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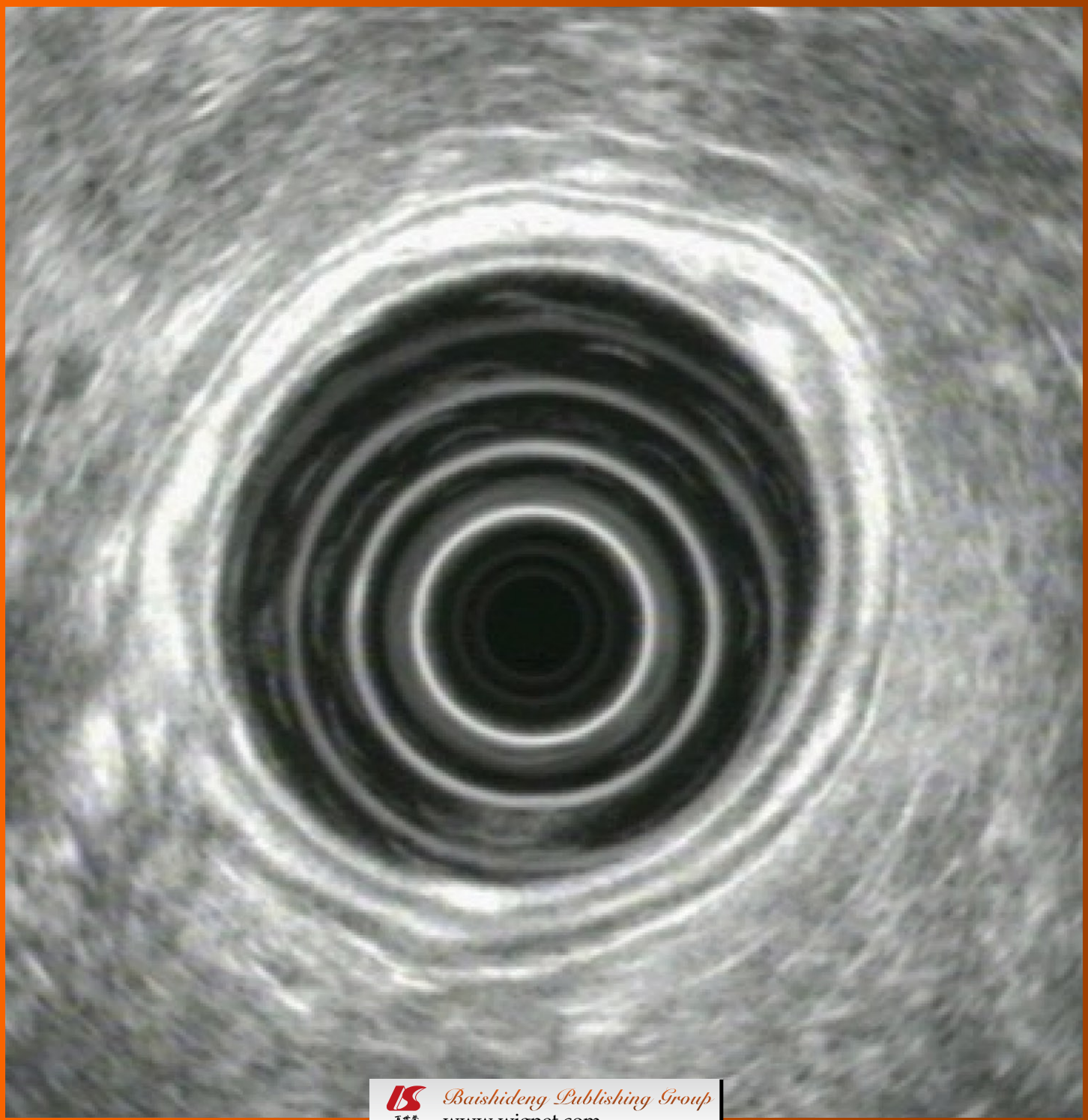

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Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
Telephone: +86-10-8538-1892
Fax: +86-10-8538-1893
E-mail: baishideng@wjgnet.com
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EDITING
Editorial Board of *World Journal of Gastrointestinal Endoscopy*,
Room 903, Building D, Ocean International Center,
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Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893
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EDITORIAL OFFICE
Hai-Ning Zhang, Director
World Journal of Gastrointestinal Endoscopy
Room 903, Building D, Ocean International Center,
No. 62 Dongsihuan Zhonglu, Chaoyang District,
Beijing 100025, China
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EDITORIAL

Capsule endoscopy compared with conventional colonoscopy for detection of colorectal neoplasms

Andreas Sieg

Andreas Sieg, Practice of Gastroenterology and University of Heidelberg, Faculty of Medicine, Bergheimer Str. 56a, D-69117 Heidelberg, Germany
Author contributions: Sieg A solely contributed to this paper.
Correspondence to: Andreas Sieg, Professor, MD, Practice of Gastroenterology and University of Heidelberg, Faculty of Medicine, Bergheimer Str. 56a, D-69117 Heidelberg, Germany. dr.andreas.sieg@t-online.de
Telephone: +49-6221-6599931 Fax: +49-6221-6599933
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Abstract

Colon capsule endoscopy (CCE) may be a means to overcome the low adherence to colorectal cancer screening. The device is an ingestible capsule with a video camera at both ends that can take photographs as it progresses through the gastrointestinal tract. PillCam colon (PCC1) may be used for structural evaluation of the large bowel following an adequate cleaning procedure. PCC1 measures 11 mm × 31 mm and has dual cameras that enable the device to acquire video images from both ends with a wide coverage area, automatic light control and a frame rate of four frames per second. The system includes a sensor array and data recorder connected to the patient during the procedure. The recorded data are downloaded to the Given Imaging Rapid workstation for review of the colon video. The second generation of PillCam Colon (PCC2) is similar to PCC1 and incorporates new developments. The angle of view has been increased to 172 degrees. It has an adaptive frame rate, alternating from 35 frames per second while in motion to 4 images when virtually stationary. The new RAPID® software now includes a simple graphic interface tool for polyp size estimation. The procedure of bowel cleansing until capsule ingestion is similar to that used for traditional colonoscopy. However it is more rigorous as the bowel cleanliness for capsule colonoscopy has to be excellent or at least good to result in an adequate sensitivity of the method. Briefly, it consists of 3.5-4 L of split dose polyethylene glycol. Oral NaP boosters are administered after 1-2 h if the capsule has entered the small bowel. Sodium phosphate (NaP) seems to be a necessary adjunct to the regimen because the total transit time is doubled without NaP. The cleansing level was considered to be good to excellent in 72%-88% in studies with PCC1. The sensitivity for significant polyps (> 6 mm or more than 3 polyps >3 mm) ranged from 63%-88% with specificities between 64%-94%. PCC2 showed an improved sensitivity of 89% and a specificity of 76%. CCE seems to be a safe and effective method of visualizing the colonic mucosa through colon fluids without the need for sedation or insufflation of air. The sensitivity of CCE to detect polyps, advanced adenomas and cancer is lower compared to optical colonoscopy but improvements will be made in the near future. With an increased recording duration, even a panenteric examination of the whole gastrointestinal tract may be possible.

Key words: Colon capsule endoscopy; Colorectal cancer; PillCam colon; Conventional colonoscopy

Peer reviewer: Stefanos Karagiannis, MD, PhD, Gastrointestinal and Liver Unit, General and Oncology Kifissia Hospital Agioi Anargiri', Kaliftaki 14564, Kifissia, Greece; Jiang-Fan Zhu, MD, Professor, Department of General Surgery, East Hospital of Tongji University, 150 Jimo Road, Pudong, Shanghai 200120, China

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INTRODUCTION

Colorectal cancer is the second leading cause of cancer

death in North America[1] and Western Europe. Screening colonoscopy was introduced in the National Cancer Prevention Program in Germany in 2002[2], even though results from randomised controlled studies on its effect on incidence and mortality of colorectal cancer were not yet available. A first evaluation of screening colonoscopy in Germany showed a detection rate of adenomas of 20%, advanced adenoma 6% and colorectal cancer 0.7%[3], similar to the detection rates in Poland[4]. However, the participation in colonoscopy screening is as low as 3%-4%[5]. In the US, a decrease in incidence and mortality of colorectal cancer may be attributed partly to an increased screening activity[1].

A means to overcome the low screening activity might be to introduce new convenient methods to reduce people's resistance. One of these methods might be colon capsule endoscopy (CCE). Small bowel capsule endoscopy has been used successfully to visualize the upper gastrointestinal tract and small bowel. The instrument is an ingestible capsule with a video camera at one end that can take photographs as it progresses through the gastrointestinal tract. The main indication for use of the small bowel capsule is obscure gastrointestinal bleeding[6] and it has been shown to be feasible and cost saving as an outpatient procedure[7]. The newly developed PillCam colon (PCC1) may be used for structural evaluation of the large bowel following an adequate cleaning procedure.

DEVICE DESCRIPTION OF THE COLON CAPSULE

PCC1

PCC1 capsule endoscope (Given Imaging Ltd., Yoqneam, Israel) was the first capsule with a battery life that enables visualization of the colon[8,9]. The capsule measures 11 mm × 31 mm and has dual cameras that enable the device to acquire video images from both ends with a wide coverage area, automatic light control and a frame rate of four frames per second. The operation time is approximately 10 h and after an initial image transmission of 3 min, the capsule enters a delay mode (of approximately 2 h), after which it spontaneously "wakes up" and restarts the transmission of images. The system includes a sensor array and data recorder connected to the patient during the procedure. The recorded data are downloaded to the Given Imaging Rapid workstation for review of the colon video. The localization display of the RAPID® software enables the physician to identify the location of findings, i.e. right, transverse or left colon segments once the main anatomical landmarks (first cecal image, hepatic flexure, splenic flexure and exit of the capsule) have been selected. RAPID® Access RT by Given Imaging allows real time visualization of capsule images. This allows localization of the device and consequently an intervention to optimize the procedure during the ongoing examination. One example is that the patient has to drink a small amount of sodium phosphate 2 h after ingestion of the capsule in order to push the capsule through the small bowel. However, he should only drink sodium phosphate if the capsule has passed the stomach because sodium phosphate may delay gastric emptying time.

PCC2

The second generation of PillCam Colon (PCC2), Given Imaging Ltd., Yoqneam, Israel, is similar to PCC1 and consists of an ingestible video capsule measuring 11.6 by 31.5 mm and has two imagers, one at each end of the capsule. The second-generation system incorporates new developments to the capsule, the data recorder and the RAPID® software[10].

The angle of view has been increased to 172 degrees (from 156 in PCC1). In order to conserve battery energy, the capsule captures images at an adaptive frame rate, alternating from 35 frames per second while it is in motion (such as in the transverse colon) to 4 images when it is virtually stationary. After swallowing, the capsule works with a low frame rate of 14 per minute until it automatically identifies the small bowel.

The new data recorder also assists and guides the medical staff and patient through the procedure. It buzzes, vibrates and displays instruction numbers in order to alert the patient to take the laxative booster or that the procedure has terminated.

The new RAPID® software now includes a simple graphic interface tool for polyp size estimation. After marking the distance from one side of the polyp to the other, the RAPID® software calculates the distance and displays the polyp size in millimetres.

PROCEDURE AND CLEANLINESS

The procedure of bowel cleansing until capsule ingestion is similar to that used for traditional colonoscopy. However, it is more rigorous as the bowel cleanliness for capsule colonoscopy has to be excellent or at least good to result in an adequate sensitivity of the method. The reason for the rigorous procedure is that with a capsule, unlike a colonoscope, fluid cannot be aspirated. If the fluid is unclear, the bowel mucosa may not be seen by CCE.

The reason for the combination of PEG with laxatives is to maintain the colon cleanliness and facilitate progression of the capsule through the gastrointestinal tract.

Briefly, it consists of a clear liquid diet with/without a small breakfast on the day before capsule ingestion and 3.5-4 L of split dose polyethylene glycol (PEG). Oral NaP boosters are administered after 1-2 h if the capsule has entered the small bowel and again 2-3 h later, followed by the administration of a bisacodyl suppository two hours after the second boost if the capsule has not been excreted (Table 1). The procedures for PCC1[8,9,11,12] and for the newly developed PCC2[10] are similar.

With this regimen 69%-84% of the capsules were excreted within 6-8 h[8-13] and 92.8% within 10 h[10]. If only conventional colonoscopy preparation was used, the excretion rates were as low as 20%. Sodium phosphate (NaP) seems to be a necessary adjunct to the regimen. In two studies, NaP was omitted from the regimen and replaced by PEG[12,13]. This resulted in a low excretion rate and the total transit time was doubled, without improvement of the

Table 1 Procedure protocols and cleansing levels

Authors	Eliakim 2006[8]	Schoofs 2006[9]	Sieg 2009[12]	Van Gossum 2009[11]	Eliakim 2009[10]	Spada 2010[13] (Standard/modified procedure)
Device	PCC1	PCC1	PCC1	PCC1	PCC2	PCC1
Day 2	Low fibre diet	-	-	-	-	-
Day 1	7-8 pm	6-9 pm	1-6 pm	6-9 pm	evening	evening
	PEG 2 L	PEG 3 L	PEG 3 L	PEG 3 L	PEG 2 L	PEG 3 L
Day 0					morning	morning
6-7 am	PEG 1 L	PEG 1 L	PEG 0.5 L	PEG 1 L	PEG 2 L	PEG 1 L
8-9 am	Tegaserod 6 mg	Domperidone 20 mg	Domperidone 20 mg	Domperidone 20 mg		Domperidone 20 mg
	Capsule ingestion	Capsule ingestion	Capsule ingestion	Capsule ingestion	Capsule ingestion	Capsule ingestion
10:00 am	NaP 30 mL	NaP 45mL	NaP 22mL	NaP 45 mL		NaP 45 mL/0.5 L PEG
	+					
12 am-1 pm	Tegaserod 6 mg		NaP 22 mL		1-2 h later NaP 45mL	
02:00 pm	NaP 15 mL	NaP 30 mL		NaP 22 mL	2 h later NaP 22 mL	NaP 22 mL/0.5L PEG
04:30 pm	Bisacodyl supp 10 mg	Bisacodyl supp 10 mg	Bisacodyl supp 10 mg		Bisacodyl supp 10 mg	Bisacodyl supp 10 mg
Cleansing level Good and excellent (%)	84.4	88	72	72	78	35/53

PCC1: PillCam Colon 1 (Given Imaging Ltd, Yoqneam, Israel); PCC2: Second generation of PillCam Colon (Given Imaging Ltd, Yoqneam, Israel).

Table 2 Sensitivity and specificity of colon capsule endoscopy for polyps 6 mm or larger performed with PCC1 and PCC2

	Eliakim[8]	Schoofs[9]	Van Gossum[11]	Spada[13]	Pilz[14]	Gay[15]	Sacher-Huvelin[16]	Eliakim[10]
Year	2006	2006	2009	2010	2010	2010	2010	2009
Device	PCC1	PCC1	PCC1	PCC1	PCC1	PCC1	PCC1	PCC2
N	84	36	328	40	36	128	545	98
Sens (%)	63	76	64	63	50	88	39	89
Spec (%)	94	64	84	87	76	76	88	76

PCC1: PillCam Colon 1 (Given Imaging Ltd, Yoqneam, Israel); PCC2: Second generation of PillCam Colon; N: Patients with complete examination; Sens: Sensitivity; Spec: Specificity.

colon cleanliness. The combination of PEG and NaP may cause problems in patients with advanced cardiovascular or renal disease as outlined below.

