), anesthesia-related complications (2%), ascites, and past abdominal surgeries. In cases where FNA was performed, 15% of reports documented the number of passes, needle size, and results of immediate cytological examination. Most reports simply stated that FNA was performed. Because of the high suspicion for tumors in nearly half of the reports, great care was placed on assessing the tumor-associated quality indicators (Table 3).

Post-Procedural QIs also primarily focused on the reason for referral. Although 81.9% of reports contained a clear summary of EUS findings, 37.2% of examinations contained findings unassociated with the original reason for referral, such as liver, stomach, or pancreatic pathology that were subsequently not documented. 79.8% of reports listed treatment recommendations, and 52.1% listed medical guidance about potential procedural adverse events, including pancreatitis and bleeding, of which none of the reports indicated if such adverse events occurred (Table 3). The post-procedural quality indicators are most vital as they allow physicians to summarize diagnostic findings, detail any EUS adverse effects, and outline treatment with proper follow-up and patient education. Upon expansion of this research to include twenty additional EUS reports in collaboration

Table 3 Endoscopic ultrasound pre-procedural, tumor-associated, post-endoscopic ultrasound quality indicators

Quality indicators	Percent documented
EUS pre-procedural ¹	
Listed indications for procedure	97%
Detailed patient description from the referring physician	82%
Received minimum six hour fast	8%
Given antibiotics per protocol prior to FNA of pancreatic cyst	40%
Listing of anesthesia administered prior to starting EUS	94%
Patient signed agreement of informed consent	61%
EUS findings consistent with or highly suspicious for tumor ²	
Description by the TNM system	5%
Tumor description (or suspected)	78%
Description of degree of tissue invasion	65%
Presence or absence of lymph nodes	46%
Reports malignant or suspicious lesions	48.50%
Post-EUS ³	
Summary of medical diagnoses	81.90%
Examination findings, even if not relevant to the reason for EUS referral, should be listed	37.20%
Treatment recommendations with respect to examination findings	79.80%
Advice given to patients after performing EUS	52.10%
Incidence of adverse events, including pancreatitis, bleeding, and/or infections and the need for hospitalization	0%

¹The above chart lists the percent of endoscopic ultrasound (EUS) reports in which pre-procedural quality indicators were documented. Indications and anesthesia were most frequently listed, while pre-procedural preparation, administration of antibiotics prior to fine needle aspiration of pancreatic cysts, and signing informed consent were less often listed in reports; ²This chart demonstrates the adherence to EUS quality indicators for lesions consistent with or suspected to be of malignant etiologies. Although tumors and depth of invasion were commonly described, the tumor, node, and metastasis system was seldom used; ³This table lists the physician adherence to post-procedural EUS quality indicators. Diagnoses, procedural findings relevant to reason for referral and treatment recommendations were most often documented whereas findings inconsistent with the reason for referral, post-procedural patient advice, and listing adverse events were far less often emphasized. FNA: Fine needle aspiration; TNM: Tumor, node, and metastasis.

with two expert US endosonographers, it was found that significantly greater adherence to quality indicators was observed.

DISCUSSION

Statistical analysis allowed the formation a quality indicator table composed of indicators prior to, during, and after EUS as proposed earlier in accordance with ACG guidelines^[9]. QI emphasized many factors including past medical conditions, current medications, comprehensive intra-procedural documentation, and implications of the procedure including treatment and potential adverse events that were not always documented. High-quality EUS examinations in particular include documenting a thorough exam, medical equipment used, nursing data, patient status, and discharge notes, among others. Physician adherence to QIs may produce a clear concise report that not only ensures a comprehensive examination, but

also that future medical providers can quickly reference a patient's past EUS^[12]. Analysis of EUS reports sent from the University of Chicago showed significantly greater adherence to the documentation of quality indicators, thus producing a higher quality report.

In regards to pre-procedural indicators, most reports were thorough in listing the indications for EUS. Frequently detailed also were the anesthesia and respective dosage of each sedative administered, although a small but significant percentage of reports failed to document this (Table 3). It is very important to describe the type and dose of sedative administered as well as any medication-related adverse effects. There was no mention of which patients were evaluated by the operating endoscopist prior to EUS. Open access is frequently used for EUS patients, and reports that lack such a description make it difficult for the echo-endoscopist to perform a thorough yet focused examination thus resulting in increasing amounts of EUS procedures in which smaller pathologic conditions may be missed that would have otherwise been detected had the patient had prior appropriate documentation. The risk of missing important findings may be even greater if the operating echo-endoscopist is unfamiliar with the patient undergoing EUS. Furthermore, 61% of reports mentioned that patients had signed forms of informed consent, which is a glaring number when one considers the ethical and legal concerns. Although it is likely that every patient had given informed consent, documentation should nevertheless report this. Forty percent of reports listed antibiotic prophylaxis when FNA was performed on pancreatic cysts. Although it is not evidence-based, expert opinion suggests benefits of prophylactic antibiotics on decreasing the infection rate after FNA of pancreatic cysts^[13]. Lastly, pre-EUS preparation consisting of a minimum of 6 h fasting was very seldom documented (8%). This indicator bears great importance because poorly prepared procedures will be of diminished quality due to impaired operator visibility and greater risk of aspiration that may increase the likelihood of missed findings and adverse events occurring during EUS.

As EUS is capable of diagnosing a wide range of pathologies in multiple organ systems, intra-procedural indicators were developed to optimize procedural effectiveness. After review of the various reports, it was discovered that they often lacked a comprehensive system for assessing and documenting organ systems, especially those not directly related to the reason for admission. For example, the adrenal glands were not listed in any of the EUS reports, although any discovered lesions may significantly impact patients' health. For this reason and others, it is important that a standardized table of quality indicators be used for documentation. The advantage of a standardized QI table is that it includes a list of all organs examined during EUS as well as a description of their structure to describe potential lesions, those that have suspicious characteristics, and also as a method to exclude regions as a cause for a patient's chief complaint

(Table 1).

Approximately half of the total reasons for EUS referral were for suspicion of malignancy. This is due to EUS being a highly sensitive and specific procedure for tumors in the GI tract and surrounding areas and thus may optimize subsequent treatment^[14]. Therefore, all suspected tumors should be staged according to the tumor, node, and metastasis system, based characteristics including tumor size, depth of invasion, and surrounding vascular involvement (Table 3). The diagnostic ability of EUS is further augmented by taking fine needle aspirations of such lesions. Although one third of the EUS reports involved FNAs, few reports documented the number of passes, the size of the needle, or if immediate cytological examination of the aspirated contents was performed. These details are necessary in evaluating the EUS procedural standards, which may be remedied by quality control to optimize FNA effectiveness^[3]. Therefore, proper diagnoses and thorough documentation based upon each of the described lesion characteristics described during EUS may further guide the decision for optimal treatment for the diverse benign and malignant conditions affecting the GI tract.

A number of interventions may lead to improved EUS quality. Granting quality recognition awards for those who have been consistently able to produce high-quality EUS reports is one such widely-implemented method^[2]. Especially in the era of quality driven markets, delivering high-quality endoscopic reports may lead to increased healthcare recognition and funding. Weak areas may be remedied *via* continuous quality control monitoring of reports listed on EMR. However, despite these efforts, the brunt of quality improvement relies on the individual physician to perform his or her duty of delivering the best medical care possible while ensuring minimal harm coming to patients. High-quality reports, as seen by evaluation of the twenty reports from the United States, also help protect and reduce the costs of litigation as proper documentation may lead to fewer malpractice lawsuits.

It must be acknowledged that EUS gives rise to infrequent but important adverse events. It was noted that while analyzing the 100 EUS reports from Israeli centers, there was no mention of adverse events that arose during EUS. Although there are always those present in healthcare systems who fail to comply with procedures and documentation policies, procedural complications should always be recorded. Such adverse events may include bleeding, infection, pancreatitis, intestinal perforation, and others should be listed^[15] as it is important for quality control purposes to identify and promptly remedy possible causes of such adverse events. Follow-up protocols should be included and clearly detailed according to EUS findings and diagnoses. The key advantage of post-procedural quality indicators is to have an area for summary of findings, diagnoses, and for medical recommendations with follow-up instructions (Table 3). It is important to note that by alone ensuring thorough EUS performance

and subsequent documentation does not cover all aspects of EUS quality control. There are many aspects of quality control that can and should be investigated in order to further augment the quality of EUS.

Summarizing important procedural findings for tailoring optimized treatment and to encourage patient follow-up is key to the long-term success of EUS and for patient care in general. Patient diagnoses must be summarized based on findings or lack thereof during EUS. As evidenced by this study, there is very little standardization was found among Israeli gastroenterologists; EUS findings need to be properly detailed with appropriate clinical correlation (Table 3). It is important as well to include incidentally discovered findings that are not connected to patients' primary complaints as these discovered lesions may significantly impact patients' future well-being and may be treated at an early stage. In adhering to a standardized QI table specific for EUS, doctors and patients alike may benefit from higher quality and more fruitful procedures while identifying cost-effective ways to remedy weak areas in its performance.

This study involved a multitude of diverse healthcare centers in Israel, each with its individual unique staff that causes variability in performing and documenting of EUS, which may or may not reflect the healthcare setting in other countries. Reports were evaluated multitude of diverse healthcare centers in Israel, causing variability in EUS performance and documentation of EUS, which may or may not reflect the healthcare setting in other countries.

In conclusion, having a standardized table including relevant quality indicators for EUS may increase the overall effectiveness and quality of EUS by ensuring comprehensive procedural documentation while simultaneously limiting error and strengthening patient education of potential findings during EUS.

COMMENTS

Background

Quality control in gastroenterology has focused on the implementation of quality indicators (QIs). Such QIs are established pre, peri, and post procedural features that various gastrointestinal societies have deemed necessary for documentation to achieve and maintain high quality in procedures and subsequent reports. Maintaining high-quality gastrointestinal procedures and reports via physician adherence to QIs may also minimize potential adverse events, and to optimize costs, thus saving hospitals and patients alike while improving patient care in the process.

Research frontiers

While quality indicators have been established for procedures such as colonoscopy, their effectiveness has not been well studied in regards to endoscopic ultrasound (EUS). This study assesses physician adherence to American Society for Gastrointestinal Endoscopy (ASGE) and European Society of Gastrointestinal Endoscopy (ESGE)-established quality indicators for EUS and offers a sample table intended for ease of implementing such QIs.

Innovations and breakthroughs

This study demonstrates that EUS reports compiled from Israeli centers most often adhered to indicators closely linked with the presenting pathology and infrequently documented a fully-detailed comprehensive report. In contrast to EUS reports evaluated from the University of Chicago, such reports were consistently found to adhere to EUS QIs. Therefore, the authors have prepared a table based on established QIs for ease of documenting a high-quality EUS report.

Applications

In using the proposed standardized table, physicians may find it easier to document high quality reports which may optimize costs, limit error, and ensure proper patient follow-up.

Terminology

Endoscopic ultrasound is a method of upper endoscopy that allows the operator to utilize ultrasound to accurately visualize deeper areas of the GI tract and to identify and biopsy suspicious lesions. Although it has been proven to be a highly accurate diagnostic method for malignancies in multiple regions of the GI tract, its effectiveness is operator dependent. Therefore, physician adherence to quality indicators via the proposed QI table is a low cost option that may augment the effectiveness of EUS that may benefit patients and healthcare providers alike.

Peer review

This study assesses physician adherence to ASGE and ESGE-established quality indicators for EUS and presents a table based on established QIs for ease of documenting a high-quality EUS report. The novelty and innovation of the research is high. The presentation and readability of the manuscript is good.

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Esophageal tuberculosis presenting with hematemesis

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(Rifampicin, Isoniazid, Pyrazinamide, Ethambutol) for 6 mo. Repeat EGD showed scarring and mucosal tags with complete resolution of the esophageal ulcer.

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Key words: Esophageal tuberculosis; Esophagogastroduodenoscopy; Hematemesis

Core tip: Esophageal tuberculosis is very rare, constituting about 0.3% of gastrointestinal tuberculosis cases. Esophageal tuberculosis presents commonly with dysphagia, cough, chest pain in addition to fever and weight loss. Complications may include hemorrhage from the lesion, development of arterioesophageal fistula, esophagocutaneous fistula or tracheoesophageal fistula. There are very few case reports of esophageal tuberculosis presenting with hematemesis due to esophageal ulceration. We report a patient with hematemesis that was later attributed to the erosion of tuberculous subcarinal lymph nodes into the esophagus.

