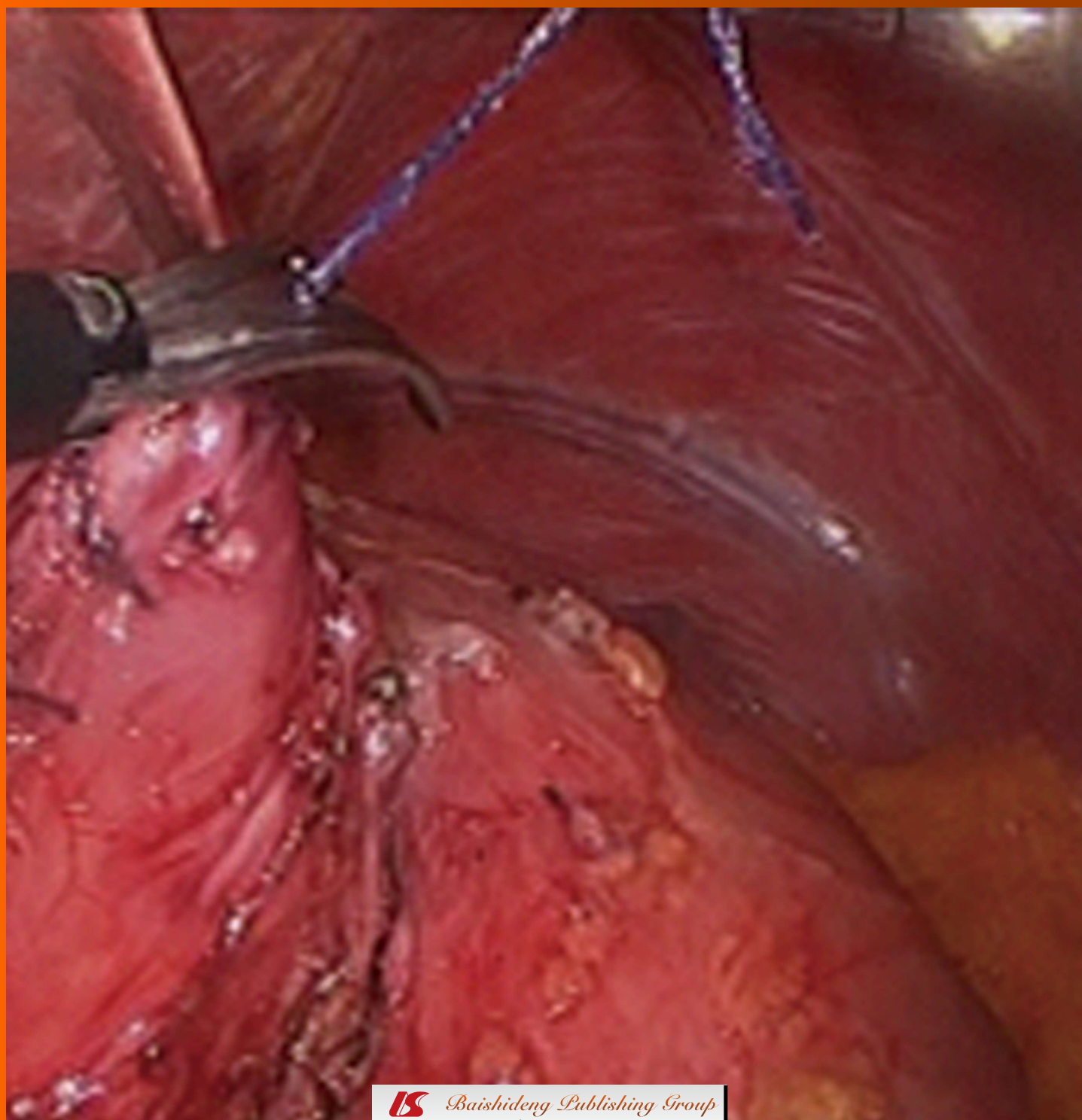


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Per-oral endoscopic myotomy for achalasia: An American perspective

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.

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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.

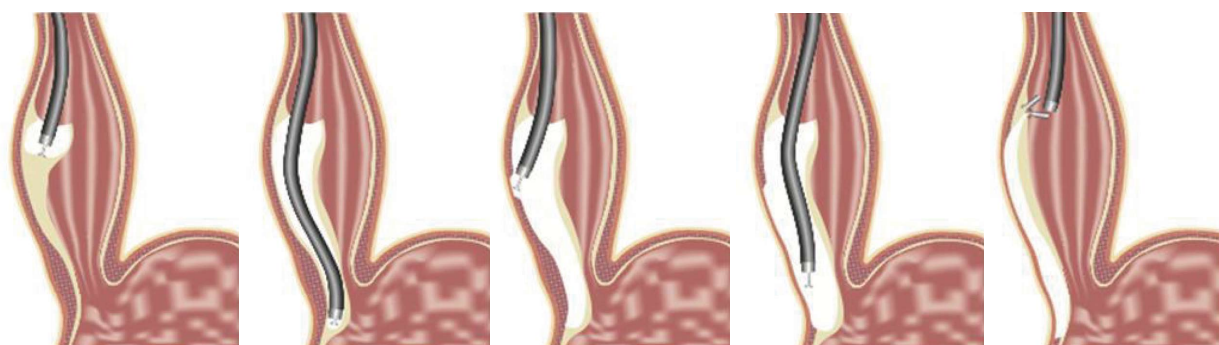


Figure 1 Per-oral endoscopic myotomy technique (© Winthrop University Hospital, 2012). A mucosal incision is performed after submucosal injection. Then, dissection of the submucosal tunnel is initiated and extended into the gastric cardia. Myotomy is performed of the circular layer and extended 2 cm 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