The cleansing level was considered to be good to excellent in 72%-88% in studies with PCC1[8,9,11,12] and 78% in a study with PCC2[10]. In one study from Italy, an adequate cleansing level was achieved in only 35% of the patients with the standard procedure containing NaP and in 53% of a modified procedure where NaP was replaced by PEG[13] with a similar regimen (Table 1). The cleansing level is significantly different in different segments of the colon[10,12] and the best results are achieved in the transverse and descending colon. The segment with the poorest cleansing level is the rectum. Future studies may improve the visibility of this part of the colon. A significant difference could not be confirmed in one study[13].

DETECTION OF LESIONS

The long-term objective of colon capsule endoscopy (CCE) is screening of the average population. In the first feasibility studies, the sensitivity for significant polyps (> 6 mm or more than 3 polyps >3 mm) was evaluated in patients with an indication for colonoscopy and ranged from 63%-88% with specificities between 64%-94%[8,9,11,13,15] (Table 2). In a small study under routine screening conditions from Switzerland, the sensitivity of significant findings was only 50% (95% CI: 19-81)[14] and in a study from France in patients at average and increased risk, the sensitivity was 39% (95% CI: 30-48)[16]. CCE was successfully used in an ambulatory practice of gastroenterology with a median transit time of 4.5 h[12]. In patients with short transit time, a panenteric examination of the upper, mid and lower gastrointestinal tract would be possible. In patients with excellent or good colon cleanliness, the sensitivity was significantly higher than in patients with poor cleanliness[11]. Meta-analyses on PCC1 with 626 patients[17] and 837 patients[18] found sensitivities for significant polyps of 69% and 76%, with specificities of 86% and 82% respectively.

A second generation capsule (PCC2) showed an improved sensitivity of 89% and a specificity of 76% in 98 patients aged 18 to 57 years scheduled to undergo colonoscopy for suspected or known colonic disease[10]. The sensitivity described is higher than with any other CCE so far but still has to be established in further studies.

To date, conventional colonoscopy is the gold standard

for detection of colorectal neoplasia, offering the ability to remove detected polyps and obtain biopsy samples with one examination in contrast to all diagnostic procedures. However, standard colonoscopy only detects about 90% of polyps 10 mm or larger[19-26]. Some studies also suggested that colonoscopy may be protective only for cancers[27] and advanced adenomas[28] in the distal but not proximal colon. The effectiveness of all screening programs depends on the quality of colonoscopy because colonoscopy is used to evaluate positive screening tests in all programs. A highly qualified colonoscopy with an adequate withdrawal time[29] is a prerequisite for all screening programs.

SAFETY

No capsule or laxatives-related adverse effects occurred during the first feasibility studies[8-10] and only mild to moderate adverse effects were reported in a multicenter trial[11]. Only 4 of 582 patients (0.7%) were unable to swallow the capsule[8-12].

COST EFFECTIVENESS

Cost-effectiveness of CCE was evaluated in a recent paper based on a mathematical Markov model[30]. With equal compliance rates, colonoscopy was more cost-effective than CCE. With a 30% increase in compliance, CCE becomes more cost-effective than colonoscopy. Moreover, future generations of capsules may improve the detection rate of polyps and thereby increase the cost-effectiveness. When both procedures are offered, patients prefer colonoscopy because of the higher sensitivity and that there is no need for a second test[31].

CONCLUSION

CCE seems to be a safe and effective method of visualizing the colonic mucosa through colon fluids without the need for sedation or insufflation of air. Colon cleanliness significantly influences the sensitivity for polyps and cancer. The sensitivity of CCE to detect polyps, advanced adenomas and cancer is lower when compared to optical colonoscopy. Improvements in capsule technology increased the sensitivity for colorectal neoplasms in PCC2 and, with the new generation of capsules, a similar sensitivity of CCE and colonoscopy may be accessible in the future. Currently, a large study on a standard screening population is not yet available. The future range of CCE in CRC screening will depend not only on sensitivity, but also on these issues: 1) Bowel preparation: The bowel preparation for CCE is more extensive than for colonoscopy as only clear liquids are allowed inside the colon. In contrast, during colonoscopy the rinse and suction techniques can be used to remove turbid fluids. The rigorous bowel cleansing required for CCE with 4 L PEG and laxatives restricts its application to healthy people. Persons with severe cardiovascular disease in whom colonoscopy may be too dangerous are not able to drink so much fluid. In some patients, especially with impairment of renal function, NaP may be not indicated because it is associated with clinically relevant electrolyte abnormalities related to the absorption of phosphate. Bowel preparation will set limits to a mass screening with CCE; 2) Reading time: The reading time of colon capsule endoscopy usually ranges between 30 and 60 min. This is a time-consuming procedure that lasts longer than a colonoscopy. Future developments may shorten the reading time by an automatic detection of neoplasms and/or a pre-reading by trained technicians; and 3) Costs: The actual costs of a colon capsule endoscopy in Germany exceed the costs for colonoscopy by about 6 times. CCE is not yet reimbursed by most of the insurance companies. The high price of CCE represents an obstacle to mass screening.

Nevertheless, a non-invasive method for CRC screening may be of interest for those reluctant to undergo colonoscopy because of its perceived inconvenience, discomfort or embarrassment as CCE seems to be an adequate alternative. The examination can even be performed in the privacy of a patient's home at the weekend, avoiding the need to take time off work. I believe that CCE will have a place as an additional screening tool for CRC in a selected and limited population.

As CCE has still some limitations (cannot insufflate air, clean or take biopsies), future capsule prototypes seem to be necessary. An increase of frame rate, angle of view and duration of the procedure seem likely[32]. With an increased recording duration, even a panenteric examination of the whole gastrointestinal tract may be possible. Improvement of visualization of the small bowel by a computed color enhancement system (FICE)[33] is under evaluation and possibly could be applied to CCE. A smart capsule with motion control and 360 degree view (Capsovision, Saratoga CA) is also under evaluation. Remote control movement will improve with the use of magnets or electrostimulation. Even an active endoscopic robot seems to be possible according to animal experiments[34].

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TOPIC HIGHLIGHT

Konstantinos Triantafyllou, MD, PhD, *Series Editor*

Endoscopic ultrasonography for gastric submucosal lesions

Ioannis S Papanikolaou, Konstantinos Triantafyllou, Anastasia Kourikou, Thomas Rösch

Ioannis S Papanikolaou, Anastasia Kourikou, Konstantinos Triantafyllou, Hepatogastroenterology Unit, 2nd Department of Internal Medicine-Propaedeutic, Attikon University General Hospital, Medical School, University of Athens, Athens 12462, Greece
Thomas Rösch, Department of Interdisciplinary Endoscopy, University Hospital Hamburg-Eppendorf, Martinistrasse 52, Hamburg 20246, Germany
Author contributions: The authors contributed equally to the writing of the manuscript.
Correspondence to: Ioannis S Papanikolaou, MD, Hepatogastroenterology Unit, 2nd Department of Internal Medicine-Propaedeutic, Attikon University General Hospital, University of Athens, Rimini 1, Haidari, Athens 12462, Greece. ispapn@hotmail.com
Telephone: +30-210-5832090 Fax: +30-210-5326422
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Abstract

Gastric submucosal tumors (SMTs) are a rather frequent finding, occurring in about 0.36% of routine upper GI-endoscopies. Endoscopic ultrasonography (EUS) has emerged as a reliable investigative procedure for evaluation of these lesions. Diagnostic EUS has the ability to differentiate intramural tumors from extraluminal compressions and can also show the layer of origin of gastric SMTs. Tumors can be further characterized by their layer of origin, echo pattern and margin. EUS-risk criteria of their malignant potential are presented, although the emergence of EUS-FNA has opened new indications for transmural tissue diagnosis and expanded the possibilities of EUS in SMTs of the stomach. Tissue diagnosis should address whether the SMT is a Gastrointestinal stromal tumour (GIST) or another tumor type and evaluate the malignant potential of a given GIST. However, there seems to be a lack of data on the optimal strategy in SMTs suspected to be GISTs with a negative EUS-FNA tissue diagnosis. The current management strategies, as well as open questions regarding their treatment are also presented.

Key words: Endoscopic ultrasound; Gastric submucosal tumors; EUS-guided fne needle aspiration; Gastrointestinal stromal tumours

Peer reviewer: Majid Abdulrahman Almadi, MD, FRCPC, Department of Gastroenterology Division, McGill University Health Center, McGill University, Royal Victoria Hospital, 687 Pine Ave West, Montreal H3A 1A1, Canada

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INTRODUCTION

Endoscopic ultrasonography (EUS) became a part of clinical practice at the beginning of the eighties and has become an excellent tool for the imaging of the gastrointestinal wall and its surrounding structures. Various studies have highlighted the value of EUS, especially in the diagnosis and staging of gastric diseases. Development of EUS-guided fine needle aspiration (EUS-FNA) in the early nineties broadened the applicability of this method by allowing tissue sampling of lesions within or accessible from the gastrointestinal tract and established EUS as an important tool in the management of patients with gastrointestinal diseases, including those of the stomach.

In this review, we evaluate the role of EUS in the diagnosis and management of gastric submucosal lesions.

PERFORMING EUS IN THE STOMACH: EXAMINATION TECHNIQUE

The variety of echoendoscopes and probes used for endosonography precludes a detailed analysis of instrument types and specifications currently in use. Aspects of EUS-

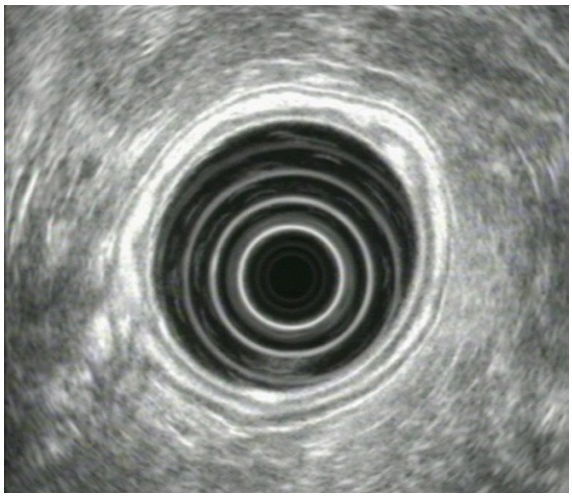

Figure 1 Gastric endoscopic ultrasonography. Note the 5 distinct layers that comprise the gastric wall.

instrumentarium have been recently reviewed[1]. In principal, EUS-imaging is currently performed with radial (360°) or linear echoendoscopes. In their latest version, these scopes are video-endoscopes coupled to electronic ultrasound processors for generation of electronic EUS-images, and are endowed with special features including Doppler, contrast, and harmonic imaging. Standard EUS usually utilizes high ultrasound frequencies, varying between 5 and 20 MHz (with 7.5 MHz being the most commonly used frequency). They produce a high-resolution image in the near field with limited penetration depth, which ranges from 1-2 to 5-6 cm, depending of the ultrasound frequency used. Gastric EUS is performed with the patient in the left lateral position, usually under conscious sedation (mostly with benzodiazepines), sometimes in conjunction with a central analgesic and, more recently, with propofol. The technique is associated with very low complication rates[2].

The transducer in most radial echoendoscopes generates radial images of 360°, which are oriented perpendicular to the shaft axis of the instrument, while linear echoendoscopes produce images directed parallel to the shaft axis of the endoscope, thus allowing for an effective and safe performance of EUS-guided fine-needle aspiration puncture (FNA) when needed. Review of the literature suggests similar performance for both types of endoscopes. However, the authors' personal experience is that this mainly applies to pancreatobiliary imaging, whereas complete gastric and perigastric scanning appears to be more difficult with linear instruments. Here, radial imaging offers a better overview of the gastrointestinal wall and paramural structures[3-5].

Acoustic coupling of the ultrasonic transducer to the gastrointestinal wall requires application of fluid as interface between the transducer and the wall. This can be achieved by either a water-filled balloon around the instrument tip or by filling of luminal organs with fluid. When performing EUS in the stomach the following scanning principles should be adhered to, in order to avoid artifacts and misinterpretation: (1) Scanning of target lesions should be perpendicular, as oblique scanning may lead to broadening and blurring of normal and pathological structures (and give rise to erroneous diagnoses or overstaging); (2) An adequate focal distance (0.5-1.0 cm, depending on the ultrasonic frequencies) should be kept; and (3) Use of higher frequencies may be help in better visualization of structures and lesions close to the EUS transducer.

The proper technique for gastric EUS-scanning generally includes conventional upper endoscopy initially, to determine the morphology and possibly identify the lesions. This is followed by the echoendoscope, which is positioned at an identified lesion and moved slightly and slowly backward and forward, with fine movements of the instrument tip. Such a technique will help depict the full extent of the lesion and its relation to neighboring organs and structures. Gastric EUS also permits evaluation of the wall-layers of the stomach, analyses of mucosal or submucosal lesions and imaging of perigastric structures. The water-filling method is the most frequently used technique to evaluate the gastric wall. The stomach is initially collapsed by aspiration, followed by introduction of 200-400 mL water into the lumen up to the fundus. The examination is done from the antrum, while the instrument is slowly withdrawn and all parts of the gastric circumference are visualized as far as possible with perpendicular scanning. However, there are challenging aspects in EUS of the stomach, especially in the prepyloric region and the gastric angle where maintaining the water level and the probe scanning perpendicular to the wall can sometimes be hard to achieve. In these cases rotating the patient may help to keep the water level constant, whereas pushing the scope in, pulling it out and then rotating it may help to achieve a perpendicular position[6]. The alternative balloon-inflation method is usually used for rapid screening of submucosal lesions and perigastric structures. The gastrointestinal wall normally consists of 5 distinct layers (Figure 1). The two inner layers (echo-rich and echo-poor) represent the interface/superficial mucosa and deep mucosa/muscularis mucosa. The third, echo-rich, layer corresponds to the submucosa, the fourth (echo-poor) to the muscularis propria, and the fifth (echo-rich) to the serosa, which is usually not easily distinguishable from the surrounding echo-rich tissue. Surrounding organs, vessels, and other structures are important for orientation and for other diagnostic purposes (e.g. tumor infiltration depth). These consist of various organs including the pancreatic body and tail, parts of the liver (especially the left lobe) and parts of the left kidney and spleen, as well as vessels such as the aorta, the vena cava (proximal stomach), the celiac trunk and the splenic and left renal veins. In everyday practice, the water-filling and the balloon-inflation methods can be combined for better imaging. There are no established values for the thickness of normal gastrointestinal wall, but a figure of 2-4 mm is usually considered to be the normal range, as well as a 1:1:1 relation between the mucosa, submucosa, and muscularis propria[6,7].

SUBMUCOSAL LESIONS

Introduction

The term submucosal lesion (SML) or submucosal tumor (SMT) includes a wide spectrum of non-neoplastic and

neoplastic conditions (benign and malignant) and is used to define an intramural growth underneath the mucosa, the exact nature of which cannot be definitely determined either by standard luminal endoscopy or by barium contrast radiography[8]. Despite the fact that the incidence of SMTs in the whole GI-tract is unknown and precise epidemiologic data are scarce, it seems that the stomach is the organ most frequently affected and it has been reported that gastric SMTs occur with an incidence of about 0.36% of routine upper GI-endoscopies (i.e. roughly one in every 300 endoscopies)[9-11]. Such findings are usually asymptomatic and incidental during various diagnostic procedures requiring endoscopy. However, when a physician encounters such a lesion, decisions of high clinical significance have to be made concerning the lesion's nature (e.g. compression on the gastric wall from the outside versus a tumor deep in the wall, under the overlying normal mucosa and if so, a benign or a malignant tumor requiring treatment). The physicians armamentarium for successfully answering these questions and adequately treating the affected patients includes transabdominal ultrasonography, CT and MRI scans, as well as diagnostic EUS carried out when indicated by EUS-guided fine-needle aspiration (EUS-FNA), (leading to treatment options such as close follow-up, endoscopic resection or surgical removal)[12].