Abstract

Esophageal tuberculosis is rare, constituting about 0.3% of gastrointestinal tuberculosis. It presents commonly with dysphagia, cough, chest pain in addition to fever and weight loss. Complications may include hemorrhage from the lesion, development of arterioesophageal fistula, esophagocutaneous fistula or tracheoesophageal fistula. There are very few reports of esophageal tuberculosis presenting with hematemesis due to ulceration. We report a patient with hematemesis that was due to the erosion of tuberculous subcarinal lymph nodes into the esophagus. A 15-year-old boy presented with hematemesis as his only complaint. Esophagogastroduodenoscopy (EGD) revealed an eccentric ulcerative lesion involving 50% of circumference of the esophagus. Biopsy showed caseating epithelioid granulomas with lymphocytic infiltrates suggestive of tuberculosis. Computerised tomography of the thorax revealed thickening of the mid-esophagus with enlarged mediastinal lymph nodes in the subcarinal region compressing the esophagus along with moderate right sided pleural effusion. Patient was treated with anti-tuberculosis therapy

Jain SS, Somani PO, Mahey RC, Shah DK, Contractor QQ, Rath PM. Esophageal tuberculosis presenting with hematemesis. *World J Gastrointest Endosc* 2013; 5(11): 581-583 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i11/581.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i11.581>

INTRODUCTION

Esophageal tuberculosis is rare, constituting about 0.3% of gastrointestinal tuberculosis cases^[1]. Usual presentation is due to dysphagia, retrosternal pain, fever, cough and weight loss. Complications may include hemorrhage from the lesion, development of arterioesophageal fistula, esophagocutaneous fistula or tracheoesophageal fistula^[2] and intramural pseudo-diverticulum^[3]. There are very few case reports of esophageal tuberculosis presenting with hematemesis due to esophageal ulceration^[2,4,5]. We report a patient with hematemesis that was due to the

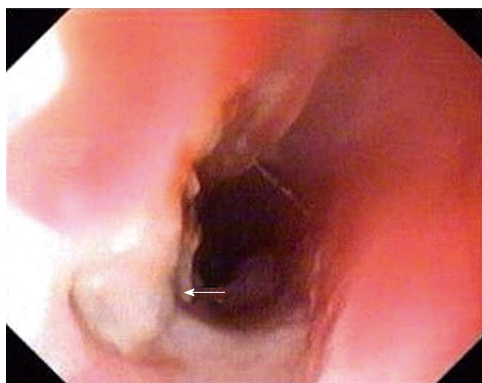


Figure 1 Esophagogastroduodenoscopy showing eccentric ulcerative lesion involving 50% of circumference of the esophagus (white arrow).

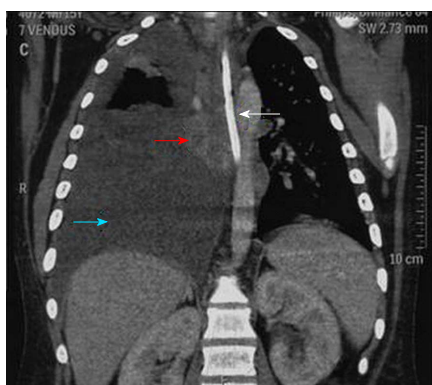


Figure 2 Computerised tomography of the thorax showing thickening of the mid-esophagus (red arrow) along with Ryle's tube *in situ* (white arrow). Right sided pleural effusion seen (blue arrow).

erosion of tuberculous subcarinal lymph nodes into the esophagus.

CASE REPORT

A 15-year-old male presented to the emergency room with five bouts of hematemesis and melena since past 2 d. There was no history of dysphagia, dyspnea, cough, abdominal pain or syncope. On examination his pulse was 110 beats per minute and blood pressure 90/60 mmHg. He appeared pale. Rest of the examination was unremarkable. Laboratory investigations revealed a hemoglobin level of 7 g/dL with normal blood chemistry. Human immunodeficiency virus screening antibody was negative. Erythrocyte sedimentation rate was 72 mm in the first hour. Patient was resuscitated and esophagogastroduodenoscopy (EGD) was performed which revealed an eccentric ulcerative lesion involving 50% of circumference of the esophagus at 26 cm from the incisors (Figure 1). Biopsy of the ulcer margin was sent for histopathological examination. It revealed caseating epitheloid granulomas with lymphocytic infiltrate suggestive of tuberculosis (Figure 2). Computed tomography (CT) of the thorax showed thickening of the mid-esophagus with enlarged mediastinal lymph nodes in the subcarinal region compressing the esophagus along with moderate right sided

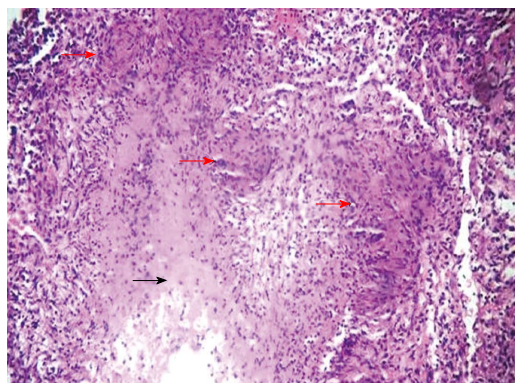


Figure 3 Histopathological examination of esophageal ulcer biopsy showing epitheloid cell granulomas (red arrows) with caseation (black arrow) in the exudate suggestive of esophageal tuberculosis (HE stain x 10).

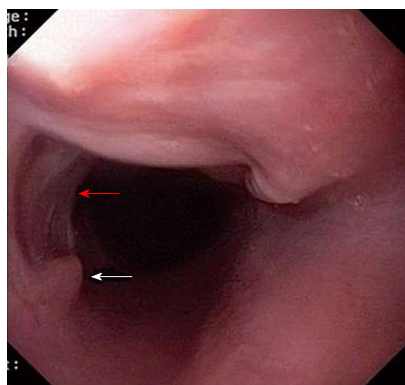


Figure 4 Esophagogastroduodenoscopy after 6 mo of anti-tuberculosis therapy showing resolution of esophageal ulcer along with scarring (red arrow) and mucosal tags (white arrow).

pleural effusion (Figure 3). Polymerase chain reaction of the tissue was highly specific for mycobacterium tuberculosis. Diagnostic thoracentesis revealed a turbid pleural exudates with pH = 7.38, glucose = 72 mg/dL, total protein = 4.3 mg/dL, total cells = 2200/mm³, consisting of 80% lymphocytes and 20% polymorphonuclear cells and lactate dehydrogenase = 724 U/L. Pleural fluid adenosine deaminase was 69 U/L, while smears, cultures and cytology, were negative. Patient was initiated on a four-drug antitubercular therapy (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol) with marked improvement in his symptoms. Repeat EGD after 6 mo showed only scarring and mucosal tags with complete resolution of the ulcer (Figure 4) and chest X-ray showed complete resolution of pleural effusion.

DISCUSSION

Esophageal tuberculosis is very rare and primary esophageal tuberculosis is seemingly even more exceptional. Esophageal tuberculosis is considered primary when there is no other detectable tubercular site and secondary when the esophagus is involved by spread from adjacent structures. Primary tuberculosis of the esophagus is extremely rare, perhaps owing to intrinsic protective

mechanisms, such as stratified epithelial lining, presence of saliva. Besides, mucous coated tubular structure, peristalsis discourages stasis and mucosal invasion by organisms, which needs a physiologically stable environment. Several mechanisms have been proposed to explain the spread of infection to the esophagus, resulting in secondary esophageal tuberculosis: (1) infection of the esophageal mucosa from swallowed tuberculous sputum; (2) contiguous extension from laryngeal and pharyngeal lesions; (3) contiguous extension from other adjacent infected structures, such as the mediastinum, hilar lymph nodes or vertebrae; (4) retrograde lymphatic spread; and (5) hematogenous infection in the course of generalized disseminated miliary tuberculosis^[2].

Common site of tubercular involvement is mid-esophagus, near carina due to proximity to mediastinal lymph nodes^[6]. Damteu *et al*^[7] in an analysis of 19 cases of esophageal tuberculosis, found that the majority of patients had direct extension from an adjacent caseous mediastinal or hilar lymph node. Most of these cases were diagnosed late and showed predominant involvement of the upper or middle third of the esophagus.

Three histomorphologically distinct types exist: (1) Ulcerous type (most common): mycobacteria initially involve submucosa of esophagus followed by formation of tubercle. As the disease progresses, caseous necrosis occurs within the nodule, followed by ulceration. Usually it is a superficial ulcer with pale grey purulent base, rough, irregular edge, only involving the mucosa and submucosa. The more serious ulcers occur rarely, often can penetrate the muscle layer, break through the esophageal adventitia resulting in esophageal perforation, esophagomediastinal fistula or esophagopleural fistula. Invasion of the trachea results in tracheoesophageal fistula. Death due to massive hemorrhage can occur due to aortoesophageal fistula. Esophageal tuberculous ulcer often has a self-healing tendency due to proliferation of fibrous tissue and scar formation, leading to local esophageal stenosis; (2) Hyperplastic type: is due to excessive amount of tuberculous granulation tissue and fibrous tissue hyperplasia. Sometimes due to massive hyperplasia, there can be false tumor-like mass (pseudo-tumor) formation into the esophageal lumen, resulting in luminal narrowing; and (3) Granular esophageal tuberculosis (least common): occurs in the severe systemic disease where the mucosa and submucosa show many gray-white nodules^[8].

Esophageal tuberculosis presents commonly with dysphagia, cough, chest pain in addition to fever and weight loss, which might simulate esophageal malignancy. Presentation with complications is rare^[2]. Hematemesis most often is due to arterioesophageal fistula with grave prognosis. In this patient upper gastrointestinal bleeding was due to ulceration in the mid-esophagus due

to erosion of tuberculous subcarinal lymph nodes.

Diagnosis of esophageal tuberculosis is difficult and a high index of suspicion is required. Plain radiography of the chest and CT scan could reveal pulmonary or mediastinal lymph node involvement. CT scan may also reveal thickening of the mid-esophagus as in our case. Endoscopy is valuable to diagnose the lesion and for achieving biopsy for histopathology and isolating the organism^[6]. Histology shows epithelioid granuloma with Langhans cells and central caseous necrosis. Classical granulomas are seen only in 50% of cases, whereas acid fast bacilli are demonstrated in less than 25%^[9]. Endoscopic mucosal biopsy has sensitivity of 22% as reported by Mokoena *et al*^[2]. Recently, cytology and polymerase chain reaction have also proven useful in cases where the initial biopsies showed non-specific changes^[10].

Anti-tubercular chemotherapy (Rifampicin, Isoniazid, Pyrazinamide, Ethambutol) for 6 to 9 mo is the main stay in the treatment. Surgical intervention is warranted if bleeding persists or gets complicated with perforation or fistula formation occur.

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Narrow band imaging with magnification for the diagnosis of lesions in the upper gastrointestinal tract

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Abstract

Endoscopy plays an important role in the diagnosis and management of gastrointestinal (GI) tract disorders. Chromoendoscopy has proven to be superior to white light endoscopy for early detection of various GI lesions. This has however been fraught with problems. The use of color stains, time taken to achieve an effect and the learning curve associated with the technique has been some of the pitfalls. Narrow band imaging (NBI) particularly in combination with magnifying endoscopy may allow the endoscopist to accomplish a fairly accurate diagnosis with good histological correlation similar to results achieved with chromoendoscopy. Such enhanced detection of pre-malignant and early neoplastic lesions in the gastrointestinal tract should allow better targeting of biopsies and could ultimately prove to be cost effective. Various studies have been done demonstrating the utility of this novel technology. This article will review the impact of NBI in the diagnosis of upper gastrointestinal tract disorders.

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Key words: Narrow band imaging; Magnifying endos-

copy; Upper gastrointestinal tract

Core tip: Narrow band imaging with magnifying endoscopy has shown promising results in improving detection and characterization of gastrointestinal lesions. This may allow better targeting of biopsies, improved prediction of histology, appropriate treatment and better patient outcomes. Most studies have been conducted in expert centers and carried out only by one or a few observers. Large-scale prospective multi center randomized trials are needed to duplicate the results achieved in these institutions.

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INTRODUCTION

Recent advances in endoscopic imaging technologies have enabled endoscopists to improve the capability of detecting and characterizing lesions in gastrointestinal tract (GIT). Amongst some of these novel technologies, narrow band imaging (NBI) appears to be the most promising. Current available data on the utility of NBI with magnification (NBI-ME) has been encouraging for Barrett's esophagus, early Oropharyngeal, esophageal and gastric cancers and to a lesser extent reflux disease and gastritis. It also has a role in aiding endoscopic resection where margin assessment is essential. This review will focus on the role of NBI-ME in the diagnosis of lesions in upper gastrointestinal tract.

ESOPHAGEAL SQUAMOUS CELL CARCINOMA

NBI enables detailed observation of the microvascu-

lature in the esophageal mucosa, described as intraepithelial papillary capillary loops (IPCL's). The NBI-ME findings of early squamous cell carcinoma (SCC) include a well-demarcated brownish area, elevated margins, loss of visible branching vessels and a type IV or type V intraepithelial papillary capillary loops pattern^[1,2]. Inoue originally described intraepithelial papillary capillary loops into 4 distinct entities: dilation, meandering, caliber changes and difference in shapes^[3,4]. Type IV intraepithelial papillary capillary loops shows 2 or 3 of the four patterns, whilst Type V intraepithelial papillary capillary loops demonstrates all 4 characteristic changes. Type III intraepithelial papillary capillary loops (minimal proliferation or meandering in a brownish area) is considered borderline or low grade intra-epithelial neoplasia. Thus, a follow up endoscopy is generally recommended for these patients. However, type II intraepithelial papillary capillary loops (enlarged but linear and regular vessels) indicates regenerative tissue or inflamed mucosa. Type I intraepithelial papillary capillary loops, are generally normal vessels with smooth, slender, regular caliber with a smaller diameter (10 μ m).

Muto *et al*^[5] conducted a multicentre randomised controlled trial on 320 patients with a history of Squamous Cell CA (SCC), comparing white light endoscopy (WLE) with NBI in the detection of Squamous Cell CA in patients with a history of head and neck Squamous Cell CA or previous esophageal Squamous Cell CA. The sensitivity of NBI for a diagnosis of superficial cancer was 100% for the oropharynx and 97.2% for the esophagus. The diagnostic accuracy was 90% when two endoscopic criteria, namely, a well demarcated brownish area and an irregular micro vascular pattern, were used.