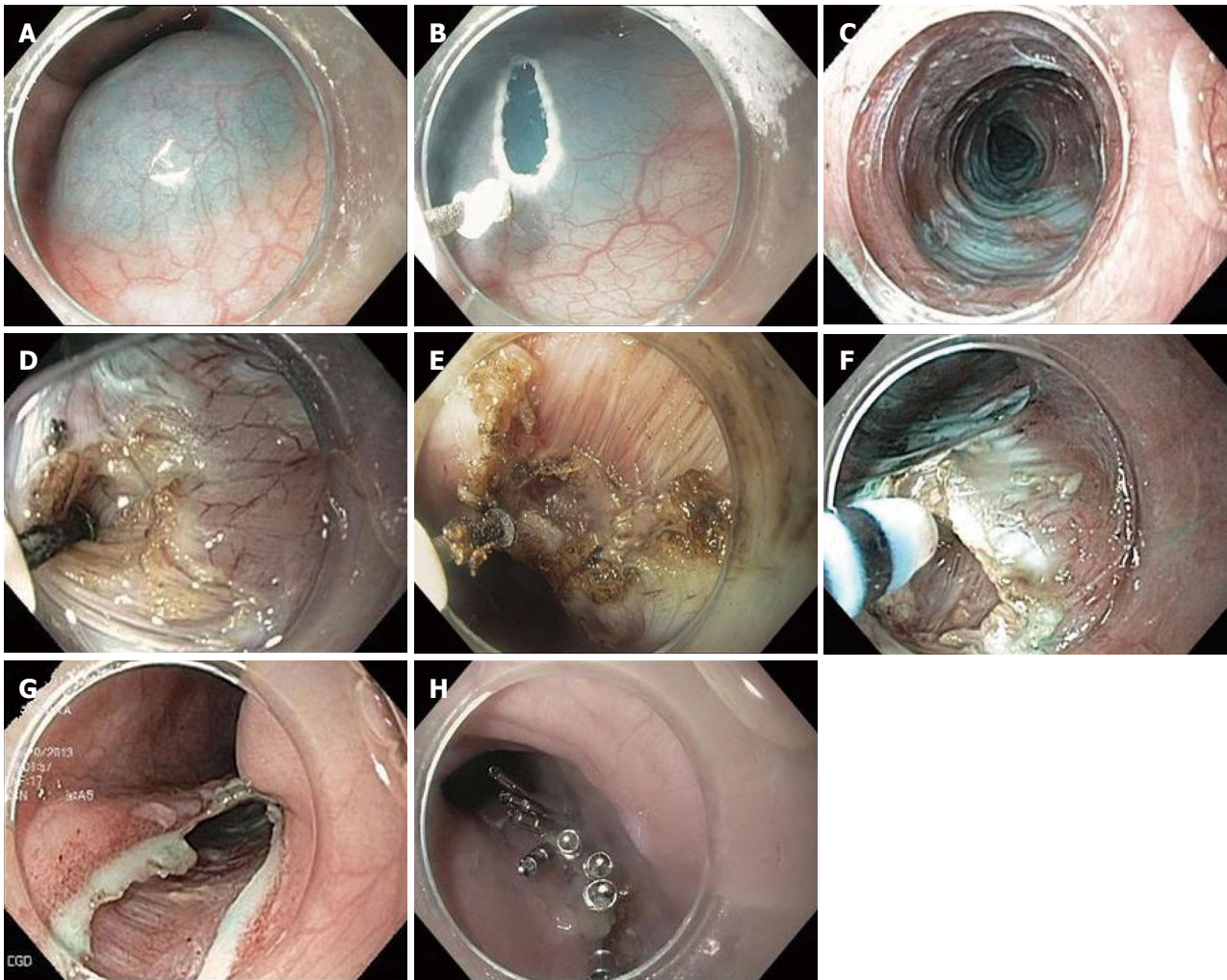


Figure 2 Per-oral endoscopic myotomy technique. A: Submucosal injection; B: Mucosal incision; C: Submucosal tunnel; D: Myotomy initiation; E: Dissection of the circular layer with longitudinal layer intact; F: Hooking of circular muscle layer with hybrid knife; G: Entrance to the submucosal tunnel; H: 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).

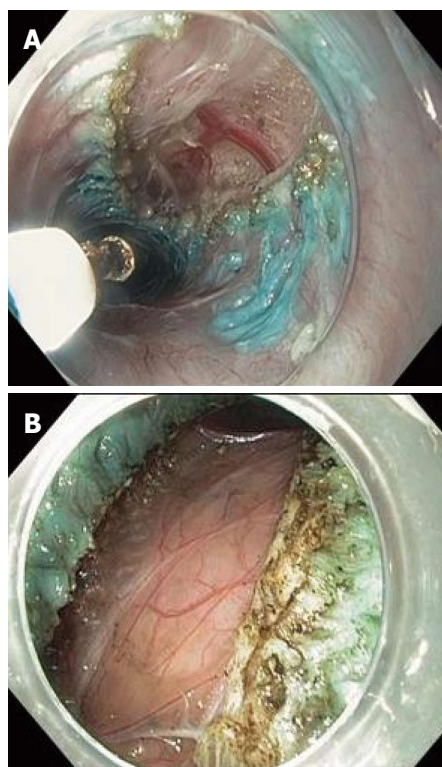


Figure 6 Full-thickness myotomy.