SMLs in EUS: EUS, EUS-FNA and other diagnostic modalities?

The diagnostic ability of EUS to clearly demonstrate the gastric wall and its layers makes it a great tool for the clinician to make the differential diagnosis of "real" SMTs (i.e. intramural tumors) from extraluminal compressions caused by either normal or pathological structures. Moreover, it can also show the layer of origin of gastric SMTs and can therefore assist in their exact characterization[11]. If EUS shows that a suspected submucosal bulge is an impression caused by a normal organ (e.g., the spleen or gallbladder), further diagnostic steps are not necessary. If the lesion is intramural, the differential diagnosis includes SMTs, cysts and vessels. Cysts usually present as anechoic, round or ovular lesions which arise from the 3rd gastric wall layer and vessels (most importantly varices) present as tubular or serpiginous anechoic formations, also usually arising from the 3rd layer, that produce a "positive" signal at electronic (Doppler-endowed) EUS. Additional information regarding the nature of tumors can be extracted from their layer of origin, echo pattern, and margin. The most frequent myogenic tumors (leiomyomas) are characteristically located in the second or forth echo-poor layer; they have an echo-poor pattern, and are more or less homogeneous and more or less well demarcated. Other lesions (granular-cell tumors, aberrant pancreas, fibroma, lipoma) have different echo patterns and usually originate from the third, echo-rich layer (submucosa), though sometimes from other layers as well (see the relevant paragraphs that follow)[7,12,13].

The identification of large SMTs can also be achieved by other imaging modalities such as barium studies, CT, MRI and even careful transabdominal ultrasound scanning with gastric water filling, the later being dependent on the experience of the examiner. Although there is a theoretical advantage of CT and MRI over EUS in staging, therapeutic planning and follow-up, i.e. the possibility to depict the full extension of a large SMT[14], nevertheless both of these methods are unable to determine the organ of origin of an SMT when dealing with significantly exophytic tumors, and have limited contribution in SMT classification in more than 50% of cases (especially gastrointestinal stromal-cell tumors). Furthermore, they cannot differentiate between malignant and benign lesions (unless in cases of obvious locally advanced or metastatic disease)[8,14]. Therefore, EUS is commonly agreed to be the best imaging modality for diagnosing and differentiating between SMLs in the GI-tract and has been shown to be consistently superior to other imaging tests[8,11,13,15]. Histopathological diagnosis cannot be made by (diagnostic) EUS alone, nor can benign lesions definitely be differentiated from malignant ones. Nevertheless, certain risk criteria have been established on EUS (size > 3 cm, inhomogeneous echo pattern, irregular margins, presence of lymph nodes) that may suggest malignancy; the most reliable of these probably being size[16]. If CT or MRI are to pose a threat to the leading role of EUS in diagnostics of SMTs, this will be with the help of new scanners which combine CT (or possibly MRI in the future) with positron emission tomography (PET), thus uniting functional and morphologic imaging. The latter depicts metabolic changes in tissue and has shown favorable results not only in the early evaluation of response of gastrointestinal stromal cell tumors (GIST) to treatment with imatinib, but seems also to be promising in the diagnosis, staging and assessment of disease recurrence in these cases[8]. Another advantage of EUS is that it can easily be combined with conventional endoscopy and EUS-guided fine-needle aspiration and biopsy (EUS-FNA). The advent of EUS-FNA, some 15 years ago, led to limited use of EUS as a mere imaging test, with the combination opening new possibilities for transmural tissue diagnosis and expanding the indications of EUS in pathologies of various organs, including SMTs of the stomach. Lately the characterization of GISTs with their inherent malignant potential has triggered a renewed interest in differential diagnosis of gastric SMTs. In this case, a final diagnosis using EUS-FNA with adequate tissue sampling and histological (aided by immunohistochemical) studies, is an attractive possibility. Tissue diagnosis of SMTs should address two questions: a) GIST versus another histology and b) malignant potential of a given GIST. The efficacy of EUS-FNA to accurately diagnose SMTs had some initial encouraging reports[17], only to be followed by the doubts of others. The tissue sampled from lesions at EUS-FNA was initially examined cytologically, but it has been recently shown that acquiring a core specimen for histological assessment is possible, even with a small number of needle passes[18]. When cytological examination is the aim, the presence of a cytopathologist during EUS-FNA, in order to obtain an adequate sample, has been strongly recommended

especially in reports from the U.S.. This is virtually impossible in Europe, due to cost and personnel issues but the problem has been overcome by increasing the number of needle passes through the lesion in question; however, there is still lack of firm data supporting this option. Furthermore, there are different options in processing the cytological samples, including smears and cell-blocks. It is logical and desirable to have close contact with the cytopathologist and discuss the EUS-FNA procedure, in order to optimize the process of EUS-FNA tissue sampling by avoiding possible mistakes or weaknesses in the technique that are apparent to the cytopathologist but not to the clinician. For example, mitotic counts and immunohistochemistry cannot be performed on smears; thus requiring cell blocks from the cytological sample[8]. Although the diagnosis of an SMT was initially made by using cytological analysis exclusively, histological tissue analysis seems to be preferable[19], e.g. when wishing to differentiate between a benign and a malignant SMT of the smooth muscles. Histology offers the possibility of immunohistochemistry and mitotic counts (necessary for differentiation of GISTs from other SMTs and for the assessment of their malignant potential) and some distinct advantages over cytology, such as standardization of tissue acquisition (defined number of biopsies, formalin fixation), analysis (later assessment, no on-site analysis, decreasing the number of diagnoses such as "indeterminate or suspicious", second opinion established) and availability of expertise. A number of studies have reported on the tissue acquisition yield and the accuracy rates of EUS-FNA. Results vary between 50% and 93%[12,17,19-21] and seem to be influenced by various factors including the lesion's size (diagnostic rate for GISTs < 2cm, 2-4cm and 4cm or more were 71%, 86% and 100%, respectively)[19], cytological versus histological assessment[12] and needle size. Recently, newer advanced types of needle aiming at larger specimens or offering other advantages have become available. The Trucut needle, previously shown to offer a limited benefit was tested and compared with conventional 22 gauge (G) needles in a small series (only 10 cases) with SMLs. Although the Trucut needle (19 G size) was inferior in terms of final diagnostic yield (70% *vs* 90%), determination of the marker c-kit to diagnose GISTs was possible in all 6 cases in whom in was indicated[22]. A larger prospective, uncontrolled study using the Trucut needle, involving 49 consecutive patients with hypoechoic gastric SMTs also showed a moderate diagnostic yield for the needle (tumor tissue adequate for diagnosis obtained in 63% of patients; 95% CI 49%-75%), whereas the samples were too small to reliably determine the mitotic index[23]. However, another study on SMTs, presented in abstract form, used a 19 G prototype needle with a mean number of 4 passes and reached a tissue yield of 74%, and this only included repeated procedures in 2 cases[24]. It seems that a obtaining a definite tissue diagnosis in SMTs can be rather difficult. For example, although differentiation between a myogenic tumor and a lipoma or a fibroma can be made even by EUS-FNA cytology alone, this is complicated, as a large tissue sample is needed and differentiation can even be difficult on frozen sections during surgery, especially when dealing with myogenic tumors. One should also have in mind possible complications such as bleeding and sepsis. Doppler-EUS examination performed prior to EUS-FNA may prevent rupture of a possible varice and antibiotic prophylaxis should be considered[8,23]. Despite the fact that the aforementioned results with EUS-FNA are at best moderate, one must keep in mind that another non-surgical alternative, namely forceps biopsy during standard endoscopy, faired significantly worse in trials than EUS-FNA (in one study 35% was submucosal representation achieved, in spite of the endoscopist's efforts to obtain submucosal tissue)[9].

To summarize, EUS (with or without EUS-FNA) remains the gold standard of non surgical diagnosis and classification of SMTs and allows decision-making regarding therapy and management of patient's with SMTs. There seems to be a lack of evidence regarding the optimal strategy in SMTs suspected to be GISTs with a negative EUS-FNA tissue diagnosis, what the optimal decision should be (i.e. EUS-FNA versus surgery) in cases of large SMTs, and also the role (and the intervals) of follow-up in cases with a small/intermediate suspicion of malignancy or an equivocal histology. These issues simply stress the need for prospective, randomized trials (possibly multi-center, in order to recruit greater numbers of patients), which will answer these and similar questions.

Appearance of various SMLs in EUS

For EUS-imaging of all SMLs there should be an initial endoscopic localization of the lesion followed by focus on the transition zone of the normal gastric wall and the SML. Here, it is easier to precisely locate the wall layer of origin. This should be followed by careful inspection and determination of the size and shape of the lesion, the regularity of its borders, its echogenic characteristsics, presence of vessels (facilitated by the Doppler-imaging possibilities of modern electronic echoendoscopes). Finally, the perigastric area should be searched for signs of infiltration of adjacent organs, metastatic disease and especially lymph nodes.

GISTs in EUS: The origin of GISTs is thought to be from multipotential mesenchymal stem cells. Therefore, myogenic and neurogenic features may be present in these tumors, which are the commonest mesenchymal tumors in the GI-tract. 65% of GISTs occur in the stomach and at upper GI-endoscopy appear as submucosal, intramural, or sometimes serosal nodules covered by an intact normal mucosa, but may also present as umbilicated lesions with a central ulceration (Figure 2A). At EUS, they are characteristically located in the fourth echo-poor layer (which corresponds to the muscularis propria) or (less often) to the second echo-poor layer (muscularis mucosae). They appear with an echo-poor pattern, and are more or less homogeneous and more or less well demarcated (Figure 2B). Signs of suspected malignancy include a large size (e.g. > 4 cm, although this cutoff is rather arbitrary), irregular borders,

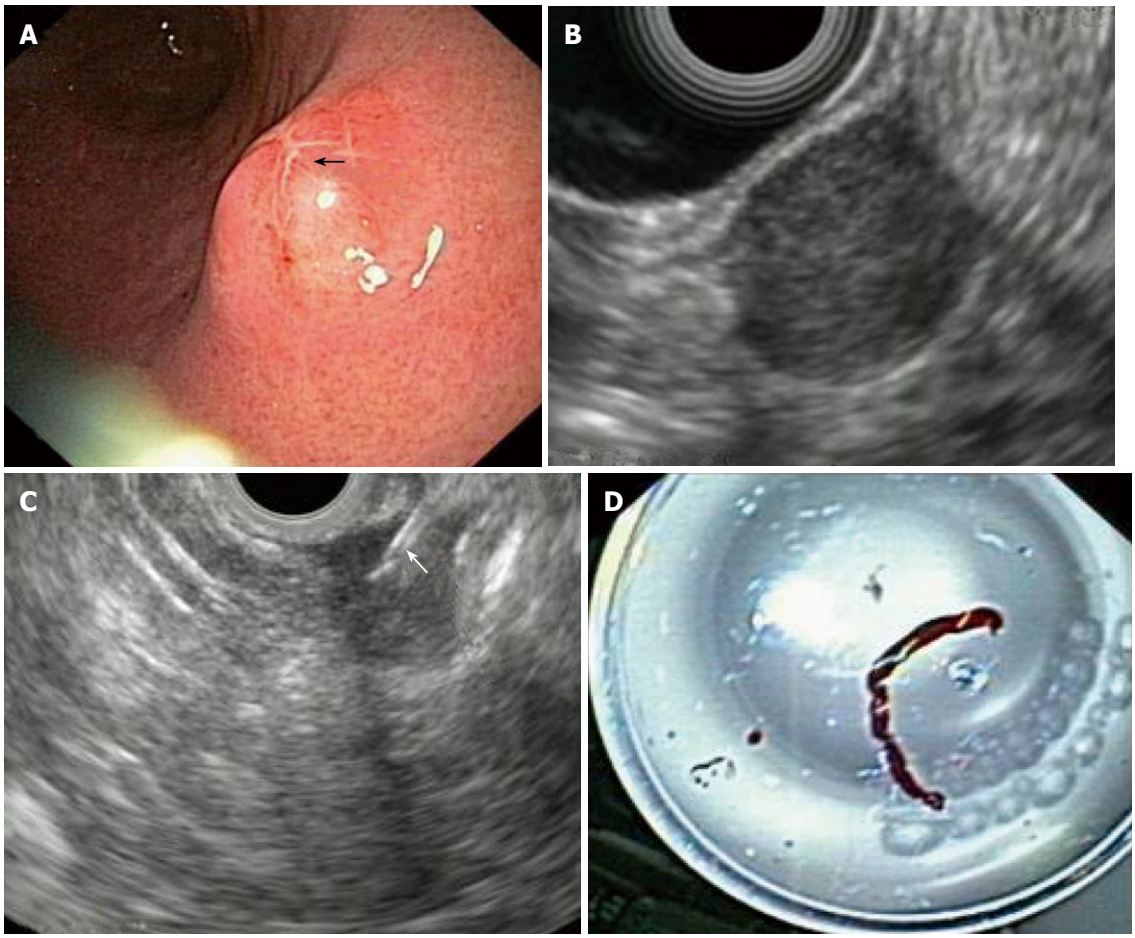

Figure 2 Gastric gastrointestinal stromal cell tumors: Endoscopic aspects, endoscopic ultrasonography-imaging and tissue sampling. A: Endoscopic image of the lesion; note that the lesion is covered by a normal mucosa with a central umbilication (black arrow); B: EUS imaging of the lesion, which is located in the 4th echo-poor layer (muscularis propria); C: EUS-FNA of the lesion; note the presence of the needle (white arrow); D: Histological specimen of the EUS-FNA. EUS: Endoscopic ultrasonography; EUS-FNA: EUS-guided fne needle aspiration.

lobulations, anechoic spaces or echogenic foci. The malignancy potential of a given GIST increases in parallel with the presence of these imaging criteria. However, as previously pointed-out, these features are only suggestive of malignant potential and only tissue diagnosis with immunohistochemistry (most GISTs are c-kit, - CD 117 and CD34 positive) and mitotic counts are diagnostic, a fact that highlights the importance of EUS-FNA in the diagnosis of these tumors (Figures 2C and 2D). About 10-30% of GISTs have a malignant behavior. However, it should be stressed that according to the current suggested terminology for GISTs, the diagnoses "benign" or "malignant" should be avoided, due to the inherent malignant potential of all GISTs and that definitions including "low", "intermediate" or "high" risk are preferred instead[7,8,12,20]. As previously mentioned, there is lack of evidence on treatment algorithms, when encountering possible gastric GISTs at endoscopy. Options could include surgical resection, EUS-FNA and close surveillance with repeat EUS-examinations. It seems that the first of these should be followed in cases of large GISTs or cases where EUS features change at follow-up, with appearance of necrosis, change of echogenicity, or increase in size. EUS-FNA (and decisions on further management according to the results of histology or cytology) is usually advocated in cases of intermediate GIST size without changes at surveillance-EUS.