Goda *et al*^[6] conducted a non-randomized comparative study of 101 lesions of esophageal Squamous Cell CA, which gauged the sensitivity and specificity of WLE, NBI and endoscopic ultrasound (EUS) in predicting the depth of superficial esophageal Squamous Cell CA. The authors concluded that all 3 modalities did not differ significantly. Kuraoka *et al*^[7] conducted a study comparing endoscopy with iodine staining to NBI. Endoscopy assisted with NBI was more useful in the detection of early esophageal Squamous Cell CA than that obtained with iodine. Another study assessed the efficacy of 1204 high-resolution esophagoscopies with NBI using a novel "Endo View" Program. Color segmentation of narrow band images apparently increased the chances of diagnosing even the smallest abnormality in the esophagus. NBI endoscopy also allowed specifying premalignant lesions in esophageal mucosa in both low grade and high-grade dysplasia (HGD)^[8].

A consensus of expert endoscopists from the Asia-Pacific region put all of this together and reported a strong agreement on importance of interpretation of both vascular architecture and surface structure of the superficial mucosa in the esophagus. NBI was useful for detection of esophageal Squamous Cell CA (100% consensus achieved), distinguishing neoplastic from non-neoplastic lesions (89% consensus), determining the ex-

tent of the neoplasia (78% consensus) and depth of the tumor (100% consensus). However, the panel of experts agreed that chromo endoscopy is still superior to delineate the extent of the tumor^[9]. They also agreed that there was no significant difference in terms of sensitivity and specificity for the assessment of the depth of tumor invasion by NBI when compared to EUS.

BARRETT'S ESOPHAGUS

Singh *et al*^[10] conducted a study on 109 patients with more than 1000 corresponding biopsies, which not only validated a simplified classification of the various morphologic patterns visualized in Barrett's Esophagus (BE) and corresponding histology with high predictive values, but also confirmed its reproducibility and repeatability when the grading system was used by both endoscopists experienced in the use of NBI and those unfamiliar with it. On the basis of the 1021 areas visualized, NBI-ME allowed correct prediction of 99% of the areas harboring intestinal metaplasia (IM) and 96% of the areas demonstrating high grade dysplasia (HGD). However intestinal metaplasia was not clearly differentiated from low grade dysplastic lesions. Mannath *et al*^[11] in a large meta analysis found a very high sensitivity and specificity of NBI in diagnosing in high grade dysplasia patients with Barrett's Esophagus.

GASTRO-ESOPHAGEAL REFLUX DISEASE AND NON-EROSIVE REFLUX DISEASE

Approximately 60% of patients with gastro-esophageal reflux disease (GERD) have normal standard endoscopy and are labeled as suffering from non-erosive reflux disease (NERD)^[12]. NBI-ME can detect microvascular changes and also enhance the contrast between esophageal and gastric mucosa^[13]. Microvascular changes of non-erosive reflux disease on NBI include increased number and dilatation of intraepithelial papillary capillary giving an inverted fir tree appearance, punctate erythema, loss of vascular palisade pattern and triangular indentation of squamo-columnar junction above the Z line^[14]. Changes below the Z line include islands of squamous epithelium and increased vascular markings^[15,16]. Some of these features were tested in a study comparing ten control subjects and eleven patients with non-erosive reflux disease confirmed by a validated questionnaire, standard endoscopy and 24-h pH-metry^[17]. The investigators proposed and explored seven different distal esophageal mucosal appearances that can be observed with a high-resolution endoscope (triangular lesions, apical mucosal breaks, palisade vessels, pin point vessels, branching vessels, villiform mucosa and serrated squamo-columnar junction). However none of these changes proved to be sufficiently sensitive and specific to justify their use as a diagnostic criterion for non-erosive reflux disease. A study conducted by Fock *et al*^[18] concluded that NBI detected a significantly higher prevalence of

micro-erosions (gastro-esophageal reflux disease 100%, non-erosive reflux disease 52.8% and controls 23%) and increased vascularity (gastro-esophageal reflux disease 95%, non-erosive reflux disease 91.7% and controls 36.7%) but a lower prevalence of round pit patterns (gastro-esophageal reflux disease 4.9%, non-erosive reflux disease 5.6% and controls 70%).

Tseng *et al*^[15] studied 82 patients where 20 were detected as having gastro-esophageal reflux disease by WLE. Out of the remaining 62 patients declared normal by WLE, NBI detected an additional 44 patients having erosions. They also demonstrated that the changes which visualized on NBI could predict a therapeutic response in patients with gastro-esophageal reflux disease. Sharma *et al*^[14] compared NBI with WLE in a prospective study of 101 patients. Patients with and without gastro-esophageal reflux disease symptoms were examined by standard WLE followed by NBI. The features seen only by NBI were compared between gastro-esophageal reflux disease patients and controls. A significantly higher proportion of patients with gastro-esophageal reflux disease had increased number (OR = 12.6), dilatation (OR = 20), tortuosity of intraepithelial papillary capillary (OR = 6.9) and increased vascularity at the squamo-columnar junction (OR = 9.3) compared with controls.

GASTRITIS AND *HELICOBACTER PYLORI*

Helicobacter pylori (*H. pylori*) is the commonest cause of chronic gastritis^[19]. This can lead to intestinal metaplasia and dysplasia; conditions which may progress onto gastric carcinoma^[20]. On NBI-ME, the normal gastric corpus and fundus have small round pits, sub-epithelial capillaries networks (SECN) in a honeycomb pattern and stellate shaped collecting venules (CV) arranged at regular intervals in deeper mucosa^[21,22]. These patterns have a 100% predictive value for normal corporal mucosa^[23]. The normal gastric antrum has a reticular pattern of circular pits and coiled elongated sub-epithelial capillaries networks. The collecting venules are situated too deep to be visible^[21,24]. *H. pylori* gastritis visualized by NBI shows a loss of collecting venules due to associated inflammation and this pattern has 100% sensitivity, 92% specificity and a positive predictive value (PPV) of 100% for *H. pylori* gastritis. *H. pylori* related atrophic gastritis is patchy starting from Incisura and progressively involves the Antrum, body and corpus. NBI findings suggestive of atrophy are loss of pits and sub-epithelial capillaries networks. The sensitivity and specificity of these findings for atrophic gastritis have been suggested to be up to 90% or above^[23].

Dalal *et al*^[25] conducted a pilot study in the stomach that concluded that when compared to WLE, abnormal findings on NBI had a sensitivity of 100% and a specificity of 90.6%; whereas WLE has a sensitivity of only 42.9% and specificity of 75%. Negative predictive value (NPV) of NBI was 100%, whereas WLE has Negative predictive value of 85.7%. However, with a small-sized

study of 25 patients, further refinement and validation of the NBI grading criteria was suggested. Banerjee and colleagues also compared NBI with WLE on 74 patients and showed that high resolution endoscopy with NBI could be a potential tool for the instantaneous real time diagnosis of *H. pylori* infection. The sensitivity, specificity, positive predictive value and negative predictive value for absence of infection were 85%, 93%, 96% and 77% respectively^[26].

SUPERFICIAL GASTRIC CANCER

As with all cancers, an early diagnosis is crucial for a good prognosis in gastric carcinoma, which is the second leading cause of cancer related deaths worldwide^[27-31]. Atrophy, metaplasia, dysplasia followed by neoplasia are the usual sequence of events^[32,33] in some of these patients. NBI may assist in identifying premalignant lesions and hence enable appropriate therapy. Amorphous pit pattern, irregular size and/or arrangement of pits or complete loss of pits along with abnormal micro-vascular pattern are associated with neoplastic lesions. Regular, round, slit or villous like pits indicate non-neoplastic lesions^[34-36]. These changes are however not always straightforward as findings can be altered by many conditions such as chronic inflammation, ulceration, atrophy or metaplasia and *H. pylori* infection^[37-39]. Superficial but elevated lesions make the visibility of micro-vascular pattern difficult^[35,40,41].

A consensus of expert endoscopists in the Asia-Pacific region agreed that NBI is not useful for detection of gastric carcinoma at an early stage. They however concurred that NBI increases sensitivity and accuracy of differential diagnosis of early gastric carcinoma (EGC) in elevated, flat and depressed lesions. NBI may also distinguish tumor margins from the surrounding normal mucosa. They also agreed that NBI has no significant role in detecting tumor depths as the narrow band of light is speculated to penetrate to only 200-250 μ m into the superficial mucosa^[9]. Approximately 40% of early gastric carcinoma are of the undifferentiated type according to Japanese literature^[42,43]. This type of early gastric carcinoma can extend subepithelially and may be covered by non-neoplastic foveolar epithelium. In undifferentiated early gastric carcinoma, it is recommended that biopsies are obtained from the surrounding mucosa to diagnose the undetectable tumor extent^[44].

Light blue crest (LBC) is a fine, blue-white line on the crest of the epithelial surface/gyri. An JK conducted a study on 42 patients and concluded that the Light blue crest sign (LBC) observed in the gastric mucosa with magnifying NBI endoscopy are highly accurate indicators of the presence of Intestinal Metaplasia (IM) and Light blue crest also correlates with progression to severe Intestinal Metaplasia. For the diagnosis of Intestinal Metaplasia, Light blue crest had a sensitivity, specificity, and accuracy of 72.1%, 96.0%, and 84.9%^[45]. Uedo *et al*^[46] tested NBI-ME on 34 patients with atrophic gastritis and demonstrated that the appearance of Light blue crest correlated

with histological evidence of Intestinal Metaplasia, with a sensitivity of 89% (95%CI: 83-96), a specificity of 93% (95%CI: 88-97), a positive predictive value of 91% (95%CI: 85-96), a negative predictive value of 92% (95%CI: 87-97) and an accuracy of 91% (95%CI: 88-95). Yao *et al*^[47] reported that the hallmark of a white opaque substance (WOS) is the presence of lipid droplets (LDs) that accumulate in the superficial part of the epithelial neoplasia within the stomach. The authors also reported that the white opaque substance in adenomas was regular and homogeneous, whereas the white opaque substance in adenocarcinomas was irregular and speckled. Ueyama *et al*^[48] suggested that the white opaque substance-positive epithelium corresponded to the dysplasia in this lesion. The presence of a white opaque substance in a gastric hyperplasia may be considered an endoscopic finding that is predictive of the neoplastic transformation of a gastric hyperplasia. Therefore, in gastric hyperplasia, white opaque substance positivity may be considered an endoscopic finding that indicates endoscopic resection^[48].

CELIAC DISEASE

Normal duodenal mucosa exhibits regularly arranged finger like villi and a regular network of capillaries on high resolution magnifying WLE^[49]. Reduced duodenal folds, scalloping of fold margins, mosaic pattern of mucosa and grooves in the mucosa are usual conventional endoscopic signs for celiac disease^[50-54]. However these findings are not reliable in patchy^[55,56] or milder cases of subtotal atrophy^[57]. Overall, the sensitivity, specificity, positive predictive value and negative predictive value for villous atrophy on NBI are 100%, 91%, 83% and 100% respectively^[58].

Banerjee *et al*^[59] mentioned earlier in 2008 that NBI may be a useful yet simple adjunctive tool for the direct visualization of villous architecture and guide to tissue sampling. This may improve the diagnostic yield as well as reduce the number of biopsy specimens that need to be taken. Singh *et al*^[60] conducted a study using NBI-ME to detect villous atrophy in patients presenting with suspected celiac disease using forty-one videos obtained from 21 patients (3 celiac disease, 18 normal). The overall sensitivity and specificity in correctly distinguishing the presence or absence of villi were 93% and 98% respectively, with inter-observer and intra-observer agreement (κ) at 0.82 and 0.86 respectively. The sensitivity and specificity in differentiating partial from total villous atrophy were 83.3% and 100% respectively, with κ at 0.73 and 0.68 respectively.

CONCLUSION

Narrow band imaging is a promising endoscopic technology which may improve the diagnostic accuracy of detecting and characterizing premalignant and neoplastic lesions in the upper gastrointestinal tract. Most studies have been conducted in expert centers and carried out by one or a few observers. Large-scale prospective

multicenter randomized trials are needed to duplicate the results achieved in these institutions. Standardization of endoscopic criteria and amalgamation of the various classifications cannot be overemphasized. Once this is achieved, teaching and learning modules for more widespread dissemination to the community will be crucial.

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Endoscopic mucosal resection of Barrett's esophagus detects high prevalence of subsquamous intestinal metaplasia

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Abstract

AIM: To report the prevalence of Subsquamous intestinal metaplasia (SSIM) in patients undergoing endoscopic mucosal resection (EMR) for staging of Barrett's esophagus (BE).

METHODS: Thirty-three patients with BE associated neoplasia underwent EMR at our institution between September 2009 and September 2011; 22 of these patients met study inclusion criteria. EMR was targeted at focal abnormalities within the BE segment. EMR was performed in standardized fashion using a cap-assisted band ligation technique, and resection specimens were assessed for the presence of SSIM. Demographic and clinical data were analyzed to determine predictors of SSIM.

RESULTS: SSIM was detected in 59% of patients. SSIM was detected in 73% of patients with short segment (< 3 cm) BE, and in 45% of patients with long-segment (\geq 3 cm) BE ($P = \text{NS}$). There was no association between presence/absence of SSIM and age, gender, or stage of BE-associated neoplasia.

CONCLUSION: EMR detects SSIM in a majority of patients with BE-associated neoplasia. While the long-term clinical significance of SSIM remains uncertain, these results highlight the importance of EMR as an optimal diagnostic tool for staging of BE and detection of SSIM, and should further limit concerns that SSIM is purely a post-ablation phenomenon.