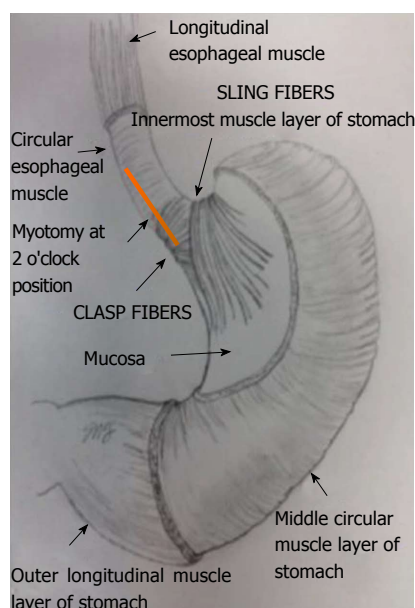


Figure 5 Human lower esophageal sphincter anatomy in relation to per-oral endoscopic myotomy myotomy orientation (© S.N. Stavropoulos, Winthrop University Hospital, 2012).

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-

fined 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 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

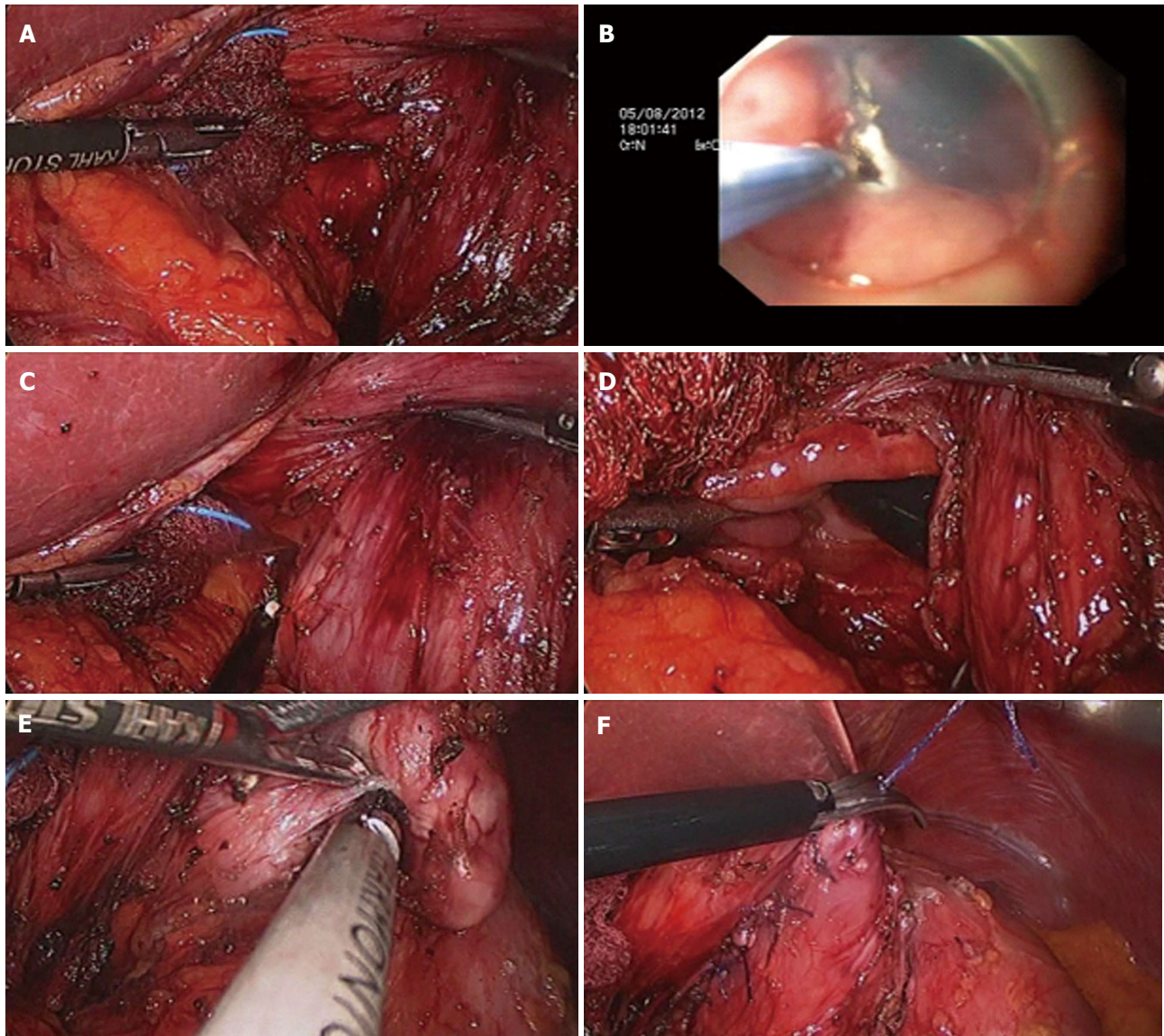


Figure 1 Procedures for hybrid natural orifice transluminal endoscopic surgery (laparoscopic assisted endoscopic full-thickness resection). A: Laparoscopic view during dissection of the attachment of the lesser omentum around the tumor site; B: Endoscopic view during precutting around the tumor using 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.