Pancreatic rests (aberrant pancreas) in EUS: Pancreatic rests or aberrant pancreas (or ectopic, or heterotopic pancreas) are foci of ectopic pancreatic tissue i.e. pancreatic tissue in other locations, lacking anatomic or vascular connection with the normal pancreas. In a surgical series they were found in about 0.25% of explorative laparotomies[24]. They can be encountered throughout the GI-tract, with the stomach being the most usual site where they are diagnosed and are usually asymptomatic, but may also manifest with symptoms including (acute or chronic) pancreatitis, bleeding ulceration or obstruction. Rarely, pancreatic rests may even mimic a malignant GIST, although EUS can usually differentiate these lesions[24]. Endoscopically, they usually present as sessile SMLs, possibly with a duct opening on their surface (Figure 3A), from which fluid may exit on pressure[8]. Aberrant pancreas normally originates in the third layer (submucosa), but may sometimes originate from other layers (i.e. second or forth wall layer) and is us-

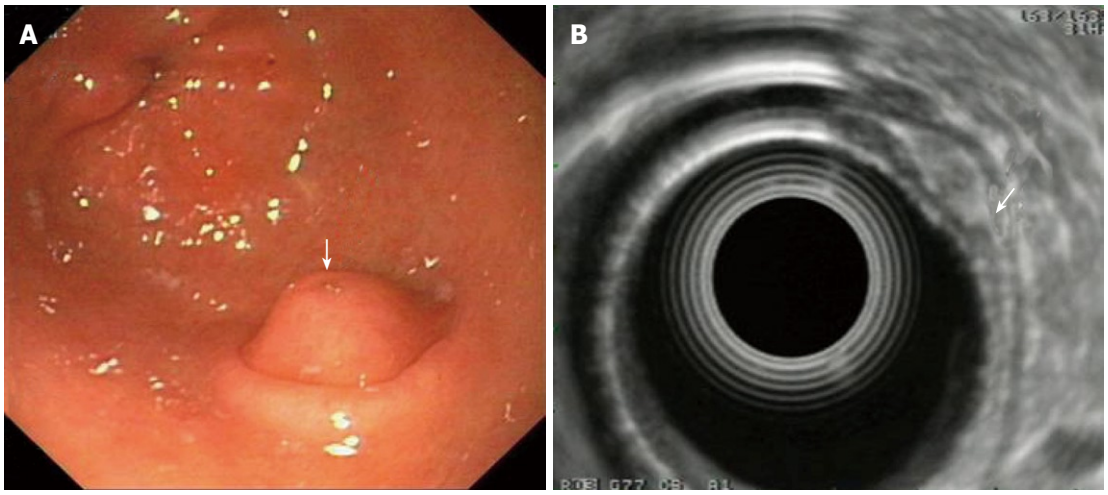

Figure 3 Pancreatic rest of the stomach: Endoscopic and endoscopic ultrasonography -imaging. A: Endoscopic image of a pancreatic rest. Note the duct opening on the surface of lesion is covered by a normal mucosa with a central umbilication (arrow); B: EUS imaging of the lesion which originates from the 3rd layer, i.e. the submucosa (arrow); note the lesion's mixed echogenicity. EUS: Endoscopic ultrasonography.

ually hypoechoic or of mixed echogenicity, including anechoic structures that correspond to ductal formations (Figure 3B). Because of their endosonographic appearance they may cause difficulties in differential diagnosis from carcinoid tumors, which have similar endosonographic characteristics[7,8,12,24,25].

Lipomas in EUS: Lipomas are benign tumors which can appear throughout the GI-tract, their most common location being the colon. Endoscopically, they usually present as solitary, yellow-colored, well-circumscribed, smooth SMLs, with a very slow (if any) rate of growth when repeat endoscopies are performed. These lesions are characteristically soft when pressure is exercised on them. In EUS, a lipoma usually presents as a hyperechoic homogenous mass, which originates from the third wall layer (submucosa)[7,8,12].

Neuroendocrine tumors: carcinoids in EUS: Carcinoid tumors are rare, slow-growing neuroendocrine tumors arising from the enterochromaffin cells disseminated throughout the bronchopulmonary system and the GI-tract, which however carry malignant potential. They are the most common type of neuroendocrine tumor located in the stomach. Gastric carcinoids are usually asymptomatic and may be incidentally discovered at GI-endoscopy. Their size is a good predictor of their risk for malignancy (with carcinoids smaller than the cutoff size of 2cm rarely being malignant). Endoscopically, carcinoids usually have the appearance of small polyps and present either as solitary lesions or in clusters. Endosonographically, gastric carcinoids are homogeneous, well demarcated, mildly hypoechoic SMLs, that originate from the first, second and/or third layer[12,13,26,27].

Granular cell tumors in EUS: Granular cell tumors are SMTs that are believed to be of neural origin (immunohistochemichal studies indicate that they originate from Schwann cells). They are rarely encountered in the GI-tract (about 8% of all granular cell tumors), whereas approximately 30% of all GI-tract granular cell tumors are located in the middle to distal esophagus. Localization in the stomach is very rare. Gastric granular cell tumors can be solitary or, more frequently, are associated with another GI-localization. In endoscopy they appear as small yellowish nodules (< 4 cm and -in about 95% of cases- < 2 cm). Granular cell tumors are usually benign in behavior, although some malignant cases (a single gastric case) have also been reported. Endosonographically they present as a hypoechoic, heterogeneous well-demarcated mass with smooth borders, arising from the second or third wall layer[8,12,13,28].

Schwannomas in EUS: Schwannomas are well-demarcated, benign nerve sheath tumors usually of the soft tissue, rarely encountered in the GI-tract, where they are often discovered incidentally as small polypoid intraluminal lesions covered by intact normal mucosa. GI-tract Schwannomas, though rare, are mostly encountered in the stomach (0.2% of all gastric tumors). The tumors are generally asymptomatic or manifest with non-specific symptoms including abdominal discomfort or as a palpable epigastric mass when exophytic growth has occurred. Bleeding may occasionally occur, in the case of deep ulceration. In standard endoscopy, gastric schwannomas may present as round or oval (multinodular) SMLs. As they usually and principally involve the submucosa and muscularis propria, endosonographically they appear as homogenous, hypoechoic, small SMLs with distinct borders, arising from the third and/or forth gastric wall layer[8,29].

Cysts in EUS: Cysts in the GI-tract are usually the result of a resolved inflammatory process, or derive from embryological development, including foregut and duplication cysts. Cystic SMLs in the GI-tract may appear as simple cysts, multicystic or solid cystic lesions. Foregut cysts are usually located in the mediastinum and categorized as bronchogenic or neurenteric, according to their embryogenic origin; EUS and EUS-FNA play a pivotal role in their diag-

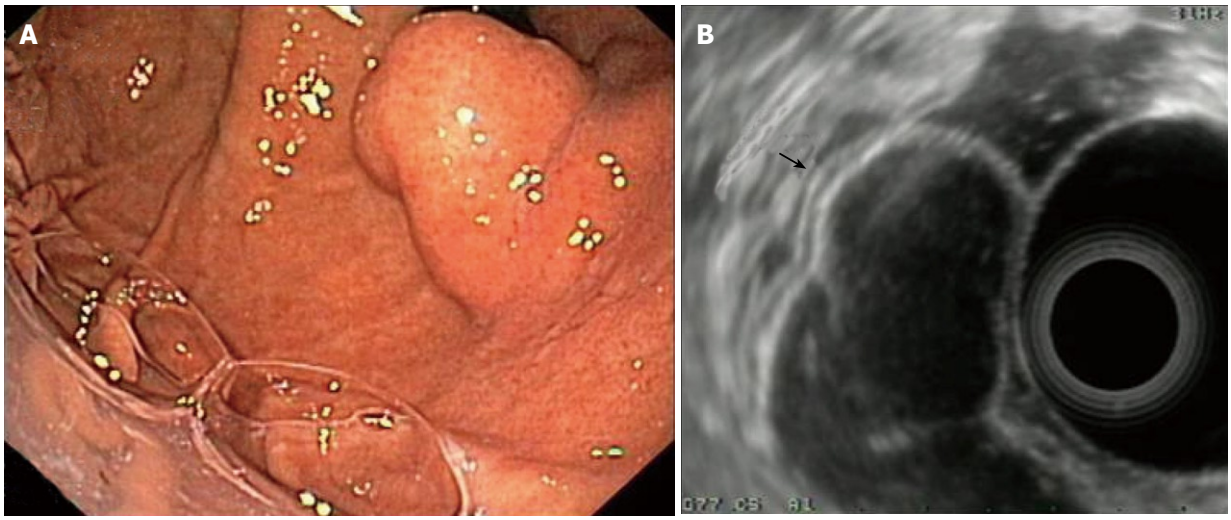

Figure 4 Duplication cyst of the stomach. A: Endoscopic image of the lesion (retrograde view); B: EUS imaging of the same lesion; note the lesion's 3-layer structure which originates from the 3rd layer, i.e. the submucosa (arrow). EUS: Endoscopic ultrasonography.

nosis. On the other hand, gastroenteric duplication cysts arise from abnormal development of the part of the dorsal foregut that becomes the GI-tract[12,13,30].

Localization of cysts in the stomach is rare and they may be either asymptomatic, or present (especially when dealing with children) with obstructive symptoms, pain, or bleeding. In standard endoscopy, cysts appear as compressible nodule structures, which protrude (to a greater or smaller extent) into the lumen of the GI-tract. Endosonograhically, they present as well-demarcated, round or oval anechoic lesions, located in the third gastric wall layer. The wall of inflammatory cysts is a single hyperechoic layer.

Duplication cysts are rare congenital abnormalities. They can occur anywhere throughout the GI-tract, with gastric duplication cysts being the most uncommon, representing only 2%-8% of all duplication cysts located in the GI-tract[31]. Characteristically, in EUS the walls of a duplication cyst may appear as a 3- or 5-layer structure due to the presence of a submucosa and a muscularis layer (Figure 4). Diagnosis of duplication cysts in adulthood is uncommon and is usually an incidental finding in clinical settings. They are usually benign, although rare cases of malignant transformation have also been described[12,13,30,31].

Gastric varices in EUS: EUS in combination with the color Doppler technique is a noninvasive method which allows us not only to definitely differentiate gastric varices from thickened gastric folds or SMLs in the stomach, but also to study the progression of hemodynamic changes in the portal venous system of affected patients and also to objectively assess the effect of pharmacological agents (or other therapies, e.g. TIPPS) on portal hypertension. EUS has also found a role in the treatment and follow up of esophageal and gastric varices[12,32]. Gastric varices usually present at the fundus or the body of the stomach as serpiginous or oval structures covered by normal mucosa, that retreat when pressed by a biopsy forceps. Tissue sampling is risky when gastric varises are suspected and therefore the diagnosis is made by means of EUS. Endosonographically, they appear as round, oval, tortuous or tubular anechoic structures within the third gastric wall layer (i.e. the submucosa). A positive signal in Doppler examination is diagnostic[32,33] (Figure 5). A thickening of the gastric wall layers, as well as the presence of gastric (or paragastric) collateral varises may also be seen[12,32,34]. The latter (together with their esophageal counterparts) may correlate with the risk of variceal bleeding[34].

Miscellaneous SMLs in EUS: (1) Gastric leiomyomas: Leiomyomas are the most common SMTs of mesenchymal origin in the esophagus, but are very rare in the stomach. Contrary to "real" GISTs, leiomyomas are almost invariably benign and therefore differential diagnosis between these two conditions is vital to therapeutic decisions. As previously mentioned, differential diagnosis of GISTs from leiomyomas is not always easy, even with help from EUS-FNA. Studies have attempted to differentiate leiomyomas from "true" (bearing a malignant potential) GISTs based on their EUS features. Leiomyomas appear endosonographically as small (< 5 cm) homogenous, hypoechoic SMTs, with smooth/distinct borders, originating from the forth or second wall layer[8]. Signs like inhomogenicity, hyperechogenic spots, a marginal halo and higher echogenicity compared to the surrounding muscle layer might appear more frequently in GISTs than in leiomyomas[35], but differentiation based merely on imaging is risky and therefore should be done only in specific conditions and with the informed of the patient. For larger lesions, surgical resection seems to be the best alternative; (2) Extrinsic compressions: Compressions on the gastric wall from organs neighboring the stomach may occasionally present as SMLs and sometimes can cause diagnostic problems. The spleen, the left hepatic lobe or even the gallbladder can produce impressions on the gastric fundus and upper body or antrum, which may appear as SMLs in standard endoscopy; in these cases, EUS has been shown to be

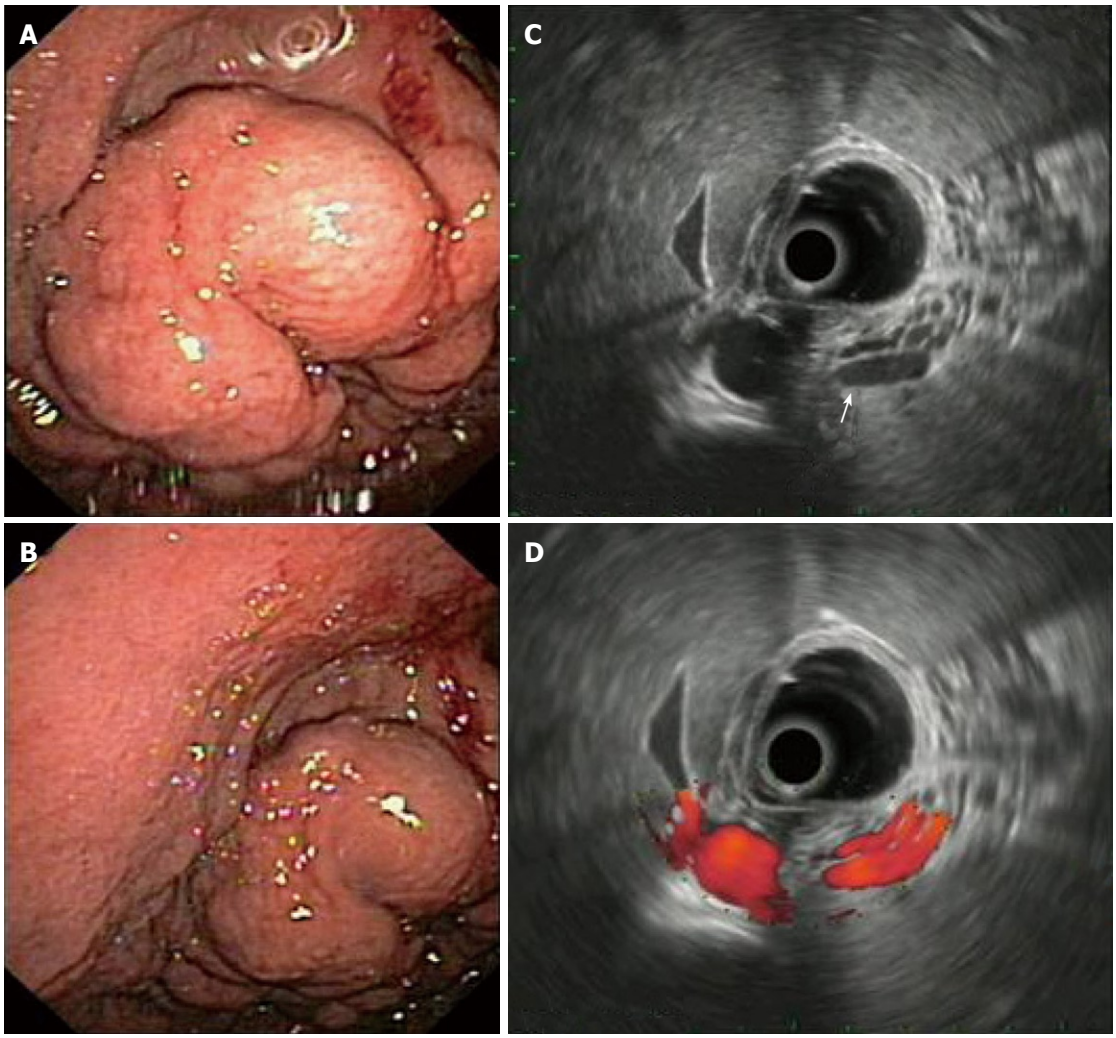

Figure 5 Gastric varices in endoscopy and endoscopic ultrasonography. A, B: Endoscopic image of gastric varices presenting as thick serpiginous structures, covered by normal mucosa; C: EUS imaging of the varices; note their tortuous, anechoic structure which originates from the 3rd layer, i.e. the submucosa (arrow); D: EUS Doppler imaging of the same varices; the positive signal denotes their vascular origin. EUS: Endoscopic ultrasonography.