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Key words: Barrett esophagus; Barrett epithelium; Endoscopy; Esophageal cancer; Pathology

Core tip: Subsquamous intestinal metaplasia (SSIM) is the term used to describe glandular Barrett's tissue which is buried beneath overlying squamous mucosa and not visible endoscopically. Esophageal forceps which fail to contain lamina propria are of insufficient depth to assess for the presence of SSIM. This study of patients with Barrett's esophagus (BE) undergoing endoscopic mucosal resection, previously naïve to endoscopic therapy, detected SSIM in 59% of patients. These findings demonstrate that SSIM is a common occurrence in the natural history of BE, and should limit concerns that SSIM is purely a post-ablation phenomenon.

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INTRODUCTION

Barrett's esophagus (BE) is defined as intestinal metaplasia of the esophageal mucosa, and is recognized as the major known risk factor for esophageal adenocarcinoma^[1]. Criteria for the diagnosis of BE have typically included the presence of endoscopically visible mucosal changes proximal to the gastroesophageal junction, with histopathology demonstrating columnar epithelium with goblet cells. The concept of subsquamous intestinal metaplasia (SSIM), often referred to as "buried Barrett's", challenges these criteria by implying that metaplastic, glandular BE tissue beneath intact surface squamous mucosa may not be endoscopically apparent, and may be detectable only by histopathologic analysis of mucosal tissue specimens containing lamina propria. A theoretical concern is that SSIM may harbor neoplastic tissue which eludes standard endoscopic surveillance.

SSIM has been reported in BE patients who have received long-term pharmacologic acid suppression therapy^[2], and both before and after endoscopic therapy in cohorts across a range of endoscopic ablation modalities including photodynamic therapy (PDT)^[3] and radiofrequency ablation (RFA)^[4,5]. Estimates of the prevalence of SSIM have varied widely across studies, with a recent systematic review indicating a prevalence ranging between 0 and 28%^[6]. This variability may in part reflect inconsistencies in biopsy technique and depth across studies.

The majority of prior studies reporting the prevalence of SSIM have been based on mucosal specimens obtained by forceps biopsy, with the high-end estimate (28%) originating from a study of endoscopic mucosal resection (EMR). EMR, frequently employed for staging of BE-associated neoplasia, offers both a greater depth and surface area of tissue acquisition when compared with forceps biopsies, and therefore may have a higher yield for detection of SSIM. Our hypothesis was that prior reports have underestimated the prevalence of SSIM, and the aim of this study was to determine the prevalence of SSIM in patients undergoing EMR for staging of BE.

MATERIALS AND METHODS

Approval to conduct this retrospective study was granted by the Vanderbilt University Institutional Review Board. A database query was performed to identify patients with BE who had undergone EMR between September 2009 and September 2011. Clinical and endoscopic data were extracted from the electronic medical record.

Endoscopic evaluations were performed by a single endoscopist (PY). Candidates for EMR included patients referred for staging of BE-associated neoplasia, with prior biopsies documenting the presence of low-grade dysplasia (LGD), high-grade dysplasia (HGD), and/or adenocarcinoma within the BE segment. EMR is per-

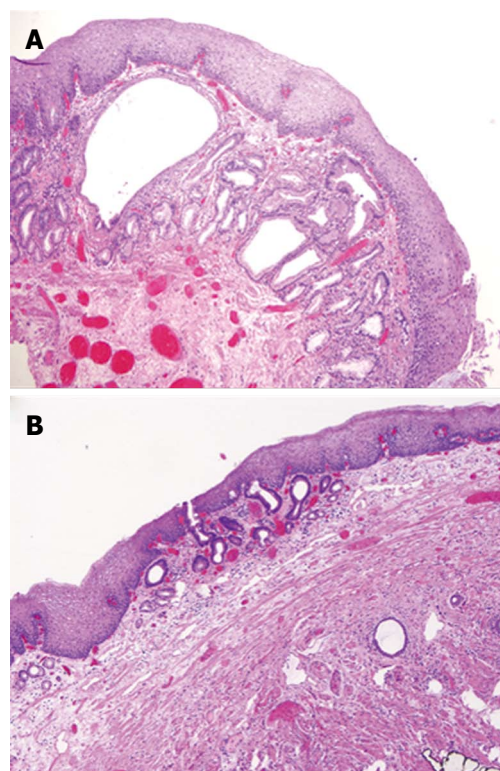


Figure 1 Esophageal endoscopic mucosal resection specimens demonstrating two morphologic subtypes of subsquamous intestinal metaplasia.

A: Subsquamous intestinal metaplasia (SSIM) with no direct extension to the mucosa; B: SSIM penetrating through the overlying squamous epithelium and onto the luminal surface.

formed as previously described^[7]. EMR are performed with a cap-assisted device (Duette Multi-Band Mucosectomy, Cook Medical, Limerick, Ireland). Resections are completed using a snare at a blended current setting (ERBE VIO 200-S electrosurgical unit, set to snare hot biopsy mode with coag effect 1 and maximum Watts 20). If necessary, piecemeal EMR is repeated until the target area has been resected.

The pathology laboratory is notified of specimen submission, and specimens are sectioned in order to preserve tissue orientation and architecture. Formalin-fixed and paraffin-embedded specimens are reviewed by two expert gastrointestinal pathologists (CS and MKW) as previously described^[7]. In cases of dysplasia, dysplasia is graded as LGD or HGD. For adenocarcinoma, a local stage is assigned (pT1a, pT1b, *etc.*) according to American Joint Committee on Cancer 7th edition staging manual.

For the purposes of this study, the presence of SSIM was assessed in each EMR specimen. SSIM was defined as glandular intestinal metaplasia within the lamina propria and without apparent continuity with surface BE. Two morphologic subtypes were identified: (1) SSIM with no direct extension to the mucosa (Figure 1A); and (2) SSIM with glands penetrating through the overlying squamous epithelium and onto the luminal surface, surrounded completely by squamous epithelium (Figure 1B).

Exclusion criteria were: (1) prior endoscopic or surgical therapy for BE; (2) the presence of invasive carcinoma detected by histopathologic analysis of the EMR speci-

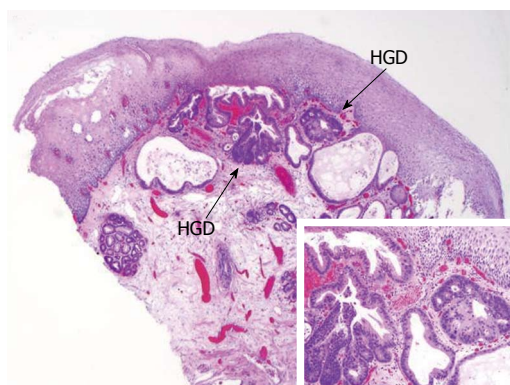


Figure 2 Esophageal endoscopic mucosal resection specimens demonstrating subsquamous intestinal metaplasia with high-grade dysplasia. HGD: High-grade dysplasia.

men; and (3) the absence of squamous mucosa in the EMR specimen. With respect to the last exclusion criteria, by definition squamous mucosa must be present in the resected specimen in order to assess for SSIM. Therefore, only EMR specimens obtained in proximity to the endoscopically visible squamocolumnar junction and including squamous tissue were eligible for analysis. EMR specimens obtained entirely from within a BE segment and not containing squamous mucosa were therefore not included.

Descriptive and univariate statistical analysis was performed using the R statistics program. A two-sided $P < 0.05$ was considered significant.

RESULTS

Thirty-three patients underwent EMR during the study time period. One patient who had undergone radiofrequency ablation prior to EMR and one patient who had undergone prior surgical esophagectomy were excluded. Five patients were excluded due to the absence of squamous tissue in the EMR specimen. An additional four patients were found to have invasive cancer (T1b or greater) and were excluded on this basis. Therefore, the final cohort consisted of 22 subjects. These 22 patients underwent a total of 26 EMR sessions (mean sessions 1.2 per patient, range 1-2). Eighty-two percent of subjects were male, and the mean age of subjects was 64 (range 41-80) years. Mean maximum BE length among the subjects was 3.8 (range 0-12) cm. Pre-EMR histopathologic diagnosis, based on forceps biopsies, was LGD in 5% (1/22), HGD in 41% (9/22), intramucosal (T1a) adenocarcinoma in 36% (8/22), and invasive adenocarcinoma in 18% (4/22) of subjects, respectively.

SSIM was detected in EMR specimens in 59% (13/22) of patients. SSIM was detected in 73% (8/11) of patients with short segment (< 3 cm length) BE and 45% (5/11) of patients with long segment (≥ 3 cm length) BE ($P = \text{NS}$). There was no association between presence/absence of SSIM and age or gender. There was no association between presence/absence of SSIM and stage of neoplasia.

Of the 13 cases with SSIM, 3 (23%) contained high-grade dysplasia in SSIM (Figure 2). Four patients underwent two EMR sessions separated in each case by 2-3 mo

intervals, and SSIM was present in the index EMR specimen in each of these patients. Adverse events of EMR were limited to esophageal stricture requiring endoscopic dilation in 5% (1/22) of patients; bleeding requiring endoscopic therapy, hospital admission and packed red blood cell transfusion in one patient; delayed bleeding requiring endoscopic evaluation but no endoscopic therapy and no transfusion in one patient; and aspiration requiring hospital admission in one patient.

DISCUSSION

This study demonstrates that SSIM is present in the majority of patients undergoing EMR for staging of BE-associated neoplasia. The prevalence of SSIM in this cohort (59%) is considerably higher than previously reported from tissue-based analysis. Prior studies have reported prevalence of SSIM ranging between 0 and 28%^[6]. The majority of these studies were based on results of forceps biopsies, which may underestimate prevalence of SSIM due to inadequate sampling of the lamina propria. A 28% prevalence rate of SSIM, often detected at or just proximal to the squamocolumnar junction, was reported in a prior study with EMR as the tissue sampling method^[8]. Our findings approach the high SSIM prevalence rate (73%) detected by optical coherence tomography imaging in a recently reported study^[9].

Our protocol consisted of focal EMR targeted at specific lesions within the BE segment. Single-session resection is confined to less than 50% of the mural circumference, in order to limit the risk of post-EMR stricture. These focal EMRs do not resect the entirety of the squamocolumnar junction, as might be achieved with a widefield EMR or endoscopic submucosal dissection technique-therefore, it is likely that our study underestimates the true prevalence of SSIM in the cohort.

This study features a systematic, regimented approach to the staging of BE-associated neoplasia, which includes close collaboration between an endoscopist trained in BE endotherapy and expert gastrointestinal pathologists, and which we believe facilitates detection of SSIM. EMR specimens were obtained and evaluated according to set protocol, which included use of specific electrocautery settings. Electrocautery settings for esophageal EMR are not standardized across practices, and may vary by endoscopist and institution, including use of "cut" versus "coag" application for resection and variations in this regard may influence the degree of thermal injury and artifact at lateral resection margins including squamous mucosa, potentially influencing the ability to detect SSIM in proximity to these margins.

This study is limited by its small size and retrospective nature, which limits the ability to assess predictors of SSIM. Details of prior duration of exposure to pharmacologic gastric acid suppression and extent of prior endoscopic biopsy surveillance of BE, both factors which can promote ingrowth of squamous islands within BE, are not available. The study also does not include control groups, for instance to assess the prevalence of SSIM in

patients with BE staged by forceps biopsy alone or the prevalence of SSIM in BE patients without neoplasia. The results of this study may not be generalizable to patients with BE without dysplasia or carcinoma.

The long-term clinical significance of SSIM remains a topic of uncertainty, particularly with respect to patients who have undergone endotherapy for BE. Cases of dysplasia and adenocarcinoma arising from SSIM have been reported following treatment of BE-associated neoplasia with PDT^[10,11] and argon plasma coagulation^[12]. A recent systematic review tallied a total of 34 reported cases of neoplasia (ranging from LGD to invasive adenocarcinoma) arising within SSIM following BE endotherapy^[6]. In some cases when neoplasia is present and involving both surface and subsquamous structures, however, it may be difficult to precisely and definitively implicate a subsquamous origin of neoplasia. In follow-up of patients treated in a randomized study of PDT, among patients with biopsies demonstrating recurrence of neoplasia, the highest grade of dysplasia/cancer was always present in surface epithelium and not contained solely in SSIM^[3].

On the other hand, SSIM is phenotypically distinct from surface BE on a molecular level. For instance, SSIM following PDT has low Ki-67 crypt proliferation rates and lower rates of aneuploidy when compared with pre-treatment BE^[13]. Additional alterations in biomarker expression in SSIM may be a consequence of relative protection from exposure to mutagenic gastric and bile acid reflux^[14]. In this regard, SSIM may in theory have a lower malignant potential than surface BE.

While the current study is not informative regarding the long-term malignant potential of SSIM, it does fundamentally alter estimates of the native prevalence of SSIM in an endotherapy-naïve cohort. This creates a critical context for the emerging role of widespread endotherapy for BE, as we aim to understand how endotherapy alters the prevalence and natural history of SSIM. Estimates of SSIM prevalence following BE endotherapy have varied widely, both within and across ablation modalities. Among a randomized study of patients treated with PDT, the prevalence of SSIM was reported to increase from 5.8% pre-treatment to 30% at 5-years post-treatment^[3]. In the AIM-Dysplasia trial, a randomized study of RFA plus proton pump inhibitor versus proton pump inhibitor alone, the prevalence of SSIM in the RFA arm was 25.2% pre-treatment, 5.1% at 12 mo post-treatment, and 3.8% at 24 mo post-treatment^[4,5]. A prospective study of RFA for treatment of nondysplastic BE, however, reported no SSIM in any of 1473 biopsy specimens from 50 subjects at 5 years post-treatment^[15].