de Leone A, Tamayo D, Fiori G, Ravizza D, Trovato C, De Roberto G, Fazzini L, Dal Fante M, Crosta C. Same-day 2-L PEG-citrate-simethicone plus bisacodyl vs split 4-L PEG: Bowel cleansing for late-morning colonoscopy. *World J Gastrointest Endosc* 2013; 5(9): 433-439 Available from: URL: <http://www.wjgnet.com/1948-5190/full/v5/i9/433.htm> DOI: <http://dx.doi.org/10.4253/wjge.v5.i9.433>

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

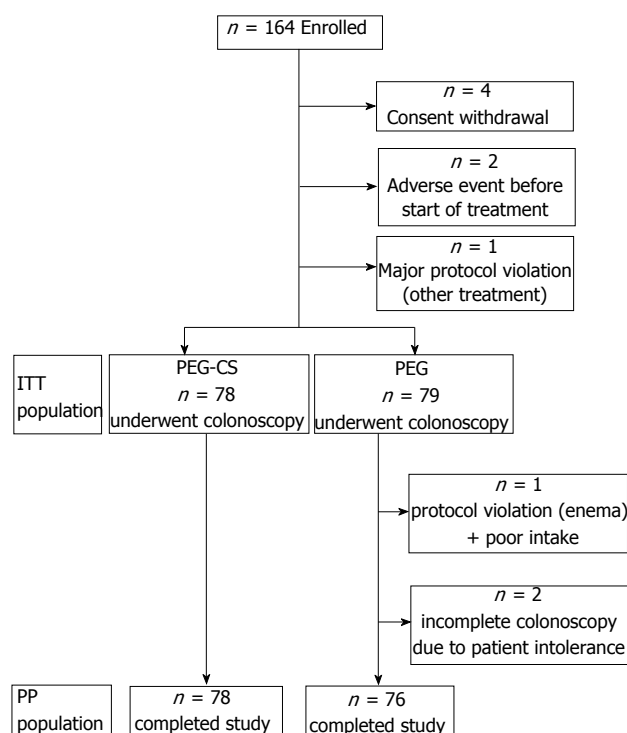


Figure 1 Study population flow chart. PEG-CS: Polyethyleneglycol-citrate-simeticone; PEG: Polyethyleneglycol; ITT: Intention to treat; PP: Per protocol.

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 (29.1)	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

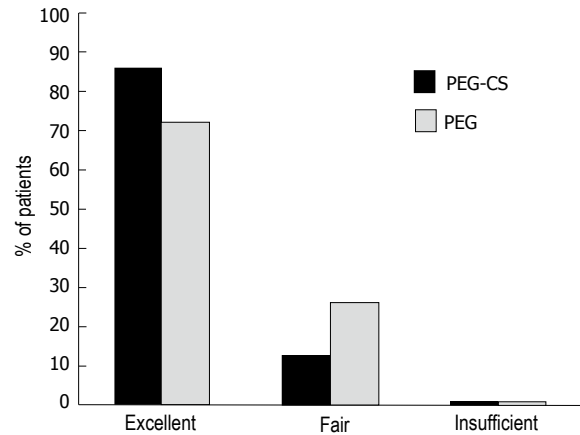


Figure 2 Mucosa visibility. PEG-CS: Polyethyleneglycol-citrate-simeticone; PEG: Polyethyleneglycol.

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.

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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.

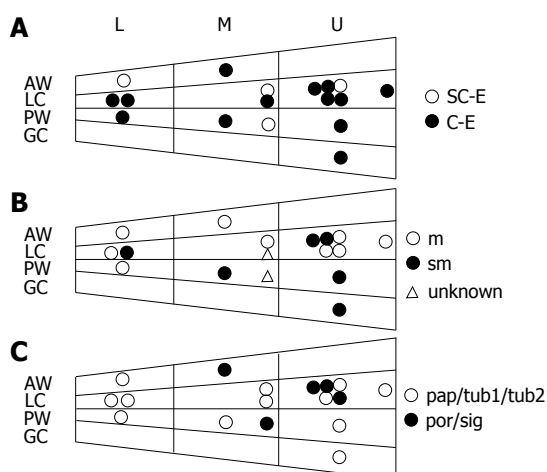


Figure 1 Locations of 17 false-negative gastric cancers. A: Open circles indicate the false-negative gastric cancer (FN-GC) lesions found by small-caliber endoscope (SC-E), and closed circles indicate the FN-GCs found by conventional endoscopy (C-E); B: Open circles indicate FN-GC lesions that invaded 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-

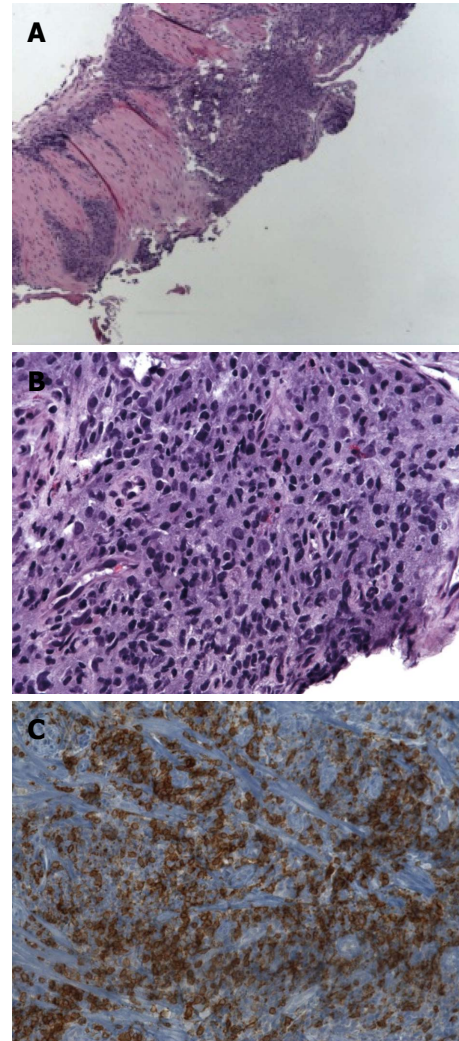


Figure 2 Photographs from the hematoxylin and eosin stain, and immunohistochemistry staining, of the biopsy samples. A: Photomicrograph shows atypical infiltrate under the mucosa of the esophagus $\times 40$ original magnification hematoxylin and eosin (HE) stain; B: The tumor cells are medium sized 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