a valuable diagnostic tool[12,13,15]. Furthermore, pathological structures, (including pancreatic pseudocysts and tumors or enlarged lymph nodes), structures of cardiovascular origin (e.g. the left atrium, or aneurysms of the aorta or the splenic artery) may also compress (or, in the case of malignant entities, infiltrate) the gastric wall. Therefore, EUS-based differential diagnosis should be performed carefully, possibly combining "usual" ultrasound frequencies of 7.5 MHz (which allow a "deeper" view and can better assess the correlation of the gastric wall with source of the impression) with higher frequencies, such as 12 MHz (for a more detailed "scanning" of the interface/gastric serosal wall and extrinsic compression) and Doppler scanning (which will present a positive signal in case of vascular lesions). These measures can help in ruling-out an infiltration of the gastric wall. Care should be taken to look for possible pathological lymph nodes[12,13]; (3) Submucosal metastases: Carcinomas or lymphomas may, although rarely, metastasize to the GI-tract (including the stomach) and appear as submucosal masses[10,12]. Their endosonographic appearance generally is that of hypoechoic, heterogeneous masses, which may originate from any (or all) of the wall layers[12,13]; and (4) Fundic gland polyps: Finally, fundic gland polyps are usually recognized by their macroscopic appearance in endoscopy. However, in doubtful cases, they can be easily removed with a biopsy forceps and be sent for histology. EUS is rarely necessary and may be difficult to perform in these cases, as optimal acoustic coupling of the ultrasonic transducer to the lesions is extremely difficult to achieve, due to the small size of the latter. However, if EUS is performed, the lesions are usually observed as hyperechoic structures originating (and remaining) in the first layer [12,36].

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Comparison between endoscopic sclerotherapy and band ligation for hemostasis of acute variceal bleeding

Gustavo Oliveira Luz, Fauze Maluf-Filho, Sérgio Eiji Matuguma, Fábio Yuji Hondo, Edson Ide, Jeane Martins Melo, Spencer Cheng, Paulo Sakai

Gustavo Oliveira Luz, Fauze Maluf-Filho, Sérgio Eiji Matuguma, Fábio Yuji Hondo, Edson Ide, Jeane Martins Melo, Spencer Cheng, Paulo Sakai, Gastrointestinal Endoscopy Unit, Hospital das Clínicas, São Paulo University Medical School, São Paulo 05612000, Brazil
Author contributions: Luz GO, Matuguma SE, Hondo FY, Ide E, Melo JM, Cheng S and Sakai P were responsible for the protocol design, acquision of data, critical revision, and approval of the final version of this manuscript; Maluf-Filho F was responsible for the conception and protocol design, drafting the article and approval of the final version of this manuscript.
Supported by department of Gastroenterology-Gastrointestinal Endoscopy Unit, São Paulo University School of Medicine.
Correspondence to: Fauze Maluf-Filho, MD, PhD, Gastrointestinal Endoscopy Unit, Hospital das Clínicas, Department of Gastroenterology, Sao Paulo University School of Medicine, Av. Olegario Mariano, 488 Sao Paulo/SP, CEP 05612000, Brazil. fauze.maluf@terra.com.br
Telephone: +55-11-3721-7986 Fax: +55-11-3884-7599
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Abstract

AIM: To compare band ligation (BL) with endoscopic sclerotherapy (SCL) in patients admitted to an emergency unit for esophageal variceal rupture.

METHODS: A prospective, randomized, single-center study without crossover was conducted. After endoscopic diagnosis of esophageal variceal rupture, patients were randomized into groups for SCL or BL treatment. Sclerotherapy was performed by ethanolamine oleate intravascular injection both above and below the rupture point, with a maximum volume of 20 mL. For BL patients, banding at the rupture point was attempted, followed by ligation of all variceal tissue of the distal esophagus. Primary outcomes for both groups were initial failure of bleeding control (5 d), early re-bleeding (5 d to 6 wk), and complications, including mortality. From May 2005 to May 2007, 100 patients with variceal bleeding were enrolled in the study: 50 SCL and 50 BL patients. No differences between groups were observed across gender, age, Child-Pugh status, presence of shock at admission, mean hemoglobin levels, and variceal size.

RESULTS: No differences were found between groups for bleeding control, early re-bleeding rates, complications, or mortality. After 6 wk, 36 (80%) SCL and 33 (77 %) EBL patients were alive and free of bleeding. A statistically significant association between Child-Pugh status and mortality was found, with 16% mortality in Child A and B patients and 84% mortality in Child C patients (P<0.001).

CONCLUSION: Despite the limited number of patients included, our results suggest that SCL and BL are equally efficient for the control of acute variceal bleeding.

Key words: Portal hypertension; Hemorrhage; Esophageal varices; Gastrointestinal endoscopy; Ligation; Sclerotherapy

Peer reviewers: Christoph Eisenbach, MD, Department of Gastroenterology, University of Heidelberg, Im Neuenheimer Feld 410, D-69210 Heidelberg, Germany; Peter Born, Professor, Chief, 2nd Department of Medicine, Red Cross Hospital, Munich, Germany

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INTRODUCTION

Although the superiority of band ligation (BL) over endo-

scopic sclerotherapy (SCL) for the secondary prophylaxis of variceal hemorrhage has been proven, the best approach for acute bleeding remains controversial. The international Baveno Ⅳ consensus[1] on portal hypertension recommends band ligation as a first-choice therapy, leaving sclerotherapy as a second-choice procedure. Ligation leads to lower complication rates and higher survival rates[2,3].

A recent meta-analysis suggested that sclerotherapy should remain as the first-choice therapy for cases of bleeding[4]. According to Triantos and colleagues[4], sclerosing agents can be injected by a catheter through the endoscope working channel immediately after the endoscopic diagnosis of esophageal variceal rupture is made. Still, these authors report that when band ligation is employed, it is necessary to withdraw the endoscope for system assembly, potentially increasing complication risk and procedural time.

Conversely, endoscopic SCL performed through the intravascular injection of a 2.5% ethanolamine oleate solution has been used in the majority of Brazilian GI endoscopy units as a low-cost, efficient procedure that is technically easy to perform[5].However, neither of these techniques has been clearly established as the best endoscopic therapy for acute variceal hemorrhage; this fact motivated the current study.

MATERIALS AND METHODS

Primary outcome and sample size calculation

The primary outcome analyzed in this trial was the rate of survival, free of variceal hemorrhage, 6 wk after the index bleeding episode. We calculated that in order to prove a difference of 15% (i.e., 90% *vs* 75%) in the primary outcome between the groups (BL and SCL) with a power of 80% and a significance level lower than 5%, each group should contain at least 112 patients. Failure of bleeding control and early re-bleeding (see "definitions" section below) were considered secondary outcomes.

Patient screening

From May 2005 to May 2007, 480 patients with bleeding secondary to esophageal variceal rupture were treated in the Gastrointestinal Endoscopy Unit of the Hospital das Clínicas of São Paulo University Medical School (HC-FMUSP) in São Paulo, Brazil. Of this total, 380 patients were excluded from the study for a number of reasons (Figure 1).

One hundred patients participated in this study, 50 in the SCL group and 50 in the BL group. Patients older than 18 years and with signs of upper GI bleeding for more than 24 h (confirmed hematemesis and melena) were considered candidates for inclusion.

Acute variceal bleeding was defined when endoscopy indicated active bleeding or the presence of a platelet-fibrin plug or gastric fundus with fresh blood, recent clots, and presence of varices, with no other potential source of hemorrhage.

Randomization and treatment

Whenever endoscopy revealed signs of bleeding secondary to the esophageal variceal rupture, patients were randomly assigned to one of two groups: endoscopic sclerotherapy or band ligation. Patients were randomized through a drawing of 100 sealed envelopes under the principle of concealed allocation. All endoscopic procedures were performed by attending physicians or residents under supervision. All patients included in this study were treated with terlipressin (2-4 mg bolus followed by a 2 mg Ⅳ maintenance dose every 4 h) and antibiotics (third generation cephalosporin or quinolone) maintained for 5 d or 48 h without signs of re-bleeding.

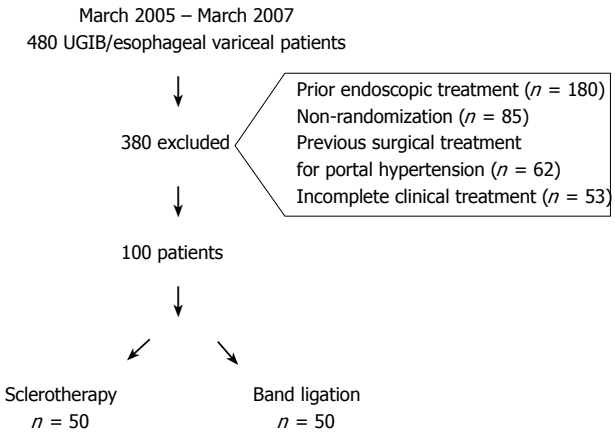

Figure 1 Flow chart of series distribution. UGIB: upper GI bleeding.

Sclerotherapy was performed according to the technique adopted in the Gastrointestinal Endoscopy Unit of HC-FMUSP. An injection of 2.5% ethanolamine-oleate was used. The sclerosing solution was injected into the lumen of the hemorrhagic varix at 5 mL increments above and below the rupture point. The maximum volume used per session was 20 mL. If randomization indicated band ligation as treatment, the endoscope was withdrawn from the patient for assembly of the six-shooter multi-band kit (MBL-6, Cook Inc., Winston-Salem, USA). Attempts were made to ligate the varix on the rupture point while also treating the other varices with the remaining bands. Whenever the exact rupture point could not be identified, ligation of all variceal tissue visible in the final 5 cm of the esophagus was performed with six elastic bands.

Ethics

This study was approved by the Scientific Ethics Committee of the Gastroenterology Department of São Paulo University Medical School (FMUSP) and by the Ethics Committee for Research Project Analysis (CAPPesp) of the Clinical Board of Hospital das Clínicas and FMUSP. All patients, or their legal representatives, signed informed consent forms.

Definitions

In order to evaluate the efficacy of both treatments, groups were compared regarding failure in bleeding control (up to 5 d), early recurrence of bleeding (5 d and 6 wk), complications, and mortality.

Failure in bleeding control was defined as the failure to

Table 1 Patient demographic characteristics and portal hypertension etiology *n* (%)

	Ligation *n* = 50	Sclerotherapy *n* = 50	
Mean age (years)	54.48	50.24	$P^1 = 0.47$
Gender			
Male	37 (74.0)	35 (70.0)	$P^2 = 0.58$
Female	13 (26.0)	15 (30.0)	
Etiology			
Alcohol	19 (38.0)	17 (34.0)	$P^2 = 0.83$
Virus	19 (38.0)	15 (30.0)	$P^2 = 0.53$
Schistosomiasis[a]	6 (12.0)	11 (22.0)	$P^2 = 0.29$
Secondary biliary cirrhosis	4 (8.0)	3 (6.0)	$P^2 = 0.99$
Cryptogenic cirrhosis	1 (2.0)	2 (4.0)	$P^2 = 0.99$
Primary biliary cirrhosis	1(2.0)	2 (4.0)	$P^2 = 0.99$
Child-Pugh Classification			
Child A	2 (4.0)	3 (6.0)	
Child B	22 (44.0)	21 (42.0)	P^1 =0.69
Child C	20 (40.0)	15 (30.0)	

P^1: Student's t test; P^2: χ^2 test; [a]: Not included in Child-Pugh classification.

control bleeding at the moment of examination, or the occurrence of re-bleeding or mortality within the first 5 d after the procedure. Failure criteria included the need for a change in technique in order to achieve hemostasis, the presence of hematemesis, or the presence of fresh blood in the nasogastric tube aspirate associated with signs of hemodynamic instability (systolic blood pressure < 100 mmHg and/or pulse > 100 bpm), or a 3-point hemoglobin level decrease within a 6 h period. Only severe locoregional complications derived from the endoscopic treatment involving surgical treatment or a longer hospital stay were considered, e.g., dissecting hematoma, dysphagia, hemorrhagic ulcer, perforation, mediastinitis, or esophageal stenosis. Bleeding-related mortality was defined as any death occurring between admission and 6 wk after admission[1].

Patient follow-up

After endoscopic treatment, patients were followed up for 6 wk through bedside appointments or telephone contact (with patients discharged before 6 wk) for analysis of re-bleeding, complications, and mortality. Whenever permitted by clinical conditions, secondary prophylaxis with band ligation (independent from the allocation group) was indicated on the 14th day after the initial procedure.

Case series

The demographic and clinical characteristics of patients from both groups are presented in Table 1.

Hemorrhage intensity was assessed as mild, moderate, or severe according to the criteria proposed by Johnston *et al*[6]. The classification of digestive hemorrhage intensity according to these criteria[6] is summarized in Table 2.

During endoscopic examination, the caliber of esophageal varices was classified as small, medium, or large (alternatively, this assessment was made according to the descriptions made by the performing physicians) according to Paquet's classification[7].

Table 2 Clinical and endoscopic findings at index bleeding *n* (%)

	Band Ligation (*n* = 50)	Sclerotherapy (*n* = 50)	
Size of Varices			
Small	10	13	
Medium	5	7	
Large	5	4	
Small/Medium	17	17	
Small/Large	2	2	
Medium/Large	11	7	
Digestive hemorrhage intensity			
Mild	15 (30)	17 (34)	
Moderate	20 (40)	19 (38)	$P = 0.32$
Severe	15 (30)	14 (28)	
Hemoglobin at admission			
mean ± SD	9.52 ± 3.25	9.47 ± 2.55	$P = 0.96$
Red spots			
Presence	46(92.8)	43(86.8)	$P = 0.64$
Absence	4 (8.8)	7 (14.8)	
Endoscopic criteria for variceal bleeding			
Active bleeding	5 (10)	10 (20)	
Platelet-fibrin plug	35 (70)	34 (68)	$P = 0.43$
Varices and gastric blood	10 (20)	6 (12)	

Red spots on variceal cords were subjectively classified as present or absent by the examining physician. The frequency of red spots is presented in Table 2, as are the mean values for hemoglobin levels at admission and the frequency of endoscopic appearance of variceal hemorrhage.

Statistical analysis

A student's *t* test was used for the comparison of means with normal distribution variables, and a Mann-Whitney test was used for means without normal distribution. A chi-square test was used to verify associations in contingency tables (occurrence data). A Fisher's exact test was used to analyze these results, namely, the comparisons of the frequencies observed in variables across the BL and SCL groups. Effects with $P < 0.05$ were considered to be statistically significant.