An important variable which may influence the ability to identify SSIM, detectable only in specimens containing lamina propria structures, is biopsy depth following BE endotherapy. A recent study reported that lamina propria is present in fewer than 40% of biopsy specimens obtained from neosquamous esophageal epithelium following BE endotherapy^[16]. Given this significant limitation, the optimal comparison would be comparison of SSIM in EMR specimens pre-therapy and EMR specimens of neosquamous epithelium post-therapy. A high-volume European center

reported no SSIM in EMR specimens from 14 patients following RFA or combined EMR/RFA therapy for BE^[17].

Yet EMR is not likely to be acceptable for routine post-treatment surveillance of BE. As the current study demonstrates, although EMR is well-tolerated by the majority of patients, there is a limited but real risk of adverse events including bleeding and esophageal stricture formation. The potential need for improved means of detection and surveillance of SSIM may present an opportunity for endoscopic imaging modalities currently in development and capable of detailed intraluminal imaging of subsurface esophageal structures, including optical coherence tomography or optical frequency domain imaging^[9,18-20]. Ultimately, a full understanding of the clinical importance of SSIM will be achievable only through future study of SSIM in tissue specimens obtained from BE patients longitudinally at multiple time points during the course of disease^[21].

In summary, this study demonstrates that EMR detects SSIM in a majority of patients with BE-associated neoplasia. This finding should further dampen concerns that SSIM is a post-ablation phenomenon, and may fundamentally alter our understanding of the natural history of BE. As EMR becomes an increasingly important and widely utilized tool in the staging and therapy of BE, further attention to the detection and reporting of SSIM is necessary in order to define the clinical significance of this variant of intestinal metaplasia.

COMMENTS

Background

Barrett's esophagus (BE) refers to intestinal metaplasia of the esophageal mucosa, and is the principal risk factor for esophageal adenocarcinoma. BE has a characteristic salmon-colored appearance and is typically readily visible on endoscopic inspection. Subsquamous intestinal metaplasia (SSIM) is the term used to describe BE tissue which is buried beneath overlying squamous mucosa and not visible endoscopically. Esophageal neoplasia arising from SSIM has been reported. As the use of endoscopic ablation therapies for BE has grown, there are concerns that ablation will accelerate development of SSIM and lead to risk of neoplasia which is invisible or elusive to standard endoscopic surveillance.

Research frontiers

There are limited data regarding the prevalence and natural history of SSIM, particularly among BE patients who have not previously undergone endoscopic treatment. Esophageal biopsies may underestimate the prevalence of SSIM due to limited depth of biopsy samples. The aim of this study was to assess the prevalence of BE among patients undergoing endoscopic mucosal resection, an endoscopic technique which allows for removal of a tissue sample of much greater surface area and depth compared to a forceps biopsy.

Innovations and breakthroughs

This is the highest reported prevalence of SSIM in patients with BE naïve to endoscopic therapy.

Applications

The finding of a high prevalence of SSIM among patients with BE may alter the authors' understanding of the natural history of BE, and provide an opportunity for new technologies capable of imaging subepithelial structures to play a role in endoscopic surveillance of BE.

Terminology

Endoscopic mucosal resection (EMR), is an esophageal tissue resection technique which has important diagnostic and therapeutic value in the endoscopic management of Barrett's esophagus neoplasia. Subsquamous intestinal metaplasia (SSIM), informally referred to as "buried Barrett's", is the term used to describe glandular esophageal epithelium which is buried beneath overlying

squamous mucosa and not visible endoscopically.

Peer review

In his study, Dr. Linsdell provides a review of the physiological, biophysical and pharmacological relevance of a class of inhibitors of the CFTR channel, *i.e.*, the ones that directly block Cl movements across the open pore. The author has to be congratulated for this excellent work. The review is clear, well organised and written, and with effective figures. It will be an interesting reading also for non-experts in the field.

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Finding the solution for incomplete small bowel capsule endoscopy

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Abstract

AIM: To evaluate whether the use of real time viewer (RTV) and administration of domperidone to patients with delayed gastric passage of the capsule could reduce the rate of incomplete examinations (IE) and improve the diagnostic yield of small bowel capsule endoscopy (SBCE).

METHODS: Prospective single center interventional study, from June 2012 to February 2013. Capsule location was systematically checked one hour after ingestion using RTV. If it remained in the stomach, the patient received 10 mg domperidone per os and the location of the capsule was rechecked after 30 min. If the capsule remained in the stomach a second dose of

10 mg of domperidone was administered orally. After another 30 min the position was rechecked and if the capsule remained in the stomach, it was passed into the duodenum by upper gastrointestinal (GI) endoscopy. The rate of IE and diagnostic yield of SBCE were compared with those of examinations performed before the use of RTV or domperidone in our Department (control group, January 2009 - May 2012).

RESULTS: Both groups were similar regarding age, sex, indication, inpatient status and surgical history. The control group included 307 patients, with 48 (15.6%) IE. The RTV group included 82 patients, with 3 (3.7%) IE, $P = 0.003$. In the control group, average gastric time was significantly longer in patients with IE than in patients with complete examination of the small bowel (77 min vs 26 min, $P = 0.003$). In the RTV group, the capsule remained in the stomach one hour after ingestion in 14/82 patients (17.0%) vs 48/307 (15.6%) in the control group, $P = 0.736$. Domperidone did not significantly affect small bowel transit time (260 min vs 297 min, $P = 0.229$). The capsule detected positive findings in 39% of patients in the control group and 49% in the RTV group ($P = 0.081$).

CONCLUSION: The use of RTV and selective administration of domperidone to patients with delayed gastric passage of the capsule significantly reduces incomplete examinations, with no effect on small bowel transit time or diagnostic yield.

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Key words: Small bowel capsule endoscopy; Prokinetic drugs; Domperidone; Incomplete examination

Core tip: Incomplete small bowel capsule endoscopy (SBCE) is an important limitation of the technique and may occur in up to 20% of patients. Delayed gastric passage of the capsule is a major factor leading to incomplete SBCE. Selective administration of oral dom-

peridone to patients with delayed gastric passage of the capsule assessed with the real time viewer (RTV) effectively reduces the rate of incomplete SBCE. The administration of domperidone does not influence small bowel transit time of the capsule. There is an overall trend towards higher diagnostic yield of SBCE when domperidone is selectively administered. The use of the RTV should be adopted systematically in patients undergoing small bowel capsule endoscopy.

Cotter J, Dias de Castro F, Magalhães J, Moreira MJ, Rosa B. Finding the solution for incomplete small bowel capsule endoscopy. *World J Gastrointest Endosc* 2013; 5(12): 595-599 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i12/595.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i12.595>

INTRODUCTION

Small bowel capsule endoscopy (SBCE) was introduced in clinical practice in 2001, and it proved to be a valuable non-invasive technique to examine the small-bowel^[1]. SBCE may be useful in a wide range of clinical settings, such as obscure gastrointestinal (GI) bleeding^[2], suspected and known Crohn's disease (CD)^[3-5], celiac disease^[6] and polyposis syndromes^[7], with a higher diagnostic yield when compared to conventional diagnostic techniques^[2,4,8-11]. An important limitation of SBCE is the possibility of incomplete examination of the small-bowel, which occurs when the capsule does not reach the cecum within the recording time of approximately 9 h. The rate of IE is approximately 20% to 30% in most studies^[12,13]. In such cases, the value of SBCE is limited by the fact that it may miss lesions located in the distal segments of the small bowel, eventually leading to the need for further examinations and increased costs^[14]. Retrospective studies identified some factors that may be associated with incomplete small-bowel SBCE examination, such as inpatient status^[14], previous abdominal surgery^[14] and prolonged gastric transit time (GTT)^[14,15], while the effect of age or medical conditions such as diabetes mellitus remains controversial^[16]. Currently, there is no consensus regarding the use of prokinetic drugs in SBCE to reduce the rate of IE with SBCE^[17]. In theory, prokinetics might be useful by improving gastric emptying, but their routine use in patients submitted to SBCE is not widely established^[17]. Randomized prospective studies failed to demonstrate an improvement in SBCE completion rates with the use of metoclopramide, administered before the procedure^[18,19]. One of the recent advances in the field of SBCE is the availability of a portable external viewer for direct monitoring of the images received during the procedure. The new Given® Data Recorder (DR3) with the real time viewer (RTV) enables real-time viewing during SBCE procedure (Figure 1). The European Society of Gastrointestinal Endoscopy (ESGE) recommended that patients at increased

risk for IE might benefit from the use of the RTV periprocedurally, with subsequent endoscopic placement of the capsule in the duodenum when indicated^[20]. The aim of our study was to assess whether the prokinetic agent domperidone, in association with the RTV, could reduce the rate of IE and improve the diagnostic yield of SBCE.

MATERIALS AND METHODS

We conducted a single center prospective interventional study, comparing the use of domperidone in association with RTV in consecutive patients undergoing SBCE from June 2012 to February 2013 (RTV group) *vs* a control group of patients who had been submitted to SBCE following the standard procedure with no use of RTV or domperidone, from January 2009 to May 2012, in our Department. The RTV images were viewed by gastroenterologists with a large experience in SBCE to check the capsule position during the procedure. The RTV was used to confirm the passage of the capsule to the small-bowel one hour after ingestion. If the capsule remained in the stomach, 10 mg of domperidone were administered *per os* and the location of the capsule was rechecked after 30 min. If it still remained in the stomach, an additional dose of 10 mg of domperidone was administered orally and after another 30 min the location of the capsule was rechecked; then if still in the stomach the capsule was placed directly in the duodenum by upper endoscopy using a basket. All patients followed a 24 h clear liquid diet and 12 h fasting prior to SBCE (PillCam® SB2, Given® Imaging Ltd. Yoqneam, Israel), and were advised not to eat for 4 h after swallowing the capsule. No oral purge was administered. Patients with obstructive symptoms, known small bowel strictures and/or in whom some bowel purge or prokinetics were used did not enter the study. One experienced gastroenterologist, with more than 100 SBCE procedures, reviewed SBCE images using RAPID Reader® (Given® Diagnostic Imaging System, Given® Imaging). The completion rate was defined as the frequency of SBCE reaching the cecum within the battery life (approximately 9 h). Gastric transit time (GTT) was recorded from the first gastric image to the first duodenum image, and small-bowel transit time (SBTT) was recorded from the first duodenum image to the first cecal image, or alternatively the last image of the small bowel if the capsule did not reach the cecum within recording time.

Statistical analysis

Continuous variables were expressed as mean \pm SD and analyzed with the unpaired *t*-test. Fisher's exact test was used to compare incomplete examinations rate and diagnostic yield between the two groups. A *P*-value of less than 0.05 was considered statistically significant. Statistical analysis was performed using SPSS® (version 17.0 for Windows®, SPSS inc®, Chicago, IL, USA). All patients gave their informed consent prior to their inclusion in



Figure 1 Real time viewer detecting the capsule inside the stomach more than one hour after ingestion.

the study.

RESULTS

A total of 84 consecutive SBCE were performed after the introduction of RTV in our Department. Two procedures were excluded because the capsule was *ad initium* passed into the duodenum under endoscopic assistance using the AdvanCE[®] delivery system. In the control group, a total of 359 SBCE were retrospectively reviewed. Forty procedures were excluded because patients had received bowel preparation with polyethylene glycol prior to SBCE in the setting of a clinical trial^[21], and another 12 patients were excluded because the capsule was immediately passed into the duodenum under endoscopic assistance using the AdvanCE[®] system, due to swallowing disorders or previous gastric surgery. Thus, a total of 82 patients using the RTV and 307 matched controls were included in the study analysis. The baseline clinical characteristics and indications for SBCE in both groups are summarized in Table 1. Variables such as age, gender, previous abdominal surgery, inpatient status and indication for SBCE were not significantly different between the two groups. The rate of IE was 15.6% ($n = 48$) in the control group *vs* 3.7% ($n = 3$) in the RTV group ($P = 0.003$). In the RTV group, domperidone was administered in 14/82 patients (17.0%), in whom the capsule remained in the stomach 1 h after ingestion, while in the control group the proportion of patients with the capsule remaining in the stomach 1 h after ingestion was 48/307 (15.6%), $P = 0.736$. In the control group, average gastric time was significantly longer in patients with IE than in patients with complete examina-

tion of the small bowel (77 min *vs* 26 min, $P = 0.003$). In the RTV group, no differences were observed in the SBTT among patients who received or did not receive domperidone (260 min *vs* 297 min, $P = 0.229$). In one patient (7.0%) out of the 14 patients in the RTV group in whom domperidone was administered, the capsule remained in the stomach two hours after ingestion, and an upper endoscopy was performed to deliver the capsule to the duodenum using a basket. SBCE positive findings were observed in 39% of the control group *vs* 49% of the RTV group ($P = 0.081$). None of the 14 patients who received domperidone had any side effect related to the drug.