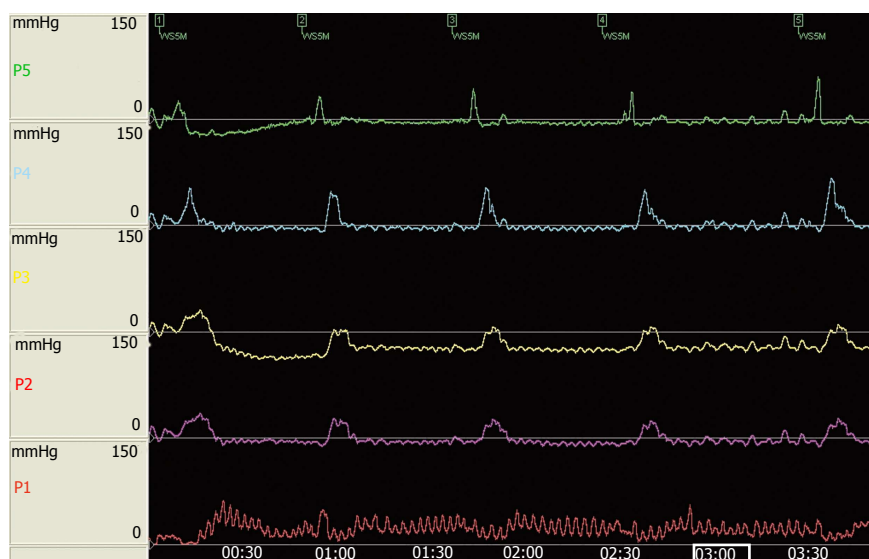


Figure 1 Esophageal manometric findings of elevated intra-esophageal resting pressure > 4 mmHg, localized at 36 cm from the nose, with superimposed cyclic pressure spikes with a frequency of 60-100/min with absence of relaxation in response to swallow (see P1 in the second swallow), typical of esophageal vascular compression.

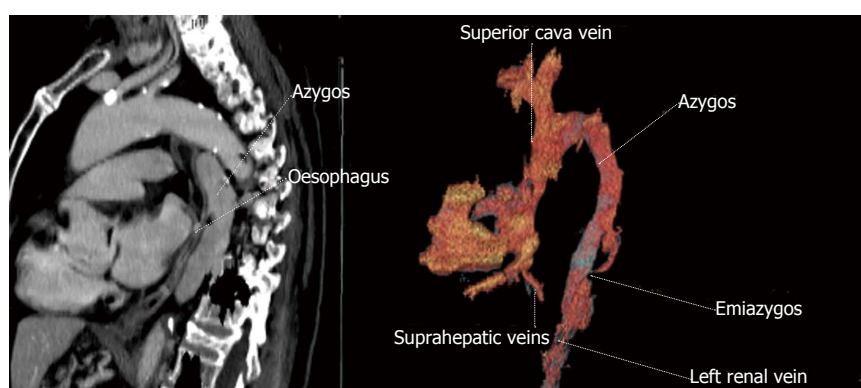


Figure 2 Computed tomography view of a dilated ascending thoracic aorta with no presence of the inferior vena cava with azygos continuation, cause of the vascular compression of esophagus.

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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Key words: Colonoscopy; Endoscopic mucosal resection; Perforation; Computed tomography scan; Abdominal pain