RESULTS

One hundred patients participated in this study, 50 in the SCL group and 50 in the BL group.

The rate of failure in bleeding control (up to 5 d) is shown in Table 3. Results did not differ when patients with schistosomiasis were excluded from the analysis (Table 4).

Among the 50 patients who underwent endoscopic SCL, seven (14%) presented re-bleeding within a 5-day period. In the BL group, 11 (22%) patients presented re-bleeding during the same period. For the 50 patients treated with BL, 218 elastic bands were applied, ranging from 3 to 6 bands per patient with an average of 4 bands per procedure.

No association was observed between the occurrence of failure in bleeding control and endoscopic treatment

Table 3 Occurrences of re-bleeding, success and mortality up to 5 d *n* (%)

Group	Re-bleeding	Success	Mortality
Sclerotherapy (n = 50)	7 (14.0)	43 (86.0)	3 (6.0)
Band Ligation (n = 50)	11 (22.0)	39 (78.0)	6 (12.0)

P = 0.63

Table 4 Occurrences of re-bleeding, success and mortality up to 5 d, excluding patients with schistosomiasis *n* (%)

Group	Success	Re-bleeding	Mortality
Sclerotherapy (n = 39)	33 (84.6)	6 (15.4)	3 (7.7)
Band Ligation (n = 44)	33 (75.0)	11 (25.0)	6 (13.6)
		P = 0.41	P = 0.49

Table 5 Occurrences of re-bleeding, success and mortality from 5 d to 6 wk *n* (%)

Group	Re-bleeding	Success	Mortality
Sclerotherapy (n = 42)	2 (4.8)	36 (86.0)	6 (14.0)
Band Ligation (n = 37)	1 (2.7)	33 (89.0)	4 (11.0)

P = 0.58

Table 6 Mortality rate through 6 wk *n* (%)

Group	Deaths through 6 wk			
	Mortality up to 5 d	Mortality after 5 d	Total Mortality	Success
Sclerotherapy (n = 45)	3 (7.0)	6 (13.0)	9 (20.0)	36 (80.0)
Band Ligation (n = 43)	6 (14.0)	4 (9.0)	10 (23.0)	33 (77.0)
				P = 0.40

(P = 0.2978). Among the patients who presented re-bleeding in the SCL group, one (2%) had schistosomiasis, two (4%) had Child-Pugh B cirrhosis, and four (8%) had Child-Pugh C cirrhosis. Likewise, among those with failure in bleeding control in the BL group, four (8%) had Child-Pugh B cirrhosis, and seven (14%) had Child-Pugh C cirrhosis. Among the total number of patients who presented re-bleeding within 5 d (18 patients), 11 (61.11%) were Child-Pugh C patients. The difference between the Child-Pugh C group and the other Child-Pugh groups regarding failure occurrence is shown by the results from the Fisher' s exact test. The probability of a Child-Pugh C patient re-bleeding within this period was 3.74-fold higher than that of a Child-Pugh A or B patient.

Among SCL patients with treatment failure, two (4%) presented failure in immediate hemostasis, requiring a change of technique to achieve hemostasis after endoscopic SCL. Bleeding in one patient was controlled through the use of cyanoacrylate. The second patient underwent esophageal balloon tamponade, which was withdrawn after 18 h, at which time a new endoscopic SCL was successfully performed. In the BL group, immediate failure during the procedure occurred in four patients (8%). The first patient was treated with complementation through endoscopic SCL. The second patient received a cyanoacrylate injection. The third patient underwent esophageal balloon tamponade, and the fourth patient underwent tamponade for 12 h, followed by cyanoacrylate injection after balloon withdrawal, and was immediately referred for trans-jugular, intra-hepatic portosystemic shunt (TIPS) placement evolving without re-bleeding through a 6-week follow-up.

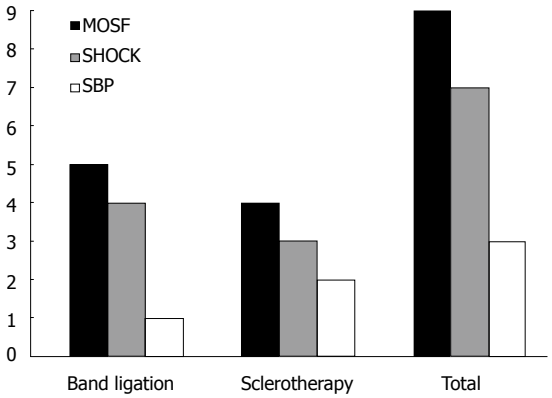

Figure 2 Causes of mortality among groups. MOSF: Multiple organ and system failure; SBP: Spontaneous bacterial peritonitis.

Between 5 d and 6 wk after the procedure, 42 SCL and 37 BL patients were considered for early re-bleeding analysis. This number excludes those patients who died in the first period (up to 5 d), as well as five SCL and seven BL patients who were lost to follow-up. Among the SCL group, two (4.8%) patients presented re-bleeding after 5 d, 36 patients (86%) survived until the end of the study, and six patients (14%) died after 5 d. In the BL group, one (2.7%) patient presented re-bleeding after 5 d, 33 (89%) survived until the end of the study, and four (11%) died (Table 5).

No additional endoscopic treatment-derived complications were observed.

Of 88 follow-up patients, 19 (21.6%) died, nine (20%) from the SCL group and 10 (23%) from the BL group (Table 6). Of these 19 deceased patients, three (16%) were Child-Pugh B, and 16 (84%), Child-Pugh C patients (P < 0.001).

Among patients who presented active bleeding on endoscopic examination (n = 15), 10 (66%) were from the SLC group, and five (34%) were from the BL group. Among this subgroup of patients, 33% mortality was observed up to 6 wk (two SCL and three BL patients), with no difference between groups (P = 0.186). The causes of death among groups are presented in Figure 2.

DISCUSSION

The general improvement in the results of the treatment of variceal acute bleeding might be attributed to better clinical management of these patients. The use of vasoactive drugs and antibiotic prophylaxis is currently mandatory for patients with variceal bleeding. Antibiotic therapy reduced the infection rate from 45% to 14%[8], bleeding recurrence

from 44% to 18%[9], and mortality rate from 48% to 15%[8]. Terlipressin was found to be as effective as an endoscopic treatment with an efficacy of 80% for acute variceal bleeding control within the first 48 hours[10].

Although the highest-level recommendation of the use of antibiotics and vasoactive drugs in the treatment of acute variceal rupture episodes is already established in the literature[11], no consensus exists regarding the preferred endoscopic treatment: band ligation or sclerotherapy.

Sclerotherapy has proven to be inferior to band ligation for primary and secondary prophylaxes of variceal hemorrhage, due to a higher number of complications, and the fact that more sessions are required to achieve variceal obliteration[12,13]. However, endoscopic SCL has still been found to be similar to BL for control of bleeding in some studies[4].

Band ligation, described by Stiegmann and colleagues[14] in 1986, acts by mechanical action; it causes the strangulation of the variceal cord, resulting in necrosis and scar formation 7-10 d later. The technical difference is provided by the number of elastic bands used, and up to 10 bands may be used in a single endoscopic procedure. Because this technique is relatively easy to perform, results are generally reproducible and homogeneous.

In contrast to BL, the intravariceal injection of sclerosing agents was the first endoscopic treatment used, nearly 50 years before the introduction of the elastic band device[15]. There are a number of variations in the endoscopic sclerosing technique, including the type of sclerosing agent used, its concentration, injected volume, and injection location (intravascular, paravascular or combined), which is reflected in the heterogeneous results of SCL presented in different publications. Moreover, this technique requires significant experience and skill of the endoscopist, and it is thus a more operator-dependent technique than band ligation.

A meta-analysis comparing the use of sclerotherapy and band ligation was published in 2006[4]. This analysis involved 12 studies with a total of 1309 patients. The efficacy of endoscopic SCL for initial hemostasis was found to be on average 95% (76%-100%), whereas BL efficacy was found to be 97% (86%-100%). Despite the better results in bleeding control obtained by band ligation, no difference in mortality was found, and these authors concluded that both band ligation and sclerotherapy can be used for the control of acute variceal hemorrhage.

A comparison of 5% ethanolamine-oleate sclerotherapy with band ligation for the treatment of acute variceal bleeding was conducted in 2006[3] in 179 patients (89 in the endoscopic SCL group and 90 in the BL group). Treatment failure occurred in 24% of SCL patients and in 10% of BL patients (relative risk: 2.4%). The major adverse effect rate was found to be 13% for those receiving endoscopic SCL and 4% for those in the BL group ($P = 0.04$). Despite the superior efficacy and safety of band ligation, the 6-week survival likelihood was similar for both groups ($P = 0.17$), with 19 deaths (21%) among SCL patients and 12 deaths (13%) among BL patients.

In the present study, the efficacy of bleeding control within the first 5 days was found to be 86% in the SCL group and 78% in the BL group ($P = 0.30$). Mortality within 6 wk was found to be 20% in the SCL group (9 patients) and 23% in the BL group (10 patients), figures similar to those found in the literature. Local adverse effects caused by SCL, such as hemorrhagic ulcer and perforation, are actually described in the literature more often[3] than was observed in this study. This suggests the refinement of the endoscopic sclerosis technique used in the Gastrointestinal Endoscopy Unit at Hospital das Clínicas of São Paulo University Medical School. An example of this refinement is the use of a sclerosing agent diluted to 2.5%, rather than the 5% employed in other studies[3].We also advocate the use of the intravascular technique and a maximum injection volume of 20 mL.

The Gastrointestinal Endoscopy Unit of HC-FMUSP has amassed over 30 years of experience using sclerotherapy for esophageal variceal treatment. The benefit of endoscopic SCL for patients with schistosomiasis, with a 95% efficacy rate in bleeding control, was demonstrated by Sakai and colleagues[5] in 1990. The importance of hepatic function in the results of endoscopic SCL was described by these authors in another study conducted in 1988[16]. Band ligation, conversely, was introduced in this unit for acute variceal bleeding control in 2004. The greater experience with SCL than BL in this unit might have favored the results of endoscopic sclerosis. It is well recognized that the presence of the distal cap with the bands reduces the endoscopic field which is specially critical during active bleeding.

In this study, 17 (17%) patients presented with liver schistosomiasis, which causes pre-sinusoidal, intra-hepatic portal hypertension with minimal damage to liver function. Due to the patient randomization process, these patients made up 22% of the sclerotherapy group and 12% of the banding group ($P = 0.29$). This uneven distribution of schistosomiasis patients could also have favored the results of the sclerotherapy group. However, no change in the results was observed when these patients were excluded from the analysis.

Failure in bleeding control and mortality were found to be more frequent in Child-Pugh C patients. Of the 18 patients who presented re-bleeding within the first 5 d, 11 (61.1%) were Child-Pugh C patients; 16 (84%) of the total deaths in the 6-week period (19 patients) were also Child-Pugh C patients. Mortality in this subgroup at the end of 6 wk was found to reach 45.7% (45% in the BL and 46.6% in the SCL group).

A comparative analysis of endoscopic sclerosis with ethanolamine-oleate and n-butyl-2-cyanoacrylate (Hystoacril®) injection for acute bleeding control in Child-Pugh C cirrhotic patients demonstrated that significant improvement can be seen with the use of Hystoacril®, according to a study conducted by our group[17] in 2001. Although Hystoacril® is traditionally recommended in patients with gastric varices[1,18], its use for esophageal varices in Child-Pugh C patients improves bleeding control results[17]. This technique has not been widely used, probably due to the risk of damage to the endoscope. Furthermore, the substance has yet to be approved by the Food and Drug Administration (FDA) for this specific purpose and, therefore, is not used

in the US. In Brazil, its registration has been approved by the national drug regulatory agency.

The economic perspective on the treatment of this complication from portal hypertension should be emphasized. A ligation device with six elastic bands currently costs $400.00 on average. In comparison, a sclerosis needle costs approximately $100.00, and the sclerosing substance costs approximately $10.00. In a setting where financial resources allocated to healthcare are scarce, the use of this less costly but similarly efficient technique is a sensible choice.

The present study was clearly too small to prove the tested hypothesis, due to the major difficulty in finding patients appropriate for inclusion in this trial. Several patients were sent to our academic tertiary referral center by other smaller hospitals, but endoscopic treatment at other locations or the absence of previous adequate clinical management precluded their inclusion in the trial. Despite the abovementioned limitations, our results suggest that sclerotherapy should not be dismissed as a possible alternative treatment of rupture of esophageal varices.

COMMENTS

Background

Upper gastrointestinal bleeding caused by rupture of esophageal varices is a common and feared complication of hepatic cirrhosis and portal hypertension. It carries a high mortality rate. The accepted treatment of the acute bleeding episode involves the use of vasoactive drugs and endoscopic treatment. Among possible endoscopic treatments, the applications of elastic bands (banding) and the injection of sclerosing agents into the varix (sclerotherapy) have been studied. For the acute bleeding episode it is not clear whether banding is superior to sclerotherapy for the definitive hemostasis.

Research frontiers

In the area of endoscopic treatment of acute variceal bleeding, one of the research hotspots is to compare endoscopic banding and endoscopic sclerotherapy for definitive hemostasis and hospital mortality.

Innovations and breakthroughs

In the present study, the authors conducted a randomized controlled trial comparing endoscopic banding and endoscopic sclerotherapy for the treatment of the acute bleeding episode of esophageal variceal rupture.

Applications

The study results suggest that both treatments are equally effective for the treatment of bleeding caused by esophageal varices.

Peer review

The authors preformed a single center randomized clinical trial comparing sclerotherapy and band ligation for the control of acute variceal bleeding. The trial was terminated prematurely before the calculated patient number estimated to need to prove a 15% difference in the primary endpoint (survival) was recruited, due to difficulties in patient recruitment. This is an interesting study on an important problem for all interventional gastrointestinal endoscopists.

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CASE REPORT

Steakhouse syndrome causing large esophageal ulcer and stenosis

Shotaro Enomoto, Kazuyuki Nakazawa, Kazuki Ueda, Yoshiyuki Mori, Yoshimasa Maeda, Naoki Shingaki, Takao Maekita, Uki Ota, Masashi Oka, Masao Ichinose

Shotaro Enomoto, Kazuki Ueda, Yoshiyuki Mori, Yoshimasa Maeda, Naoki Shingaki, Takao Maekita, Masashi Oka, Masao Ichinose, Department of Gastroenterology, School of Medicine, Wakayama Medical University, 811-1 Kimiidera, Wakayama City, Wakayama 641-0012, Japan
Shotaro Enomoto, Kazuyuki Nakazawa, Department of Gastroenterology, Nishimurakai Koyo Hospital, 40 Tsuhada, Wakayama City, Wakayama 640-8315, Japan
Uki Ota, Ota Medical Clinic, 424-1 Ota, Wakayama City, 640-83-23 Wakayama, Japan
Author contributions: Enomoto S and Nakazawa K contributed equally to this work; Enomoto S wrote the paper; Nakazawa K made preparations for this paper; Ueda K, Mori Y, Maeda Y and Ota U performed clinical endoscopy; Shingaki N and Maekita T analyzed data, Oka M and Ichinose M contributed to critical review of the article; All authors read and approved the final manuscript.
Correspondence to: Shotaro Enomoto, MD, PhD, Department of Gastroenterology, School of Medicine Wakayama Medical University, 811-1 Kimiidera, Wakayama City, Wakayama 641-0012, Japan. shoe@orion.ocn.ne.jp
Telephone: +8173-447-1335 Fax: +8173-445-3616
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Abstract

A 66-year-old man developed dysphagia during dinner and was evaluated 2 d later in our hospital because of persistent symptoms. Upper gastrointestinal endoscopy showed no impacted food, but advanced esophageal cancer was suspected based on the presence in the upper esophagus of a large irregular ulcerative lesion with a thick white coating and stenosis. Further imaging studies were performed to evaluate for metastases, revealing circumferential esophageal wall thickening and findings suggestive of lung and mediastinal lymph node metastases. However, dysphagia symptoms and the esophageal ulcer improved after hospital admission, and histopathological examination of the esophageal mucosa revealed only nonspecific inflammation. At the time of symptom onset, the patient had been eating stewed beef tendon (*Gyusuji nikomi* in Japanese) without chewing well. Esophageal ulceration due to steakhouse syndrome was therefore diagnosed. The lung lesion was a primary lung cancer that was surgically resected. Although rare, steakhouse syndrome can cause large esophageal ulceration and stenosis, so care must be taken to distinguish this from esophageal cancer.