DISCUSSION

SBCE emerged as a valuable non-invasive diagnostic technique to investigate the entire small-bowel. However, a major drawback is the rate of incomplete examinations, reaching up to 20% to 30%^[12,13]. Some conditions have been associated with incomplete small bowel examination, such as inpatient status^[14] or previous abdominal surgery^[14], while the effect of age or medical conditions such as diabetes mellitus remain controversial^[16]. Importantly, delayed GTT has been consistently reported as a leading cause of incomplete small bowel examination^[14,15]. Our study supports the hypothesis that the systematic use of the RTV included in the new Given[®] Data Recorder (DR3), in association with domperidone to overcome delayed gastric transit in selected cases, enhances the completion rate of SBCE. Domperidone is a type II dopamine antagonist similar to metoclopramide, with similar effects on gastric emptying but with lower central side effects^[22]. Domperidone is not approved by the FDA for use in the United States but is widely used in Europe. To our knowledge, none of the published studies in this area used domperidone as a prokinetic to improve cecal intubation rates. A recent randomized controlled trial which used intramuscular metoclopramide 15 min before capsule ingestion, reported a decrease in GTT with no change in SBTT or complete examination rate^[23], reinforcing that it may also be influenced by other variables. In our study, domperidone significantly contributed to reduce the rate of IE. The drug was only administered in patients with delayed gastric passage of the capsule, documented with the RTV. Moreover, there was no significant difference in SBTT among patients who received or did not receive domperidone. The fact that the SBTT was similar in patients receiving or not domperidone (260 min *vs* 297 min, respectively, $P = NS$) is relevant, because it supports the hypothesis that delayed gastric emptying may be a more determinant factor leading to incomplete SBCE than delayed transit of the capsule in the small bowel; the fact that the transit time of the capsule in the small bowel is not significantly reduced by the prokinetic is also important, because a faster passage of the capsule through the small bowel has been associated with lower diagnostic yield

Table 1 Control group *vs* real time viewer group: Baseline characteristics and outcomes *n* (%)

	Control group (<i>n</i> = 307)	RTV group (<i>n</i> = 82)	<i>P</i> -values
Age (mean ± SD), yr	49.7 ± 20.7	48 ± 20.5	0.518 ¹
Gender (male/female)	(136/171)	(32/50)	0.452 ²
History of abdominal surgery	24 (8)	12 (15)	0.083 ²
Inpatient status	38 (12.3)	10 (12.2)	1.00 ²
Clinical indication			0.079 ³
OGIB-occult	117 (38)	26 (32)	
OGIB-overt	46 (15)	6 (7)	
Suspected CD	83 (27)	29 (35)	
CD staging	33 (11)	11 (14)	
Other indications	28 (9)	10 (12)	
Incomplete examination	48 (15.6)	3 (3.7)	0.003 ²
Positive findings	120 (39)	40 (49)	0.081 ³

P-values were calculated using unpaired *t*-test¹, Fisher's exact test² (b) and Pearson χ^2 ³. OGIB: Obscure gastrointestinal bleeding; CD: Crohn's disease; RTV: Real time viewer.

of SBCE^[24]. Indeed, Westerhof *et al*^[24] found a positive correlation between the diagnostic yield of SBCE and longer small bowel transit time, irrespective of whether the capsule reached the cecum within recording time. In our series, despite the reduction of IE, we did not find a significantly higher diagnostic yield in the RTV group (49% *vs* 39% in the control group). Recently, Gao *et al*^[20] showed that delivering the capsule to the duodenum by upper endoscopy using a basket in patients with delayed gastric transit, identified with RTV, improved the rate of complete small-bowel examinations, resulting in higher diagnostic yield of SBCE. We could speculate whether it would be useful to routinely place the capsule in the duodenum with the AdvanCE[®] from the beginning of the examination. However, this strategy would be both invasive and add costs to a procedure that is already expensive. Moreover, it is not possible to accurately predict to which patients it would be helpful, making it unsuitable to implement as a routine procedure in clinical practice. In our study, only one patient in the RTV group required endoscopic-assisted placement of the capsule into the duodenum. Our results support that to overcome delayed gastric transit time identified by the RTV, non-invasive procedures such as selective administration of oral domperidone to patients with delayed gastric passage of the capsule documented with the RTV, should be the method of choice. This strategy has the merit of strictly selecting the patients to undergo pharmacological and/or flexible endoscopic intervention. Further studies are needed to support the association between complete examination and higher diagnostic yield of SBCE^[25]. Although this was not a prospective randomized clinical trial, both groups were homogeneous regarding the most common conditions associated with incomplete SBCE. In conclusion, our results support that the use of RTV to monitor the position of the capsule during SBCE and administration of domperidone in the case of delayed gastric passage, significantly enhances the completion rate of SBCE. Whether such strategy could contribute

to improve the diagnostic yield of SBCE will require further investigation.

COMMENTS

Background

In up to 20% of patients undergoing small bowel capsule endoscopy (SBCE) the examination is incomplete. This is a major limitation of this expensive technique, leading to further examinations and expended time and resources. There is ongoing debate on which factors are associated with incomplete examinations and what are the optimal strategies to overcome this issue.

Research frontiers

It has been consistently shown that delayed gastric passage of the capsule is a major factor leading to incomplete examinations. The authors evaluated the effect of the prokinetic drug domperidone for improvement of completion of SBCE, with the routine use of real time viewer (RTV) included in the Data Recorder DR3.

Innovations and breakthroughs

After confirmation with RTV for the presence or absence of the capsule in the stomach at 1 h, selective administration of 10 mg domperidone to those patients with delayed gastric passage of the capsule has the effect to decrease gastric transit time and leads enough to bring down the rate of incomplete examinations, without affecting small bowel transit time.

Applications

This simple and very practical method significantly reduced the rate of incomplete examinations of SBCE. Thus, the authors suggest that the use of the RTV and administration of domperidone for those patients with delayed gastric passage of the capsule should become the standard of practice.

Terminology

SBCE incomplete examination occurs when the capsule does not reach the cecum within the battery lifetime. The RTV is included in the Data Recorder DR3 (Given[®]), allowing for the real time location of the position of the capsule inside the GI tract. Domperidone is a type II dopamine antagonist which may be used to promote gastric emptying.

Peer review

In this study, Cotter *et al* demonstrate that the systematic use of RTV to recognize patients with delayed gastric passage of the capsule, and selective oral administration of domperidone to these patients is not only an easy and very practical method but also is beneficial for significant reduction of the rate of IE, without affecting small bowel transit time.

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Repeat endoscopic submucosal dissection for recurrent gastric cancers after endoscopic submucosal dissection

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Abstract

AIM: To clarify the safety and efficacy of repeat endoscopic submucosal dissection (re-ESD) for locally recurrent gastric cancers after ESD.

METHODS: A retrospective evaluation was performed of the therapeutic efficacy, complications and follow-up results from ESD treatment for early gastric cancers in 521 consecutive patients with 616 lesions at St. Luke's International Hospital between April 2004 and November 2012. In addition, tumor size, the size of resected specimens and the operation time were compared between re-ESD and initial ESD procedures. A flex knife was used as the primary surgical device and a hook knife was used in cases with severe fibrosis in the submucosal layer. Continuous variables were analyzed using the non-parametric Mann-Whitney *U* test and are expressed as medians (range). Categorical

variables were analyzed using a Fisher's exact test and are reported as proportions. Statistical significance was defined as a *P*-value less than 0.05.

RESULTS: The number of cases in the re-ESD group and the initial ESD group were 5 and 611, respectively. The median time interval from the initial ESD to re-ESD was 14 (range, 4-44 mo). *En bloc* resection with free lateral and vertical margins was successfully performed in all re-ESD cases without any complications. No local or distant recurrence was observed during the median follow-up period of 48 (range, 11-56 mo). Tumor size was not significantly different between the re-ESD group and the initial ESD group (median 22 mm vs 11 mm, *P* = 0.09), although the size of resected specimens was significantly larger in the re-ESD group (median 47 mm vs 34 mm, *P* < 0.05). There was a non-significant increase observed in re-ESD operation time compared to initial ESD (median 202 min vs 67 min, respectively, *P* = 0.06).

CONCLUSION: Despite the low patient number and short follow-up, the results suggest that re-ESD is a safe and effective endoscopic treatment for recurrent gastric cancer after ESD.

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Key words: Endoscopic submucosal dissection; Recurrent gastric cancer; Gastric cancer; Endoscopic mucosal resection; Therapeutic endoscopy

Core tip: Although endoscopic submucosal dissection (ESD) is widely accepted as one of the standard treatments for early gastric cancers, there are few reports on re-ESD in the literature. This study clarifies that re-ESD is a safe and effective endoscopic treatment for locally recurrent gastric cancers after ESD.

Shimamura Y, Ishii N, Nakano K, Ikeya T, Nakamura K, Takagi K, Fukuda K, Suzuki K, Fujita Y. Repeat endoscopic submucosal dissection for recurrent gastric cancers after endoscopic submucosal dissection. *World J Gastrointest Endosc* 2013; 5(12): 600-604 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i12/600.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i12.600>

INTRODUCTION

Early gastrointestinal neoplasms have a low frequency of lymph node and distant metastases, which enables less invasive treatments using therapeutic endoscopy^[1-4]. Endoscopic mucosal resection (EMR) is an accepted minimally invasive treatment for early gastrointestinal neoplasms^[5-9]. Endoscopic submucosal dissection (ESD) is a safe and effective endoscopic treatment technique that directly dissects the submucosal layer allowing *en bloc* resection of early gastric cancers (EGCs). It improves the quality of life compared with surgical treatment and has an important role in the treatment of EGCs^[10-13]. Although ESD yields histologically complete resections, cases of locally recurrent gastric tumors after initial ESD still occur^[14-16].

There is currently no established standard treatment for these recurrent lesions, and there are few reports on repeated ESD (re-ESD) procedures. Therefore, the aim of the present study was to clarify the safety and efficacy of re-ESD for locally recurrent gastric cancers.

MATERIALS AND METHODS

Study populations

The clinical database of all patients who underwent ESD for EGCs at St. Luke's International Hospital, Tokyo was retrospectively reviewed. Gastric ESD was performed in a total of 521 consecutive patients with 616 lesions and re-ESD was performed in five locally recurrent gastric cancers between April 2004 and November 2012. Gastric cancer treatment guidelines were applied to all re-ESD cases including those issued in 2004 and 2010 by the Japanese Gastric Cancer Association as well as the proposed extended criteria of Gotoda *et al*^[17,18].

Re-ESD methods

Re-ESD was performed with a conventional single-accessory-channel endoscope (GIF-Q260J; Olympus Medical Systems, Tokyo, Japan). Marking dots for the incision were made 3-5 mm outside of lesion margins with a flex knife^[19-21] (Flex Knife™, KD-630L; Olympus Medical Systems, Tokyo, Japan) (Figure 1A and B). A solution of 0.4%-0.5% sodium hyaluronate was injected into the submucosal layer beneath the lesion, and circumferential incisions were made around the marking dots with a flex knife. In cases where severe fibrosis prevented injection of the sodium hyaluronate solution, a hook knife (Hook Knife, KD-620LR; Olympus Medical Systems) was used for the dissection of the fibrotic layer^[22-24] (Figure 1C). Hemostatic forceps (SDB2422; Pentax Co, Tokyo, Japan)

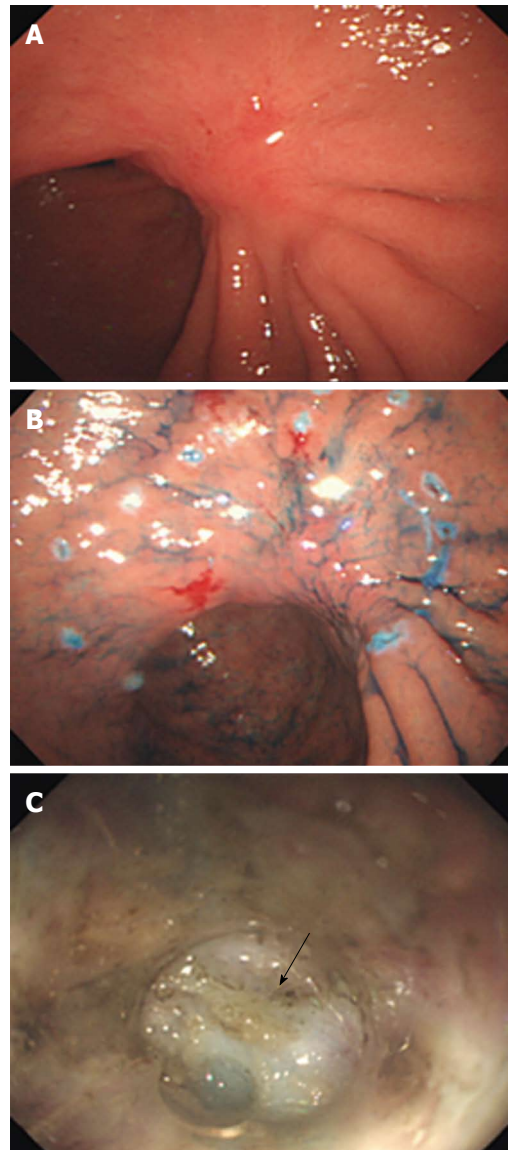


Figure 1 Conventional endoscopic view. A: Showing locally recurrent gastric cancer located in the lesser curvature of the gastric angulus; B: Marking dots for the incision delineating the outside margin of the lesion; C: Severe submucosal fibrosis was observed through a small-caliber transparent hood (arrow).

were used during the procedure to control bleeding while the re-ESD was completed (Figures 2 and 3).