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

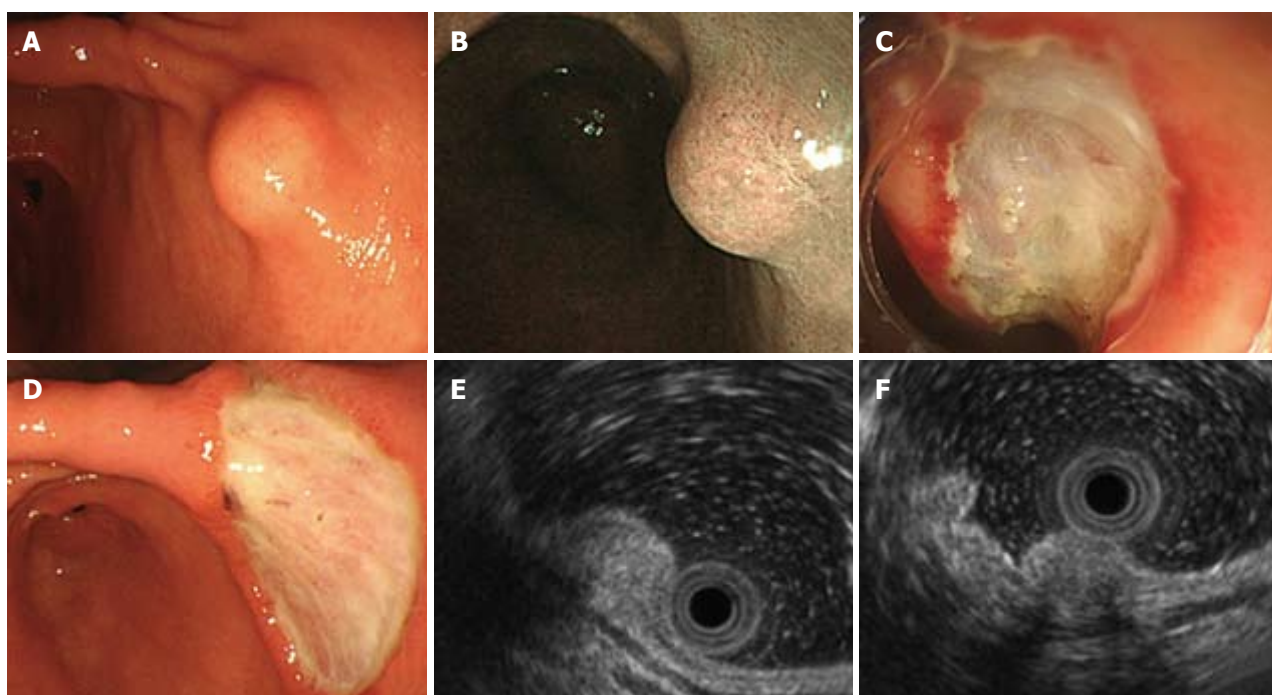


Figure 1 Endoscopic ultrasonography findings of visualized submucosal tumor. A: Endoscopy shows 10-mm shows submucosal tumor (SMT) in lesser curvature of lower corpus of stomach; B: Narrow-band endoscopic imaging SMT covered by normal gastric mucosa; C: Endoscopic submucosal dissection (ESD) for SMT; 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-

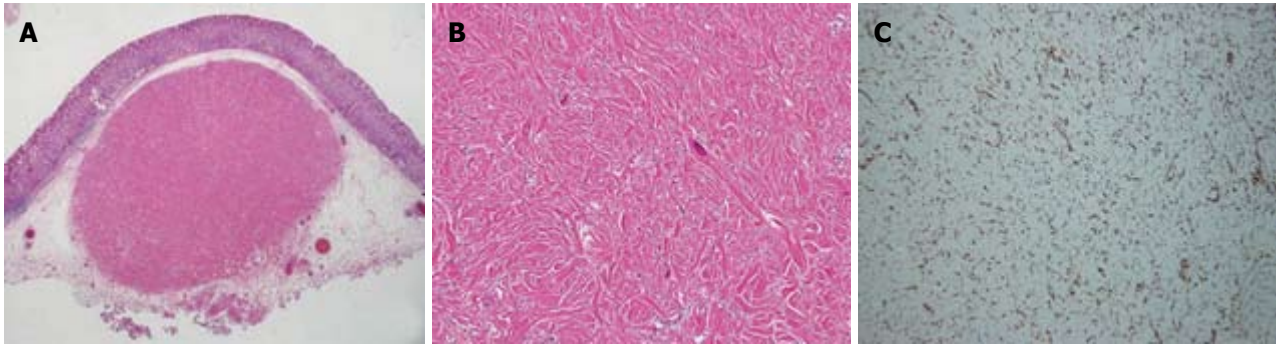


Figure 2 Pathological findings of resected small mucosal tumor. A: Complete submucosal tumor resection was confirmed; B: Hypocellular, spindle-cell tumor has densely hyalinized, collagenous matrix, scattered lymphoplasmacytic aggregates, some psammomatous foci and dystrophic calcification, Spindle-cells 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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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.

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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

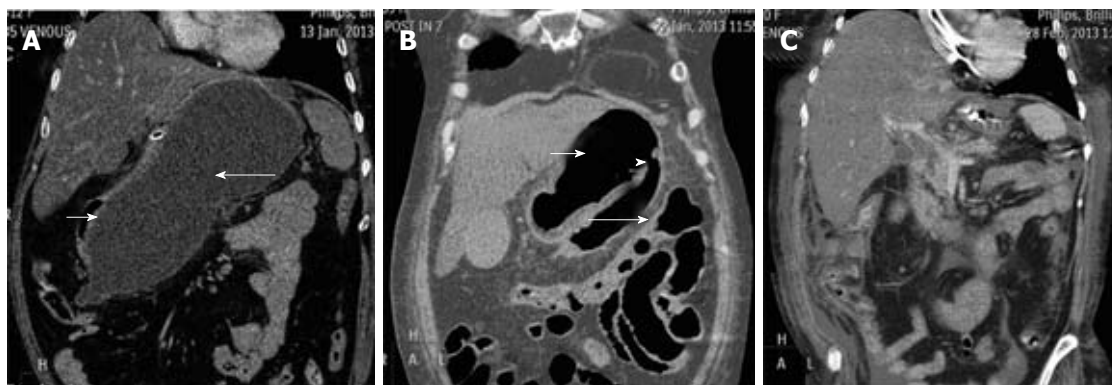


Figure 1 Computerized Tomography of abdomen showing pseudocyst of pancreas. A: Large pseudocyst (long arrow) causing extrinsic compression of stomach (short arrow); B: Ruptured pseudocyst of pancreas (long arrow) draining through a rent (arrowhead) into stomach (short arrow); C: Complete resolution of 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