Key words: Esophageal stenosis; Esophagus; Ulcer; Dysphagia; Steakhouse syndrome

Peer reviewers: Mitsuhiro Asakuma, MD, PhD, Assistant Professor, Department of General and Gastroenterological Surgery, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan; David J Desilets, MD, PhD, Chief, Division of Gastroenterology, Springfield Bldg, Rm S2606, Department of Medicine, Assistant Professor of Clinical Medicine, Tufts University School of Medicine, Springfield Campus, Baystate Medical Center, Springfield, MA 01199, United States

Enomoto S, Nakazawa K, Ueda K, Mori Y, Maeda Y, Shingaki N, Maekita T, Ota U, Oka M, Ichinose M. Steakhouse syndrome causing large esophageal ulcer and stenosis. *World J Gastrointest Endosc* 2011; 3(5): 101-104 Available from: URL: http://www.wjgnet.com/1948-5190/full/v3/i5/101.htm DOI: http://dx.doi.org/10.4253/wjge.v3.i5.101

INTRODUCTION

Steakhouse syndrome is a condition in which food impaction of the esophagus occurs after eating a piece of food, especially a meat bolus, without adequate chewing[1]. The symptoms, clinical presentation and endoscopic findings of steakhouse syndrome require differentiation from other esophageal disorders, and must be considered in patients complaining of dysphagia. We report herein a case of

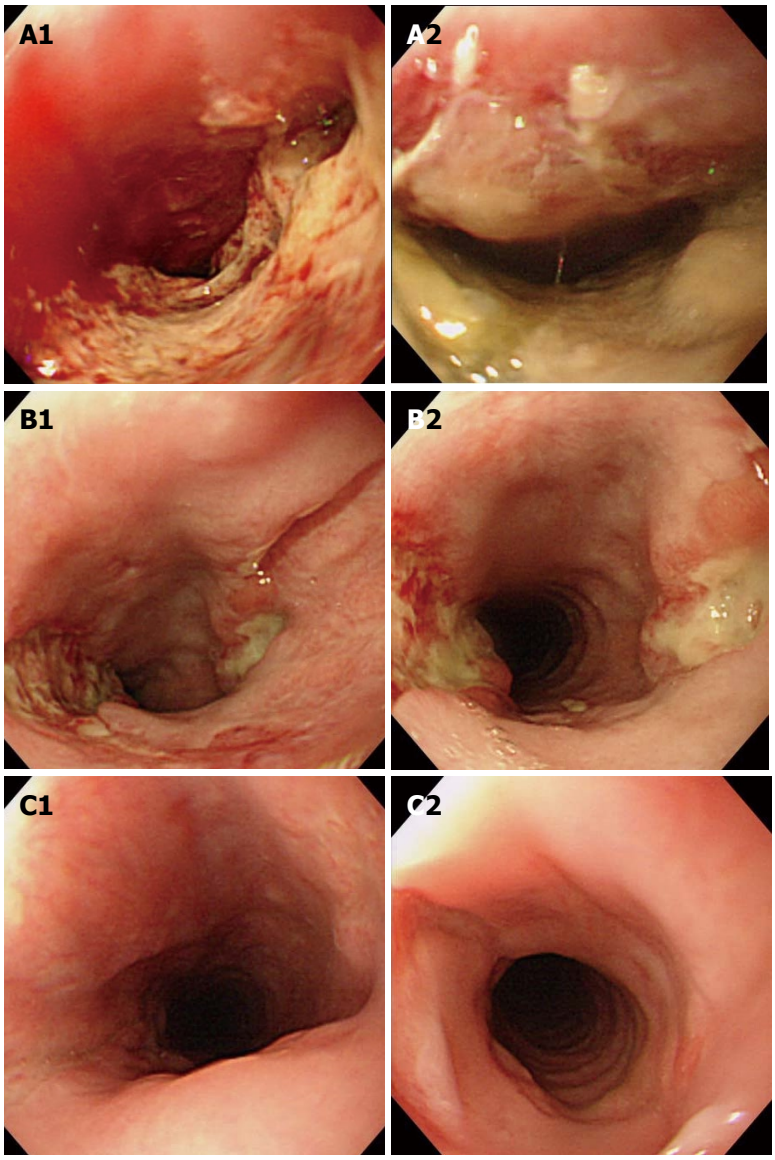

Figure 1 Course of endoscopic findings. A: Findings on initial endoscopy (day 3). An ulcerated lesion covered by a thick white coating is seen in the upper esophagus. The esophageal lumen is narrowed, with easy friability. No distinct surrounding ridge is evident, but ulcer margins are irregular; B: Findings on second endoscopy (day 9). Deep ulceration with a whitish coating is seen at the 3 and 9 o'clock positions in the lumen. Compared to the initial endoscopic findings, esophageal stenosis has improved; C: Findings on third endoscopy (day 23). The white coating has disappeared, and the esophageal ulcer is healed and scarred.

steakhouse syndrome causing esophageal ulceration and stenosis that had to be distinguished from esophageal cancer. We also compare the findings with 4 previous steakhouse syndrome cases that we have treated.

CASE REPORT

A 66-year-old man could not eat or drink anything during dinner (day 1 of onset). Due to persistent dysphagia, he was evaluated late at night in an urgent care center (day 2). The physician on duty diagnosed possible esophageal cancer and recommended gastroenterology consultation. After the patient returned home, dysphagia continued without improvement in the ability to eat, so he was evaluated 2 d later at our hospital (day 3). The patient had no history of specific diseases, and his family history was unremarkable. Lifestyle history included smoking 25 cigarettes/d for 46 years, but no regular alcohol intake.

Blood tests at the time of evaluation showed leukocytosis (white blood cells, 16 800/mm^3) and a mild inflammatory reaction (C-reactive protein, 2.9 mg/dL). Emergency endoscopy performed the same day revealed an irregular ulcerated lesion with a thick white coating in the upper esophagus (16 cm from the incisors) extending 4 cm longitudinally (Figure 1A). The lesion occupied about two-thirds of the circumference of the esophageal lumen. No solid food impaction was observed in this area. Esophageal stenosis was evident. Insertion of the scope distal to the lesion was difficult, but possible.

Endoscopic examination of the esophageal ulcer showed no surrounding ridge or distinct elevation but, because of the ulcer size and extension, irregular ulcer margins, esophageal stenosis, edematous surrounding mucosa and friability, advanced esophageal cancer was suspected. Endoscopic biopsy of the ulcer margins was therefore performed. Distal to the lesion in the mid and lower esophagus, no esophagitis or other findings were observed. The only finding noted in the stomach was atrophic gastritis. As the patient had difficulty eating, he was admitted to our hospital. No fever or chest pain was apparent but, because of the inflammation, the patient was placed on a nil-by-mouth regimen and given intravenous fluids with antibiotics.

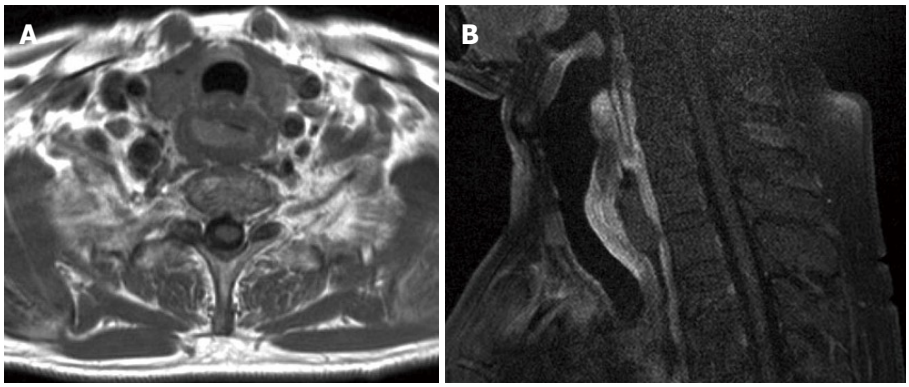

Figure 2 Magnetic resonance imaging (MRI) findings. A: Chest T1-weighted MRI, transverse section. Circumferential wall thickening is seen in the cervical esophagus; B: Chest MRI with gadolinium contrast, sagittal section. Esophageal wall thickening extends about 4 cm, and a contrast effect is evident.

Further evaluation was performed on admission for a suspected diagnosis of advanced esophageal cancer. Tumor markers carcinoembryonic antigen (CEA; 13.8 ng/mL) and carbohydrate antigen 19-9 (CA19-9; 38 U/mL) were elevated. Cytokeratin 19 fragment (CYFRA; 1.2 ng/mL) was within normal limits. Chest magnetic resonance imaging (MRI) revealed circumferential wall thickening in the cervical esophagus, and gadopentate dimeglumine (Gd-DTPA) enhanced MRI showed a contrast effect (Figure 2A and B). In the right lung apex, enhanced MRI revealed a 2-cm nodule with contrast enhancement. This lesion could not be identified on chest radiography because of overlap with the superior mediastinum and an indistinct appearance. Positron emission tomography/computed tomography using F-18 fluoro-deoxy-glucose (FDG PET/CT) was performed to exclude systemic metastasis due to esophageal cancer. This showed circumferential wall thickening of the cervical esophagus, with abnormal uptake of FDG in this area [Standardized uptake value (SUV) max = 4.8]. FDG PET/CT also showed the 2-cm nodule in the right lung apex, with abnormal uptake of FDG in the same area (SUV max = 7.1). In addition, abnormal FDG uptake was seen in the bronchial and anterior mediastinal lymph nodes and lymph node metastases were suspected. No metastases were found in other distant organs. At this point, the differential diagnosis had to include esophageal cancer with lung metastases or multiple primary esophageal and lung cancers.

However, histopathology of the esophageal biopsy revealed only nonspecific inflammation, and dysphagia improved during hospitalization. A second endoscopy was therefore performed on day 9. This showed deep ulceration with a white coating at the 3 and 9 o'clock positions in the lumen, although the ulceration was smaller, and stenosis of the esophageal lumen had improved (Figure 1B). A third endoscopy was performed on day 23. The white coating had disappeared, and the esophageal ulcer had healed and scarred (Figure 1C). When the patient was asked again about what he was eating when the symptoms developed, he confirmed having swallowed a piece of "stewed beef tendon (*Gyusuji nikomi* in Japanese)" without sufficient chewing before the onset of dysphagia. Beef tendon is a tough meat and is used as a food in some Asian countries, including Japan. Furthermore, the impacted food was not extracted by vomiting and was spontaneously swallowed. However, dysphagia continued without improvement in the ability to eat. Based on this, esophageal ulcer associated with steakhouse syndrome was diagnosed. With regard to the right lung lesion, primary lung cancer was diagnosed, and right upper lobectomy was performed. The histopathological diagnosis was mixed-type adenocarcinoma. Tumor markers have normalized, and the patients' clinical course has been good.

DISCUSSION

Steakhouse syndrome, first reported by Norton *et al*[1] in 1963, is caused by food impaction in the esophagus. Examination of the upper gastrointestinal tract for a foreign body often reveals a true foreign body in younger patients, whereas food bolus is more common in older patients[2,3]. When endoscopy reveals solid food impaction, an endoscopic polypectomy snare or grasping forceps can be used for extraction. If a fragmenting meat bolus is identified, a push technique can be performed[2,4].

Table 1 lists the details of 5 cases of steakhouse syndrome that we have treated, including the present case. In our previous 4 cases, emergency endoscopy showed food impaction, and the impacted food was treated endoscopically. None of the previous 4 patients displayed esophageal ulceration. However, in the present patient, endoscopic findings differed from those in the previous 4 cases, warranting differential diagnosis from esophageal cancer. These findings were: 1) absence of obvious impacted food on initial endoscopy; 2) large esophageal ulceration; and 3) edematous esophageal mucosa with severe lumen stenosis.

One reason for the ulcer formation may be the particular patient history in this case. Namely, the previous 4 patients were evaluated on the same day or the day after onset of food impaction symptoms. However, the current patient was evaluated at our hospital 3 d after symptom onset, thereby delaying endoscopy. Delaying endoscopic removal of food impaction risks the possibility of esophageal perforation or respiratory impairment[2,3], and large esophageal ulcers, as seen in our patient, have almost never been reported in steakhouse syndrome. Even among case reports in which evaluation has continued for some time after the onset of food impaction symptoms, only shallow geographic ulcers have been reported[5], but esophageal ulcers were absent in many cases[6]. In 4 of our 5 cases, including this patient, meat was the cause of impaction.

Table 1 Clinical findings in our 5 cases of steakhouse syndrome

Case	Age (years)	Causative food	Location	Endoscopic findings	Therapy
1	78	Beef steak	Upper esophagus	Food impaction	Food extracted with grasping forceps
2	17	Chicken steak	Middle esophagus	Food impaction	Food pushed into stomach with endoscope tip
3	51	Beef steak	Upper esophagus	Food impaction	Food extracted with grasping forceps
4	85	Apple	Upper esophagus	Food impaction, erosion	Food pushed into stomach after fragmenting with grasping forceps
5 (present report)	66	Stewed beef tendon	Upper esophagus	Esophageal ulcer, stenosis	NPO and intravenous fluids

NPO: Non per os.

Similarly, the site of food impaction was the upper esophagus in 4 cases. The method of cooking the meat-roast (3 previous patients) or stew (current patient) differed, but whether this had any effect on ulcer formation is unclear.

In this case, we concluded that the esophageal ulcer resulted from some mechanism due to food impaction, but we cannot exclude the possibility of a reverse phenomenon in which an esophageal ulcer formed first for some reason, followed by food impaction at the site where esophageal stenosis had developed. As possible causes for esophageal food impaction, several underlying obstructive lesions should be considered. These include esophageal webs and rings[1,7], esophageal hiatal hernia[8], reflux esophagitis with stricture[9], postoperative anastomotic strictures[7], and malignant lesions[9,10]. However, in this case, a malignant etiology was excluded and, because no erosions, ulcers, or inflammation were present in the mid or lower esophagus, reflux esophagitis in the upper esophagus was considered unlikely. In addition, given the ulcer characteristics and healing process, a specific type of esophagitis or ulceration, such as viral or fungal, was also unlikely. Pill-induced esophageal ulcers are fairly common. The lesion is mainly due to entrapment of the pill and /or its chemical composition. However, in this case, the patient did not take any prescribed medication. Furthermore, since no food impaction in the esophagus was proven in this case, the diagnosis of steakhouse syndrome seemed uncertain. As mentioned above, other diseases that might cause an esophageal ulcer were ruled out. This case may have developed due to both food impaction coupled to a thermal burn at the site,causing such a severe ulceration with stenosis to develop in just 3 d.