Pathological assessment

Perpendicular sections at 2 mm intervals of re-ESD specimens were evaluated. Treatment was considered curative if specimens did not indicate invasion deeper than the submucosal or lymphovascular layer or show lateral and vertical margin involvement. *En bloc* resection was defined as resection of the entire lesion in one piece. All resections were categorized according to the National Comprehensive Cancer Network (NCCN) as follows: negative resection margin (R0), microscopic tumor infiltration (R1), and macroscopic residual tumor (R2). Endoscopic examinations and computed tomography (CT) were performed at 6 mo after re-ESD to check for local



Figure 2 View of the post-endoscopic submucosal dissection ulcer.

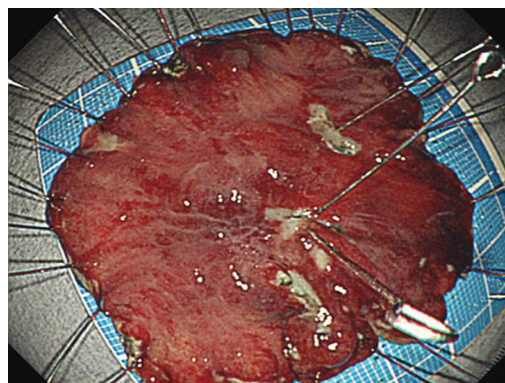
Figure 3 *En bloc* resection of the tumor without any complications.

Table 1 Characteristics of 5 initial endoscopic submucosal dissection cases

Patient No.	Sex	Age, yr	Tumor location	Macroscopic type	Tumor size, mm	Specimen size, mm	Operation time, min	Histological type	Resection margin category
1	Male	78	LB LC	I + IIa	23	40	69	Tub2	R0
2	Male	67	LB PW	IIc	8	37	70	Tub1	R0
3	Male	64	Ant PW	IIa + IIc	14	36	47	Tub1	R0
4	Male	76	Ang PW	IIc	65	70	442	Tub2	R1
5	Male	51	Ang LC	IIc	40	45	44	Tub2	R0
Median		67			23	40	69		

Ang: Angulus; Ant: Antrum; LB: Lower body; LC: Lesser curvature; PW: Posterior wall; R0: Negative resection margin; R1: Microscopic tumor infiltration; Tub1: Well differentiated adenocarcinoma; Tub2: Moderately differentiated adenocarcinoma; I: Elevated lesion; IIa: Slightly elevated lesion; IIc: Slightly depressed lesion.

Table 2 Characteristics of re-endoscopic submucosal dissection in 5 cases

Patient No.	Time after initial ESD, mo	Macroscopic type	Tumor size, mm	Specimen size, mm	Operation time, min	Histological type	Resection margin category	Complication
1	44	IIa	22	47	210	Tub2	R0	None
2	9	IIc	8	45	82	Tub1	R0	None
3	14	IIc	11	32	43	Tub1	R0	None
4	12	IIc	27	59	353	Tub1	R0	None
5	4	IIc	42	77	202	Por	R0	None
Median	14		22	47	202			

R0: Negative resection margin; Tub1: Well differentiated adenocarcinoma; Tub2: Moderately differentiated adenocarcinoma; Por: Poorly differentiated adenocarcinoma; IIa: Slightly elevated lesion; IIc: Slightly depressed lesion; ESD: Endoscopic submucosal dissection.

recurrence as well as lymph node and distant metastases.

Statistical analysis

Continuous variables were analyzed using the non-parametric Mann-Whitney *U* test and are expressed as median (range). Categorical variables were analyzed using a Fisher's exact test and are reported as proportion. Statistical significance was defined as a *P*-value less than 0.05.

RESULTS

The characteristics of the initial ESD for 5 cases are summarized in Table 1. One patient was considered R1 with positive horizontal margins, but others were considered R0 with complete resection. Of the initial ESD proce-

dures evaluated, 97.6% (601/616) were *en bloc* resections, 1.3% (8/616) required additional surgical intervention due to an incomplete resection (such as deep invasion of the tumor or lymph vascular invasion), 1.3% (8/616) resulted in postoperative bleeding, and 1.8% (11/616) had perforation. Pathological evaluation resulted in categorization of 95.3% (587/616) of resections as R0, with the remaining 4.7% (29/616) as R1 resections.

Five of the 616 cases developed locally recurrent tumors and were treated by re-ESD (Table 2). The median time interval from the initial ESD to re-ESD was 14 (range, 4-44 mo). *En bloc* resections with free lateral and vertical margins were successfully performed without any complications in all re-ESD cases. Furthermore, there were no local or distant recurrences observed during the follow-up period, at a median of 48 (range, 11-56 mo).

Table 3 Comparisons between re-endoscopic submucosal dissection and initial endoscopic submucosal dissection cases

	Re-ESD (n = 5)	Initial ESD (n = 606)	P value
Tumor size	22 mm	11 mm	0.09
Median (range)	(8-42 mm)	(1.5-65 mm)	
Specimen size	47 mm	34 mm	0.02
Median (range)	(32-77 mm)	(13-92 mm)	
Operation time	202 min	67 min	0.06
Median (range)	(43-353 min)	(10-510 min)	

ESD: Endoscopic submucosal dissection.

There was no significant difference in tumor size between re-ESD cases and all initial cases (22 mm *vs* 11 mm). However, there was a tendency for increased operation time for ESD procedures (202 min *vs* 67 min, $P = 0.06$), and re-ESD specimens were significantly larger than the initial resected specimens (47 mm *vs* 34 mm, $P = 0.02$) (Table 3).

DISCUSSION

ESD is accepted as one of the standard treatments for EGCs, enabling large *en bloc* resections. While this procedure typically results in histologically complete resections, cases of locally recurrent gastric tumors have occurred, with reported incidence rates between 0% and 3%^[14-16,25]. Laparoscopic wedge resection, intragastric surgery, and laparoscopic-associated distal gastrectomy are some of the invasive treatment options for locally recurrent gastric cancers^[26-28]. A recent report by Higashimaya *et al.*^[25] documented re-ESD as a minimally invasive, safe and effective procedure in a series of recurrent EGCs. In this study, re-ESD was successfully performed by *en bloc* resection with free lateral and vertical margins without any complications. Treatment of locally recurrent gastric cancers using the re-ESD technique results in less pain, less mortality, and shorter hospital stays, which obviates invasive surgical interventions.

Re-ESD operations tended to take longer than the initial ESD procedures, possibly because the tumor specimens were larger in size. The re-ESD procedure is considered technically difficult as a result of severe fibrosis in the submucosal layer that occurs at the site of the initial ESD. There is currently no efficient ESD method for lesions with submucosal fibrosis, therefore the surrounding tissue should first be dissected to evaluate the anatomical structure, followed by dissection towards the fibrotic lesion. Of additional importance in performing ESD and re-ESD procedures is the selection of an appropriate electrosurgical knife, such as a flash knife, flex knife, dual knife, or as in this study, the hook knife, which was used to dissect the submucosal layer with severe fibrosis.

Several limitations of this study should be noted. First, the study was of a retrospective design involving a limited number of cases from a single center, as the recurrence rate after ESD is very low. Second, even though experienced endoscopists performed the re-ESDs, the success

rate depends on the technical proficiency of the endoscopists and the condition of the lesion. Although structural differences may result in variations in technical difficulty, this study did not establish whether the location of the lesion or macroscopic type affects the difficulty of the procedure.

In conclusion, this study demonstrates that re-ESD is a safe and effective endoscopic treatment for locally recurrent gastric cancer after ESD. As a result of the limited case number, further studies evaluating larger sample sizes and longer follow-ups are needed to assess the use of this procedure as a standard treatment for recurrent gastric tumors.

COMMENTS

Background

Endoscopic resection has been accepted as a minimally invasive treatment for early gastrointestinal neoplasms. Endoscopic submucosal dissection (ESD) allows for the dissection of the submucosa with resection of lesions *en bloc*. Although complete resection is expected in this procedure, incidences of local recurrence after the initial ESD are not fully eliminated. There is currently no standard treatment for these locally recurrent gastric cancers.

Research frontiers

There are few reports on repeat endoscopic submucosal dissection (re-ESD) for locally recurrent gastric cancers, and the safety and efficacy of this procedure have not been unequivocally addressed. In this study, the authors encountered 5 cases of recurrent gastric cancers, which were successfully treated with re-ESD procedures.

Innovations and breakthroughs

Repeat ESD for locally recurrent gastric tumors is not yet considered a standard treatment. This study demonstrates the safety and efficacy of the re-ESD technique. Furthermore, comparisons were made of tumor size, resected specimen size, and operation time between initial ESD and re-ESD procedures.

Applications

By demonstrating that re-ESD is a safe and effective therapy, this study presents a strategy for the treatment of patients with recurrent gastric tumors.

Terminology

ESD is a minimally invasive endoscopic technique for the treatment of early gastrointestinal neoplasms allowing direct dissection of the submucosal layer of the lesion with *en bloc* resection. Re-ESD is an endoscopic treatment technique for gastric tumors that locally recur after an initial ESD.

Peer review

The authors describe the treatment of recurrent early gastric cancers with re-ESD in a retrospective study. Five cases of recurrent tumors that were encountered following ESD treatment of early gastric cancer are described and analyzed. The employment of re-ESD procedures resulted in successful treatments with no observed complications, which may facilitate the establishment of this method as a standard treatment for recurrent gastric lesions.

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A case of neuroendocrine tumor G1 with unique histopathological growth progress

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Abstract

A gastric neuroendocrine tumor (NET) is generated from deep within the tissue mucosal layers. In many cases, NETs are discovered as submucosal tumor (SMT)-like structures by forming a tumor mass. This case has a clear mucosal demarcation line and developed like a polyp. A dilated blood vessel was found on the surface. The mass lacked the yellow color characteristic of NETs, and a SMT-like form was evident. Therefore, a nonspecific epithelial lesion was suspected and we performed endoscopy with magnifying narrow-band imaging (M-NBI). However, this approach did not lead to the diagnosis, as we diagnosed the lesion as a NET by biopsy examination. The lesion was excised by endoscopic submucosal dissection. The histopathological examination proved that the lesion was a polypoid lesion although it was also a NET because the tumor

cells extended upward through the normal gland ducts scatteredly. To our knowledge, there is no previous report of NET G1 with such unique histopathological growth progress and macroscopic appearance shown by detailed examination using endoscopy with M-NBI.

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Key words: Neuroendocrine tumor G1; Demarcation line; Polypoid growth; Magnifying narrow-band imaging; Submucosal tumor

Core tip: Neuroendocrine tumors which infiltrate into the mucosa may develop a polypoid appearance mimicking a primary epithelial process.

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INTRODUCTION

Gastric neuroendocrine tumors (NETs) are relatively rare lesions representing approximately 7% of all neuroendocrine tumors and less than 1% of all stomach neoplasms^[1]. Most gastric NETs are found incidentally during upper gastrointestinal (GI) endoscopy^[2-6]. Gastric NETs usually have the endoscopic appearance of a submucosal tumor because they grow from deep within the mucosal layers and the tumor mass is yellow. The yellow submucosal tumor (SMT) can be detected by white light and the dilated blood vessel on the surface, which is considered to be a secondary change. Gastric NETs comprise 7%

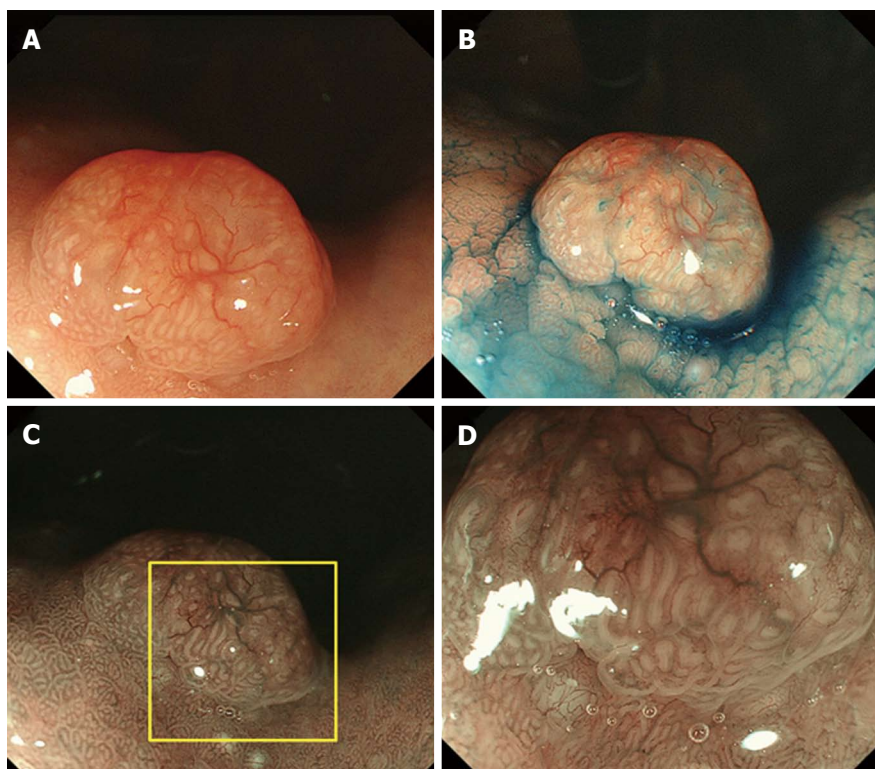


Figure 1 An 8-mm protruded lesion was shown at upper endoscopy. A: Upper endoscopy revealed an 8-mm protruded lesion on the anterior wall of the stomach body. The lesion is the same color as background mucosa and it is not yellow; B: Indigo carmine dye permitted the lesion's demarcation line to become more distinct; C, D: There were dilated vessels on the surface, but neither irregular microvessel patterns nor irregular microsurface patterns were observed by magnifying narrow-band imaging.