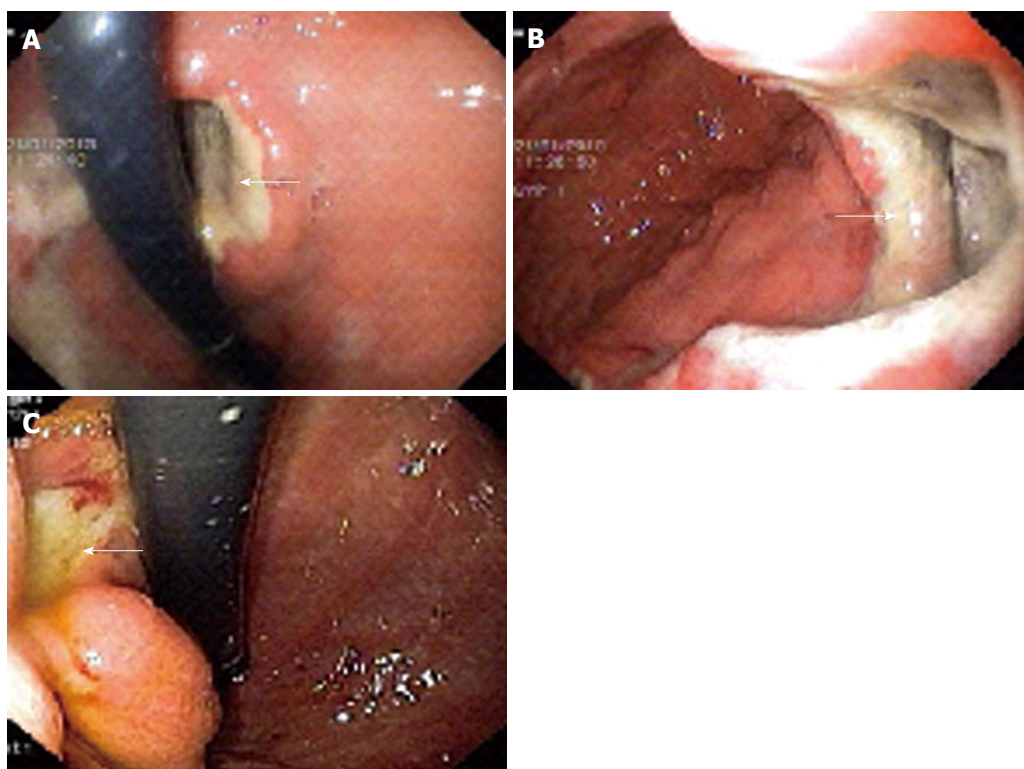


Figure 2 Oesophagogastroduodenoscopy showing pseudocyst of pancreas. A, B: Orifice (arrow) of the fistula between stomach and the pseudocyst of pancreas; C: Ulcer (arrow) at the site of healed fistulous communication between pancreatic pseudocyst and stomach.

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-

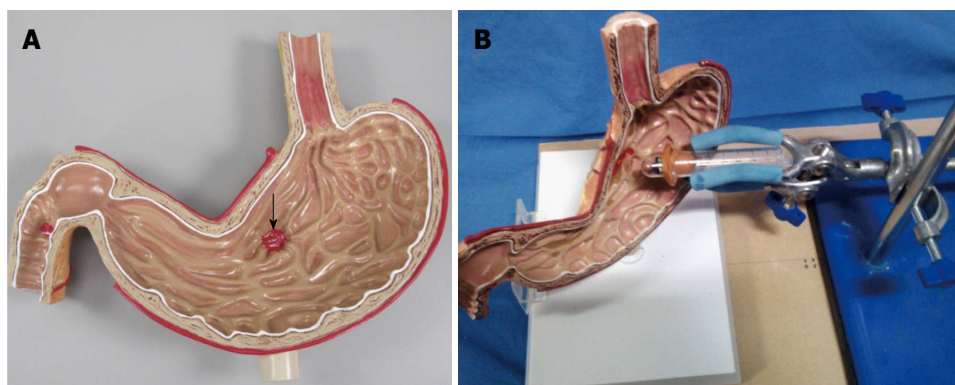


Figure 1 Phantom model (A) and task simulator setting (B). A: The arrow points to the gastric ulcer ("1/2 diameter and 3/16" depth).

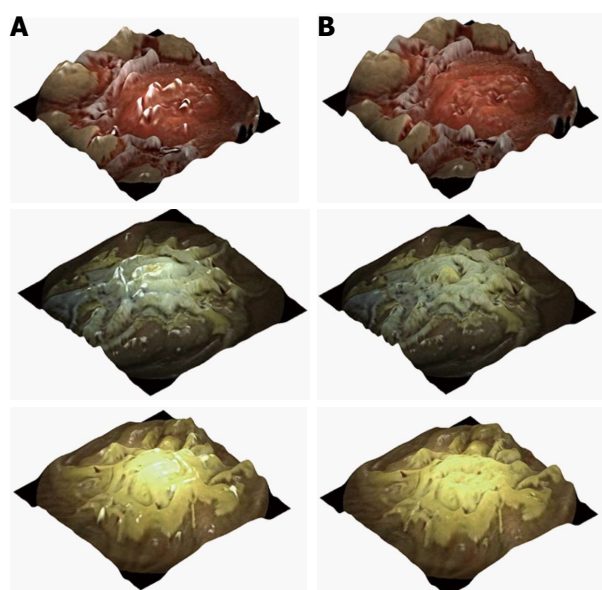


Figure 2 Three-dimensional representation of images captured for the 3 models: red, white and yellow. A: Original three-dimensional (3-D) represented images; B: The processed 3-D represented images using the highlight suppression algorithm.