In conclusion, we have reported a case of steakhouse syndrome, which should be considered in the differential diagnosis for patients complaining of dysphagia. Although rare, extensive esophageal ulceration and stenosis due to food impaction, as seen in this patient, can occur. Findings of food impaction may thus be missed on endoscopy. Unless the physician elicits a careful history, the patient may fail to mention anything about what they ate. Thus, in steakhouse syndrome, a careful history at initial evaluation is very important, particularly regarding food type and characteristics, circumstances surrounding ingestion, and time of ingestion.

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CASE REPORT

Gastroesophageal junction tear from HALO 90® System: A case report

Ellen Gutkin, Alan Schnall

Ellen Gutkin, Alan Schnall, Division of Gastroenterology, New York Hospital Queens, NY 11355, United States
Author contributions: Gutkin E and Schnall A contributed equally to the work.
Correspondence to: Ellen Gutkin, DO, Division of Gastroenterology, New York Hospital Queens, 56-45 Main Street Flushing, NY 11355, United States. ellen.gutkin@gmail.com
Telephone: +1-718-670-2559 Fax: +1-718-670-2456
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Abstract

Gastric antral vascular ectasia often results in chronic gastrointestinal bleeding with few options for effective treatment. The Halo® 90 system has been newly approved for this indication. A 56 year old male with ETOH cirrhosis and gastrointestinal bleeding from gastric vascular ectasia presented for endoscopy with Halo® 90 radiofrequency ablation. Over the past two years he had undergone multiple bipolar electric coagulation and argon plasma coagulation treatments. Despite this therapy, he continued to receive monthly blood transfusions. We therefore opted to treat the vascular anomalies with the Halo® 90 system utilizing radiofrequency ablation. Upon withdrawal of the endoscope post procedure, mild resistance and bleeding was noted at the gastroesophageal junction. Repeat endoscopy revealed a submucosal tear at the gastroesophageal junction. This is the first reported complication of the Halo® 90 system when used for gastric antral vascular ectasia.

Key words: Halo® 90; Radiofrequency ablation; Gastric antral vascular ectasia; Cirrhosis; Endoscopy; Complications

Peer reviewers: Adam Donald Farmer, DR, Wingate Institute of Neurogastroenterology, 26 Ashfield Street, London E1 2AJ, United Kingdom

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INTRODUCTION

Gastric antral vascular ectasia (GAVE) can present in patients with cirrhosis and portal hypertension, as well as patients with autoimmune disease[1]. GAVE is characterized by red patches or spots in either diffuse or linear array in the antrum of the stomach[1]. These vascular ectasias can lead to acute or chronic hemorrhage and iron deficiency anemia[2]. The initial management of these patients includes endoscopic argon plasma coagulation; however, despite repeat APC, some patients require frequent transfusions. Evaluation for liver transplantation should also be performed as vascular ectasias have been noted to improve post transplant[2]. Other therapies include Nd:YAG (neodymium:yttrium-aluminum-garnet) laser coagulation but this carries a higher risk of perforation given the deeper thermal effect. Endoscopic sclerotherapy, heater probe, cryotherapy and banding in the antrum of the stomach have also been described in the literature[2]. When endoscopic therapy is unsuccessful, surgery with antrectomy can be considered but carries a high surgical risk, especially in the cirrhotic patient[1].

The BARRX-Halo® is a radiofrequency ablation system (RFA) used for endoscopic treatment of Barrett's esophagus[3]. The device can be fitted with a balloon (Halo® 360) or an electrode plate (Halo® 90). The Halo® 90 radiofrequency ablation system has been newly approved for treatment of gastric antral vascular ectasia. Only once case series of its use exists in the literature and no complications of its use have been reported until now.

CASE REPORT

A 56 year old male with ETOH cirrhosis and gastrointestinal bleeding from gastric vascular ectasia (Figure 1) presented for endoscopy with Halo® 90 radiofrequency ablation. He had undergone multiple bipolar electric coagulation and argon plasma coagulation treatments over the past two years. He was maintained on double dose proton pump inhibitors, sucralfate suspension, as well as estrogen for stabilization of vascular endothelial membranes and B-blockers for portal hypertension. Over the past two months his transfusion requirement increased to four units of packed red cells monthly and he had undergone three treatments with the argon plasma coagulator without diminution of bleeding. We therefore opted to treat the vascular anomalies with the Halo® 90 system utilizing radiofrequency ablation.

On endoscopy, multiple vascular ectasias were seen throughout the stomach, with an abundance of lesions in the antrum along with fresh blood. The area was treated with Halo® 90 RFA at four sites (48 ablations at 12 joules/40 watts). The gastroesophageal junction (GEJ) was viewed multiple times and was normal other than the presence of vascular anomalies. Upon withdrawal of the endoscope, there was mild resistance felt at the GEJ and immediate bleeding was noted (Figure 2). When the instrument was removed from the patient, the Halo® probe was alongside but no longer attached to the scope. The endoscope was reinserted and a mucosal/submucosal tear was noted at the GE junction which was not amenable to placement of Hemoclips. The bleeding was self-limited and ceased spontaneously. There was no endoscopic evidence of perforation. The exact mechanism of the esophageal tear remains unclear. The patient did not retch during the exam, nor was the withdrawal of the endoscope rapid or forceful, but we surmise that it was a result of the Halo® system as it dislodged from the endoscope.

The patient was subsequently admitted to the hospital for twenty-four hours for monitoring; there was no free air seen on radiological imaging and his blood counts remained stable.

One month later, a follow up endoscopy revealed healing of the GE junction tear and there was dramatic improvement and diminution of the antral vascular anomalies without bleeding. The patient's hemoglobin has increased to 15 mg/dL without any further transfusion requirement.

DISCUSSION

Gastric antral vascular ectasia often results in chronic gastrointestinal bleeding with few options for effective treatment. The Halo® 90 system has been newly approved for this indication and appears to have promising results. A recent pilot study of six patients with GAVE using the Halo® system showed a reversal of transfusion requirements in 5/6 patients[4]. No complications were reported in that study.

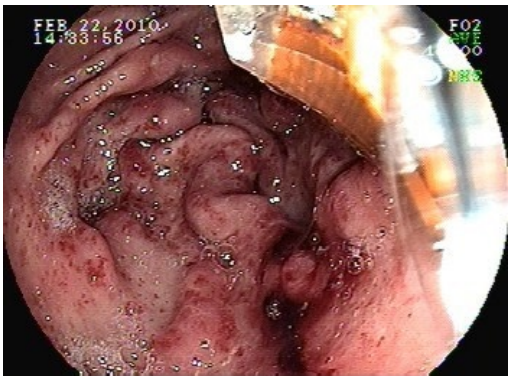

Figure 1 Gastric antral vascular ectasia.

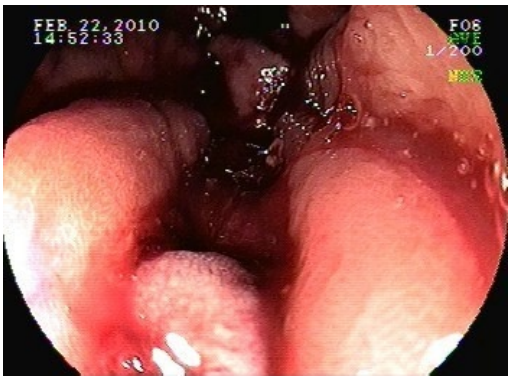

Figure 2 Gastroesophageal junction tear.

This is the first reported complication of the Halo® 90 system when used for GAVE. Despite the lack of definitive proof, we believe that the use of a foreign body hood placed above the Halo® 90 device when gastric manipulations are performed would prevent trauma to the GE junction; upon withdrawal of the endoscope the hood would retract over the device and avoid complications similar to ours.

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Maher Aref Abbas, MD, FACS, FASCRS, Associate Professor of Surgery, Chief, Colon and Rectal Surgery, Chair, Center for Minimally Invasive Surgery, Kaiser Permanente, 4760 Sunset Blvd, 3rd Floor, Los Angeles, CA 90027, United States

Majid Abdulrahman Almadi, MD, FRCPC, Department of Gastroenterology Division, McGill University Health Center, McGill University, Royal Victoria Hospital, 687 Pine Ave West, Montreal H3A 1A1, Canada

Mitsuhiro Asakuma, MD, PhD, Assistant Professor, Department of General and Gastroenterological Surgery, Osaka Medical College, 2-7 Daigaku-machi, Takatsuki, Osaka 569-8686, Japan

Peter Born, Professor, Chief, 2nd Department of Medicine, Red Cross Hospital, Munich, Germany

Carlo Calabrese, MD, PhD, Researcher, Department of Clinical Medicine, University of Bologna, Via Massarenti 9, 40138 Bologna, Italy

David J Desilets, MD, PhD, Chief, Division of Gastroenterology, Springfield Bldg, Rm S2606, Department of Medicine; Assistant Professor of Clinical Medicine, Tufts University School of Medicine, Springfield Campus, Baystate Medical Center, Springfield, MA 01199, United States

Christoph Eisenbach, MD, Department of Gastroenterology, University of Heidelberg, Im Neuenheimer Feld 410, D-69210 Heidelberg, Germany

Adam Donald Farmer, Dr, Wingate Institute of Neurogastroenterology, 26 Ashfield Street, London E1 2AJ, United Kingdom

Stefanos Karagiannis, MD, PhD, Gastrointestinal and Liver Unit, General and Oncology Kifissia Hospital Agioi Anargiri', Kaliftaki 14564, Kifissia, Greece

Taro Osada, MD, PhD, Associate Professor, Department of Gastroenterology, Juntendo University, 2-1-1 Hongo Bunkyo-ku Tokyo 113-8421, Japan

Marmo Riccardo, Postgraduate Specialist, Head, Gastroenterology Unit, Azienda Sanitaria Locale Salerno, Presidio Ospedaliero Polla (SA), Via Luigi Curto Polla, 84037, Italy

Carlos Robles-Medranda, MD, Head of the Endoscopy Division, Ecuadorian Institute of Digestive Disease (IECED), San Antonio Clinic, Av. Reales Tamarindo y Tennis Club, Portoviejo, Manabi-Ecuador, Casilla 13-01-266, Ecuador

Jiang-Fan Zhu, MD, Professor, Department of General Surgery, East Hospital of Tongji University, 150 Jimo Road, Pudong, Shanghai 200120, China

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9. Gastro Forum München
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13th Duesseldorf International Endoscopy Symposium
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February 13-27, 2011
Gastroenterology: New Zealand CME Cruise Conference
Sydney, NSW, Australia

February 24-26, 2011
Inflammatory Bowel Diseases 2011-6th Congress of the European Crohn's and Colitis Organisation
Dublin, Ireland

February 24-26, 2011
2nd International Congress on Abdominal Obesity
Buenos Aires, Brazil

February 26-March 1, 2011
Canadian Digestive Diseases Week
Westin Bayshore, Vancouver
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March 03-05, 2011
42nd Annual Topics in Internal Medicine
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British Society of Gastroenterology Annual Meeting 2011
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International and Interdisciplinary Conference Excellence in Female Surgery
Florence, Italy

April 15-16, 2011
Falk Symposium 177, Endoscopy Live Berlin 2011 Intestinal Disease Meeting, Stauffenbergstr. 26
Berlin 10785, Germany

April 18-22, 2011
Pediatric Emergency Medicine: Detection, Diagnosis and Developing Treatment Plans
Sarasota, FL 34234, United States

April 20-23, 2011
9th International Gastric Cancer Congress, COEX, World Trade Center, Samseong-dong
Seoul 135-731, South Korea

April 25-27, 2011
The Second International Conference of the Saudi Society of Pediatric Gastroenterology, Hepatology & Nutrition
Riyadh, Saudi Arabia

April 28-30, 2011
4th Central European Congress of Surgery
Budapest, Hungary

May 07-10, 2011
Digestive Disease Week
Chicago, IL 60446, United States

May 12-13, 2011
2nd National Conference Clinical Advances in Cystic Fibrosis
London, England, United Kingdom

May 21-24, 2011
22nd European Society of Gastrointestinal and Abdominal Radiology Annual Meeting and Postgraduate Course
Venise, Italy

May 25-28, 2011
4th Congress of the Gastroenterology Association of Bosnia and Herzegovina with international participation, Hotel Holiday Inn
Sarajevo, Bosnia and Herzegovina

June 11-12, 2011
The International Digestive Disease Forum 2011
Hong Kong, China

June 13-16, 2011
Surgery and Disillusion XXIV Spigc
II ESYS, Napoli, Italy

June 22-25, 2011
ESMO Conference: 13th World Congress on Gastrointestinal Cancer
Barcelona, Spain

September 10-11, 2011
New Advances in Inflammatory Bowel Disease
La Jolla, CA 92093, United States

September 10-14, 2011
ICE 2011-International Congress of Endoscopy, Los Angeles Convention Center, 1201 South Figueroa Street
Los Angeles, CA 90015, United States

September 30-October 1, 2011
Falk Symposium 179, Revisiting IBD Management: Dogmas to be Challenged, Sheraton Brussels Hotel
Brussels 1210, Belgium

October 19-29, 2011
Cardiology & Gastroenterology Tahiti 10 night CME Cruise
Papeete, French Polynesia

October 22-26, 2011
19th United European Gastroenterology Week
Stockholm, Sweden

October 28-November 02, 2011
ACG Annual Scientific Meeting & Postgraduate Course
Washington, DC 20001, United States

November 11-12, 2011
Falk Symposium 180, IBD 2011: Progress and Future for Lifelong Management, ANA Interconti Hotel, 1-12-33 Akasaka, Minato-ku
Tokyo 107-0052, Japan

December 01-04, 2011
2011 Advances in Inflammatory Bowel Diseases/Crohn's & Colitis Foundation's Clinical & Research Conference
Hollywood, FL 34234, United States

World Journal of Gastrointestinal Endoscopy

Online Submissions: http://www.wjgnet.com/1948-5190office
wjge@wjgnet.com
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World J Gastrointest Endosc 2011 May 16; 3(5): I-V
ISSN 1948-5190 (online)

GENERAL INFORMATION

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Acknowledgments

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Chinese journal article (list all authors and include the PMID where applicable)

2 **Lin GZ**, Wang XZ, Wang P, Lin J, Yang FD. Immunologic effect of Jianpi Yishen decoction in treatment of Pixu-diarrhoea. *Shijie Huaren Xiaohua 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

Organization as author

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

Both personal authors and an organization as author

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. *HRSA Careaction* 2002; 1-6 [PMID: 12154804]

Books

Personal author(s)

10 **Sherlock S**, Dooley J. Diseases of the liver and billiary 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**, Schorfheide AM. Adolescent pregnancy. 2nd ed. Wieczorek RR, editor. White Plains (NY): March of Dimes Education Services, 2001: 20-34

Conference proceedings

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

Statistical data

Write as mean ± SD or mean ± SE.

Statistical expression

Express *t* test as *t* (in italics), *F* test as *F* (in italics), chi square test as χ^2 (in Greek), related coefficient as *r* (in italics), degree of freedom as υ (in Greek), sample number as *n* (in italics), and probability as *P* (in italics).

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Italics

Quantities: *t* time or temperature, *c* concentration, *A* area, *l* length, *m* mass, *V* volume.
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Ocean International Center,
No. 62 Dongsihuan Zhonglu,
Chaoyang District, Beijing 100025, China
E-mail: wjge@wjgnet.com
http://www.wjgnet.com
Telephone: +86-10-5908-0038
Fax: +86-10-8538-1893

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