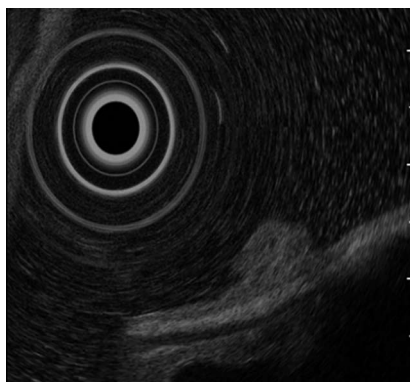


Figure 2 Endoscopic ultrasonography. Endoscopic ultrasonography showed a protruding lesion 8 mm in diameter in the mucosal layer that did not affect the submucosal layer.

of all gastrointestinal NETs and 2% of all excised gastric polyps^[7,8]. Randi *et al*^[9] classified gastric NETs into three subtypes. Type I NETs typically arise from enterochromaffin-like cell (ECL) hyperplasia, which is stimulated by hypergastrinemia on a background of atrophic gastritis, especially type A gastritis. Type II lesions are associated with gastrinomas resulting in Zollinger-Ellison syndrome (ZES). Type III lesions are a sporadic disease associated with normal gastrin levels. In type I and II diseases, several polyps are often seen in clusters. However, type III lesions are usually solitary. The surrounding mucosa may be macroscopically normal, especially in type III lesions.

Additionally, there may be evidence of atrophy (type I) or associated peptic ulcer (type II). Here, we report a case of a type I gastric NET without submucosal tumor shape that extended through the normal gland ducts and developed with polypoid growth.

CASE REPORT

A 61-year-old man presented to his primary care physician with the complaint of mild epigastralgia. An upper GI endoscopy revealed an 8-mm, well-demarcated, protruding lesion on the anterior wall of the stomach body. Therefore, the patient was referred to our hospital. The lesion did not have the reddened appearance of strong inflammation and erosion on the surface like a hyperplastic polyp. The surrounding mucosa was not atrophic. In addition, the lesion was solitary (Figure 1A, B), which contrasts fundic gland polyps that develop as multiple small polyps. Therefore, we performed an endoscopy with magnifying narrow-band imaging (M-NBI) for further evaluation. There were dilated vessels on the surface of the lesion, but there were neither irregular microvessel patterns nor irregular microsurface patterns that indicated neoplastic change under M-NBI (Figure 1C, D). However, the lesion was considered an epithelial neoplasm because the demarcation line was distinct. The pathological evaluation of the biopsy specimen showed the mass was a NET. Endoscopic ultrasonography showed a protruding lesion in the mucosal layer that did not affect the sub-

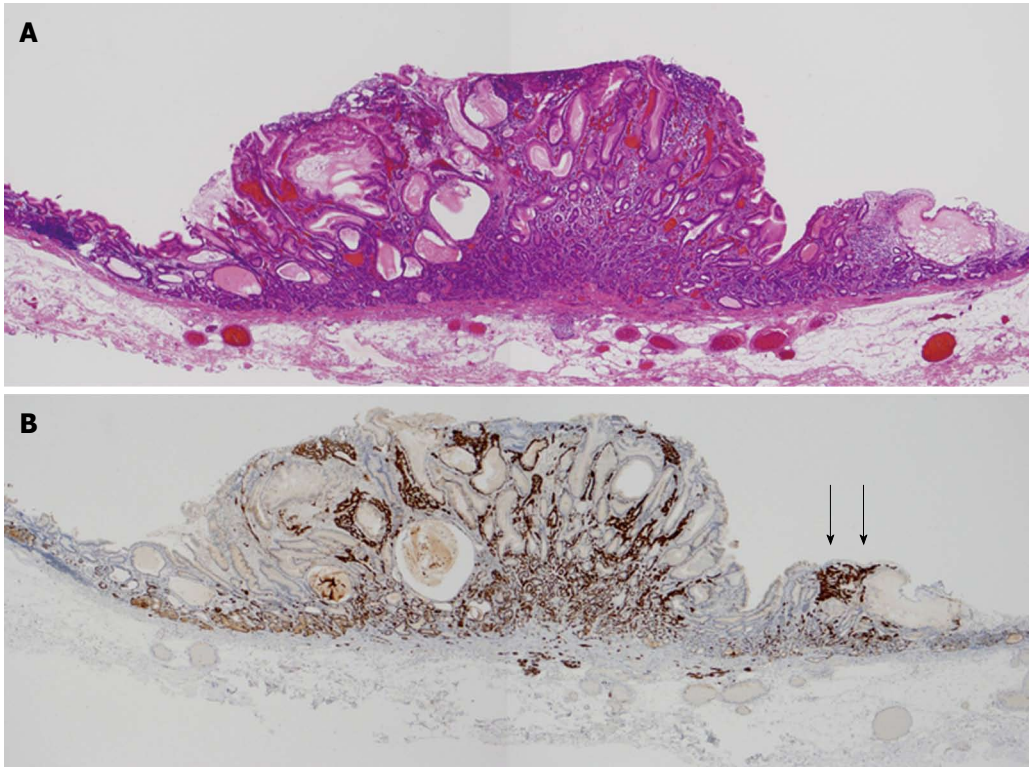


Figure 3 Histological examination of the resected specimen. A: Microscopic examination of the completely resected specimen revealed a neuroendocrine tumor presenting in both the mucosal layer and submucosal layer (hematoxylin and eosin staining); B: Immunohistochemistry for synaptophysin showed that the tumor extended through the normal gland ducts randomly. Enterochromaffin-like cell micro-nests were observed below the normal mucosa (arrow).

mucosal layer (Figure 2).

The laboratory tests revealed normal serum pepsinogen I and serotonin levels, but a markedly increased serum gastrin level (1400 pg/mL; normal range, < 170) and parietal cell antibody level ($\times 20$; normal range, < $\times 9$). The test for anti-*Helicobacter pylori* IgG was negative. Whole body imaging procedures (CT-scan and abdominal ultrasonography) did not reveal metastatic involvement of any other organ.

We determined the lesion was an atypical gastric NET and conducted endoscopic submucosal dissection. The histopathologic findings of the resected lesion led to the diagnosis of a neuroendocrine tumor of 8 mm \times 9 mm. The tumor cells extended through the normal gland ducts scatteredly and infiltrated the submucosal and mucosal layers (Figure 3). Analysis by immunohistochemistry showed positivity for chromogranin A, synaptophysin, and CD56. The Ki-67 proliferation index was 1% (Figure 4). There were numerous ECL hyperplasias and micronests observed under the protruded lesion and in the normal mucosa around the lesion (Figure 3B, yellow arrow). According to the updated Sydney System, intestinal metaplasia was absent. Activity (granulocytic infiltration), inflammation (lymphocytic and mononuclear cell infiltration) and atrophy were moderate at the fornix mucosa and body of the stomach.

As a result of our analysis, we diagnosed the case as a type I neuroendocrine tumor G1 with a very atypical morphological and pathological growth that developed in

the background of type A gastritis.

DISCUSSION

Type I NET is the most common lesion type and comprises approximately 70% to 80% of all gastric carcinoids^[5,10-12]. According to the World Health Organization's histological classification of gastrointestinal endocrine tumors, a well-differentiated endocrine tumor (synonymous with carcinoid) is defined as an epithelial tumor of usually monomorphous endocrine cells. These tumors have mild or no atypia, grow in the form of solid nests, trabeculae, or pseudoglandular tumors, and are restricted to the mucosa or submucosa^[13]. Due to these features, most gastrointestinal NETs have the appearance of submucosal tumors and are visibly yellow by endoscopic examination. However, in the present case, the tumor extended through the normal gland duct scatteredly and did not present a submucosal tumor shape. The result was a well-demarcated polypoid growth presenting like an epithelial neoplasm by endoscopy. The lesion was not yellow and did not present as a tumor except for the mass. Moreover, the lesion did not have the appearance of a hyperplastic polyp and fundic gland polyp.

The percentage of gastric carcinoids amongst all gastric malignancies has increased from 0.3% to 1.77% since the 1950s. The proportion of gastric carcinoids among all gastrointestinal carcinoids has increased from 2.4% to 8.7%^[7]. One reason for the increased detection

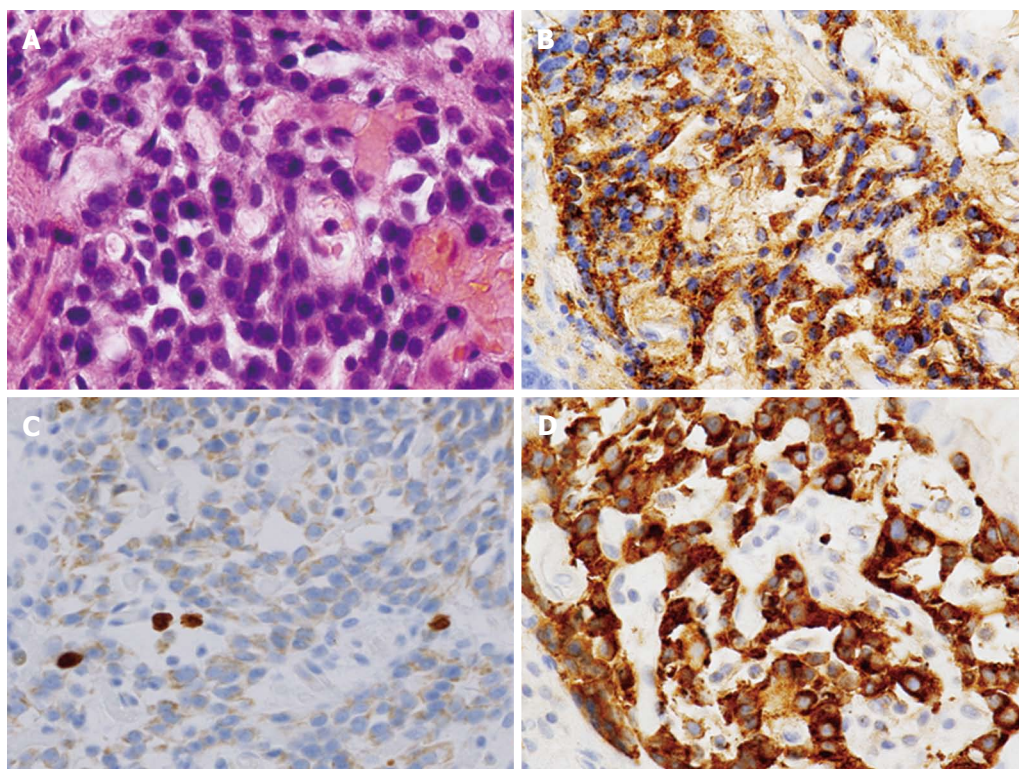


Figure 4 Histological examination of the resected specimen. A: Hematoxylin and eosin staining of the lesion; B: Immunohistochemistry revealed positivity for chromogranin A; C: Only a few positive stained cells were found for Ki-67 and a proliferation index of 1% was evident by immunohistochemistry; D: Immunohistochemistry showed positivity for synaptophysin.

rate is undoubtedly increased awareness of these lesions among pathologists and endoscopists. Additionally, the widespread use of endoscopy and biopsies and the application of immunohistochemical methods have increased detection rates^[14]. The increased detection rate has been accompanied by the detection of morphologically and histopathologically untypical lesions. In this report, we present a gastric NET with the unique histopathological growth progress. The lesion did not present as a submucosal tumor but mimicked the endoscopic appearance of epithelial neoplasms.

In the present case, diagnosis by the endoscopic appearance under white light and M-NBI was very difficult. We could not reach a diagnosis until the histopathologic findings of the excised lesion were available. Current methods using M-NBI for the diagnosis of lesions with the endoscopic appearance of typical differentiated adenocarcinoma have been developed and established, especially for the diagnosis of well differentiated adenocarcinoma. However, lesions that are confusing and cannot be diagnosed only by endoscopic appearance have been discovered repeatedly. In these cases, biopsies remain necessary. The present case was one such case.

To our knowledge, a NET G1 showing such a macroscopic appearance and histopathological growth progress has not been reported previously. We believe that this is the first report of a NET G1 with such unique histopathological growth progress, including an examination the pathological findings of the excised lesion and the endoscopic appearance under magnifying NBI in detail.

COMMENTS

Case characteristics

A 61-year-old man with the complaint of mild epigastralgia.

Clinical diagnosis

An 8-mm, solitary, well-demarcated, protruding lesion was observed on the anterior wall of the stomach body.

Differential diagnosis

Fundic gland polyp, hyperplastic polyp, adenocarcinoma.

Laboratory diagnosis

A markedly increased serum gastrin level (1400 pg/mL; normal range, < 170) and parietal cell antibody level ($\times 20$; normal range, < $\times 9$); other laboratory tests were within the normal limits.

Imaging diagnosis

Endoscopic ultrasonography showed a protruding lesion in the mucosal layer that did not affect the submucosal layer.

Pathological diagnosis

The biopsy specimen showed the mass was not an epithelial tumor but a neuroendocrine tumors (NETs).

Treatment

The tumor was resected by endoscopic submucosal dissection.

Experiences and lessons

NETs sometimes lack submucosal tumor-like form and mimic epithelial neoplasms if the tumor cells extended through the normal gland ducts scatteredly.

Peer review

NETs which infiltrate into the mucosa may develop a polypoid appearance mimicking a primary epithelial process.

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