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-

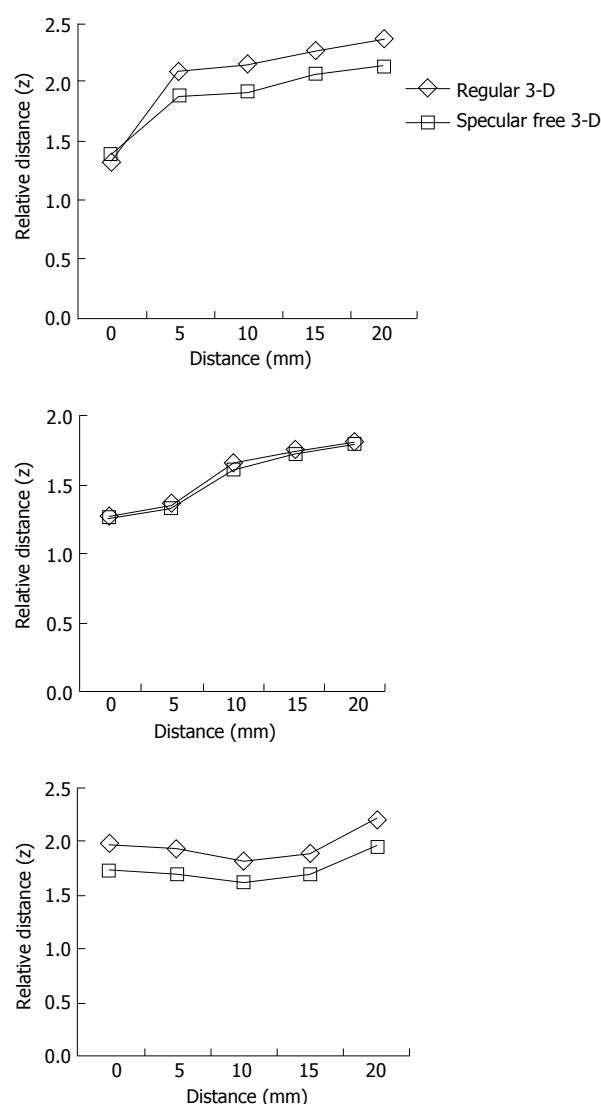


Figure 3 Relative distance of three-dimensional representation calculated over images taken from various distances of the capsule from the models.

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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- 2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarhoea. *Shijie Huaren Xiaobua Zazhi* 1999; **7**: 285-287

In press

- 3 **Tian D**, Araki H, Stahl E, Bergelson J, Kreitman M. Signature of balancing selection in Arabidopsis. *Proc Natl Acad Sci USA* 2006; In press

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- 4 **Diabetes Prevention Program Research Group**. Hypertension, insulin, and proinsulin in participants with impaired glucose tolerance. *Hypertension* 2002; **40**: 679-686 [PMID: 12411462 PMID:2516377 DOI:10.1161/01.HYP.0000035706.28494.09]

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- 5 **Vallancien G**, Emberton M, Harving N, van Moorselaar RJ; Alf-One Study Group. Sexual dysfunction in 1, 274 European men suffering from lower urinary tract symptoms. *J Urol* 2003; **169**: 2257-2261 [PMID: 12771764 DOI:10.1097/01.ju.0000067940.76090.73]

No author given

- 6 21st century heart solution may have a sting in the tail. *BMJ* 2002; **325**: 184 [PMID: 12142303 DOI:10.1136/bmj.325.7357.184]

Volume with supplement

- 7 **Geraud G**, Spierings EL, Keywood C. Tolerability and safety of frovatriptan with short- and long-term use for treatment of migraine and in comparison with sumatriptan. *Headache* 2002; **42** Suppl 2: S93-99 [PMID: 12028325 DOI:10.1046/j.1526-4610.42.s2.7.x]

Issue with no volume

- 8 **Banit DM**, Kaufer H, Hartford JM. Intraoperative frozen section analysis in revision total joint arthroplasty. *Clin Orthop Relat Res* 2002; (**401**): 230-238 [PMID: 12151900 DOI:10.1097/00003086-200208000-00026]

No volume or issue

- 9 Outreach: Bringing HIV-positive individuals into care. *HRS-A Careaction* 2002; 1-6 [PMID: 12154804]

Books

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- 10 **Sherlock S**, Dooley J. Diseases of the liver and biliary system. 9th ed. Oxford: Blackwell Sci Pub, 1993: 258-296

Chapter in a book (list all authors)

- 11 **Lam SK**. Academic investigator's perspectives of medical treatment for peptic ulcer. In: Swabb EA, Azabo S. Ulcer disease: investigation and basis for therapy. New York: Marcel Dekker, 1991: 431-450

Author(s) and editor(s)

- 12 **Breedlove GK**, Schorheide AM. Adolescent pregnancy. 2nd ed. Wiczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

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- 13 **Harnden P**, Joffe JK, Jones WG, editors. Germ cell tumours V. Proceedings of the 5th Germ cell tumours Conference; 2001 Sep 13-15; Leeds, UK. New York: Springer, 2002: 30-56

Conference paper

- 14 **Christensen S**, Oppacher F. An analysis of Koza's computational effort statistic for genetic programming. In: Foster JA, Lutton E, Miller J, Ryan C, Tettamanzi AG, editors. Genetic

programming. EuroGP 2002: Proceedings of the 5th European Conference on Genetic Programming; 2002 Apr 3-5; Kinsdale, Ireland. Berlin: Springer, 2002: 182-191

Electronic journal (list all authors)

- 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>

Patent (list all authors)

- 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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